sec., then cooled rapidly and dissolved in the minimum amount of benzene. One volume of hexane was added and the solution developed on alumina–lime–Celite (45 × 4.5 cm.) with benzene:hexane (2:1):

243	empty section
135	dark red (all-*trans*)
8	interzone
53	pale red (*cis*-I)
11	empty section

A thin zone containing the *cis*-II and -III was washed into the filtrate. The *cis*-I zone was eluted with benzene + 5% alcohol and the solvents were removed to yield a yellow, powdery residue. The combined yields of *cis*-I obtained as described from 250 mg. of the *trans* form were dissolved in benzene and developed on magnesia–Celite (30 × 4.5 cm.) with benzene + 3% alcohol:

95	empty section
41	dark red (all-*trans*, mostly formed *de novo*)
14	interzone
63	red (*cis*-I)
87	empty section

The *cis*-I fraction was recrystallized from hot benzene by dropwise addition, with stirring, of methanol; yield 25 mg. of yellow needles, m.p. 165.5–167°; $E^{mol.}_{1\ cm.}$ 5.67 × 10^4 at λ_{max} 385.5 mμ (in hexane).

Anal. Calcd. for $C_{24}H_{18}$: C, 94.08; H, 5.92. Found: C, 94.10; H, 5.76.

5-*cis*-Biphenylenephenylhexatriene (*"cis*-II").—Three 100-mg. portions of the all-*trans* compound were melted, kept at 270–275° for 30 sec., then cooled rapidly, dissolved in benzene and developed with benzene + 8% acetone on magnesia-Celite (45 × 4.5 cm.):

31	empty section
120	dark red (all-*trans* + some *cis*-I)
113	interzone
48	red (*cis*-II)
6	interzone
31	pale red (*cis*-III)
101	empty section

After elution the *cis*-II isomer was rechromatographed on a similar column using benzene + 9% acetone as the developer; thus, some *trans* compound was eliminated; yield 8.3 mg. of pale yellow flat prisms, m.p. 122–123.5°; $E^{mol.}_{1\ cm.}$ 5.25 × 10^4 at λ_{max} 385 mμ (in hexane). For analysis the sample was recrystallized from ethanol.

Anal. Calcd. for $C_{24}H_{18}$: C, 94.09; H, 5.92. Found: C, 93.89; H, 6.06 (corrected for 0.35% ash).

TABLE III

RATIOS OF THE *trans* AND *cis* FORMS IN STEREOISOMERIC MIXTURES OF BIPHENYLENEPHENYLHEXATRIENE

Steric form treated	Treatment	Ratio in recovered substance *trans*:*cis*-I:*cis*-II:*cis*-III	Loss (% of starting material)
trans	Iodine cat.[a]	92:8:trace:trace	18
trans	Irradiation[b]	No effect	
trans	Insolation[c]	No effect	
trans	Refluxing[d]	No effect	
trans	Melting cryst.[e]	78.5:16.5:4:1	21
cis-I	Iodine cat.[a]	94:6:trace:trace	23
cis-I	Irradiation[b]	2:98:0:0	1
cis-I	Insolation[f]	34:66:0:0	1
cis-I	Refluxing[d]	No effect	
cis-II	Iodine cat.[a]	~99:~1:0:0	26
cis-II	Irradiation[g]	3:0:97:0	1
cis-II	Refluxing[d]	No effect	
cis-III	Iodine cat.[h]	20:80:0:0	24
cis-III	Irradiation[g]	~0:~7:0:93	1
cis-III	Refluxing[d]	No effect	

[a] 2 min. at 60 cm. from light source (Pyrex flask). [b] 60 min. at 10 cm. from Photoflood bulb (Pyrex). [c] 120 min. in moderately intense sunlight (Pyrex). [d] Hexane solution refluxed for 30 min. in the dark. [e] 30 sec. at 320°. [f] 20 min. in intense sunlight (Pyrex). [g] 30 min. at 10 cm. from Photoflood bulb (Pyrex). [h] 30 min. at 200 cm. from light source (quartz cell); iodine 0.1% of substance.

3,5-Di-*cis*-biphenylenephenylhexatriene (*"cis*-III").—The *cis*-III fraction from the above column was combined with that obtained from 200 mg. of the all-*trans* form and developed with benzene + 9% acetone on magnesia-Celite (20 × 3.5 cm.):

11	empty sections
10	red (all-*trans*)
64	interzone
23	pale red (*cis*-II)
10	interzone
42	red (*cis*-III)
40	empty section

Yield 3.8 mg. of pale yellow crystals, m.p. 118.5–121°, $E^{mol.}_{1\ cm.}$ 4.83 × 10^4 at λ_{max} 379 mμ (in hexane).

PASADENA, CALIFORNIA

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, CHEMICAL DIVISION, MERCK & CO., INC.]

Synthesis of 8-Hydroxy-2-keto-5-methoxy-4a-methyl-2,3,4,4a,9,10-hexahydrophenanthrene

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8-Hydroxy-2-keto-5-methoxy-4a-methyl-2,3,4,4a,9,10-hexahydrophenanthrene has been prepared as a potential intermediate for the synthesis of 11-oxygenated steroids. The reactions used to convert 5-hydroxy-8-methoxytetralone-1 to 5-hydroxy-8-methoxy-1-methyltetralone-2 offer a general method for the synthesis of hydrophenanthrenes. The Robinson-Mannich base reaction to form the potential ring A has been broadened to include the use of aqueous reaction media.

This paper describes the synthesis of 8-hydroxy-2-keto-5-methoxy-4a-methyl-2,3,4,4a,9,10-hexahydrophenanthrene (XIX) and some related compounds. The method of synthesis was based in part on the previously described[2] preparation of 8-chloro-4a-ethyl-2-keto-5,6-dimethoxy-2,3,4,4a,9,10-hexahydrophenanthrene, a potential intermediate for the synthesis of morphine. Syntheses of the rather similar steroid intermediates, 8-hydroxy-2-keto-4a-methyl-2,3,4,4a,9,10-hexahydrophenanthrene[3] and 2-keto-5,8-dimethoxy-4a-methyl-2,3,4,4a,9,10-hexahydrophenanthrene[4] (XVIII) through somewhat different approaches have been

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(2) R. Ghosh and R. Robinson, *J. Chem. Soc.*, 505 (1944).

(3) J. W. Cornforth and R. Robinson, *ibid.*, 1855 (1949).

(4) C. A. Grob and W. Jundt, *Helv. Chim. Acta*, **31**, 1691 (1948).

reported. In the latter cases as well as in the present work, the potential ring A of the steroids was formed through use of the well known Robinson–Mannich base synthesis.[5] Our work extends and simplifies this convenient method by using aqueous systems for the condensation. 8-Hydroxy-2-keto-5-methoxy-4a-methyl-2,3,4,4a,9,10-hexahydrophenanthrene differs from the other condensed hydroaromatic systems referred to above in that it contains a protected potential C-11 oxygen as well as a hydroxyl group at the potential C-14 position to serve as a point of attachment of ring D.

Hydroquinone dimethyl ether (I) was condensed with succinic anhydride in nitrobenzene solution in the presence of two moles of aluminum chloride. During the reaction preferential demethylation of the methoxyl group *ortho* to the side chain occurred to yield β-(2-hydroxy-4-methoxybenzoyl)-propionic acid (II). The benzoylpropionic acid (II) was hydrogenated at high pressure over copper–chromium oxide catalyst in an aqueous alkaline solution to γ-(2-hydroxy-5-methoxyphenyl)-butyric acid (III).

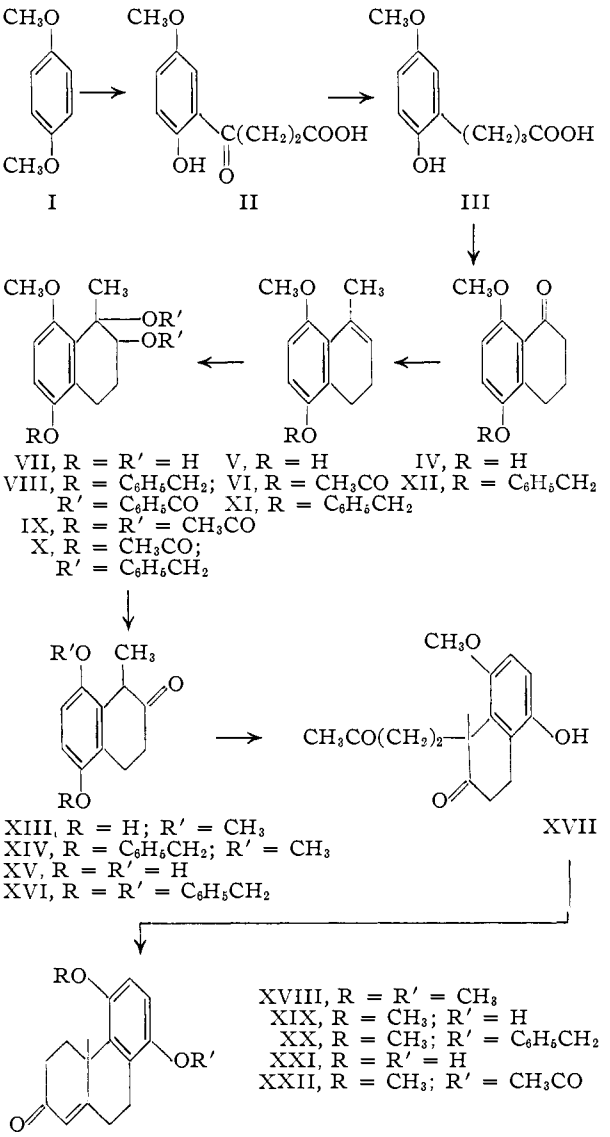
The phenylbutyric acid (III) was cyclized to 5-hydroxy-8-methoxytetralone-1 (IV) with 85% sulfuric acid. Inverse addition of an excess of methylmagnesium iodide in ether solution to a pyridine solution of the α-tetralone (IV), yielded the intermediate tertiary alcohol, 1,5-dihydroxy-8-methoxy-1-methyl-1,2,3,4-tetrahydronaphthalene. This intermediate alcohol was not isolated because it dehydrated during the work-up of the reaction mixture to give 4-methoxy-5-methyl-7,8-dihydronaphthol-1 (V). Normal addition of the α-tetralone (IV) to methylmagnesium iodide in ether solution gave an insoluble complex, and addition to the carbonyl group did not take place. From this reaction, starting material IV and the demethylated product, 5,8-dihydroxytetralone-1 were isolated.

In an attempt to eliminate the formation of an insoluble Grignard complex, the phenolic 5-hydroxy group of the α-tetralone (IV) was converted to a 5-benzyloxy group, by reaction with benzyl bromide. However, reaction of the product, 5-benzyloxy-8-methoxytetralone-1 (XII), with methylmagnesium iodide failed. 1-Benzyloxy-4-methoxy-5-methyl-7,8-dihydronaphthalene (XI) was prepared, however, by reaction of the dihydronaphthol (V) with benzyl bromide. In addition, acetylation of the dihydronapthol (V) yielded 1-acetoxy-4-methoxy-5-methyl-7,8-dihydronaphthalene (VI).

The dihydronaphthol (V) was converted to the osmate ester by treatment with osmium tetroxide. Reductive hydrolysis of the osmate ester with sodium sulfite afforded 1,2,5-trihydroxy-8-methoxy-1-methyl-1,2,3,4-tetrahydronaphthalene (VII). The trihydroxy compound was rearranged with dilute sulfuric acid to 5-hydroxy-8-methoxy-1-methyltetralone-2 (XIII). The β-tetralone (XIII) also was prepared from 1-acetoxy-4-methoxy-5-methyl-7,8-dihydronaphthalene (VI) using red lead oxide in acetic acid. The acetoxydihydronaphthalene (VI) was oxidized in acetic acid solution with red lead oxide to a mixture of *cis*- and *trans*-1,2,5-triacetoxy-8-methoxy-1-methyl-1,2,3,4-tetrahydronaphthalene (IX). In dilute alcoholic sulfuric acid the *cis*- and *trans*-triacetates (IX) rearranged to the β-tetralone (XIII) in almost quantitative yield. The over-all yield of β-tetralone obtained by this latter procedure was better than that obtained using osmium tetroxide.

Other methods for obtaining the β-tetralone XIII included treatment of the dihydronaphthol V with either monoperphthalic or perbenzoic acid and subsequent rearrangement of the intermediate triol VII. However, the yields using these procedures were very low. When 1-acetoxy-4-methoxy-5-methyl-7,8-dihydronaphthalene (VI), having a protected phenolic group, was oxidized with perbenzoic acid, the yield was improved.

1-Benzyloxy-4-methoxy-5-methyl-7,8-dihydronaphthalene (XI) reacted with perbenzoic acid to give 5-benzyloxy-1,2-dibenzoxy-8-methoxy-1-methyl-1,2,3,4-tetrahydronaphthalene (VIII). Rearrangement with aqueous ethanolic sulfuric acid



(5) *Cf.* E. C. duFeu, F. J. McQuillin and R. Robinson, *J. Chem. Soc.*, 53 (1937), and subsequent papers.

produced the benzyloxy β-tetralone (XIV). The product was identical with that prepared by reaction of benzyl bromide with the β-tetralone (XIII).

5,8-Dihydroxy-1-methyltetralone-2 (XV) was prepared from 5-hydroxy-8-methoxy-1-methyltetralone-2 (XIII) by demethylation with pyridine hydrochloride. The diol XV was converted to 5,8-dibenzyloxy-1-methyltetralone-2 (XVI) by reaction with benzyl bromide.

Condensation of the β-tetralone (XIII) with 4-diethylaminobutanone-2 methiodide afforded 8-hydroxy-2-keto-5-methoxy-4a-methyl-2,3,4,4a,9,10-hexahydrophenanthrene (XIX). This Robinson–Mannich base reaction[5] was improved by using an aqueous alcoholic solution of potassium hydroxide as the condensing agent instead of potassium ethoxide in anhydrous ethanol. As the yields in the Robinson–Mannich base reaction were low (<50%), some effort was directed toward obtaining a better conversion. In one variation of the reaction, the intermediate 5-hydroxy-8-methoxy-1-methyl-1-(3-ketobutyl)-tetralone-2 (XVII) was isolated. The cyclization to form ring A was completed by treatment of the intermediate XVII with acid which produced the hexahydrophenanthrene (XIX). However, the yields in this two-step procedure were no better than those in the one-step process. It was felt that side reactions involving the free phenolic hydroxyl group of the starting β-tetralone (XIII) might have been a cause of the low yields. With this in mind, the Robinson procedure was applied to the benzyloxy derivative XIV. 8-Benzyloxy-2-keto-5-methoxy-4a-methyl-2,3,4,4a,9,10-hexahydrophenanthrene (XX) was obtained and was shown to be the same as the compound obtained by benzylation of the hexahydrophenanthrene (XIX). The small improvement in yield in this procedure was negated by the extra steps required to carry it out. Finally, a method for adding ring A using methyl vinyl ketone in place of 4-diethylaminobutanone-2 methiodide was worked out. The tetrahydropyranyl derivative of the β-tetralone (XIII) reacted with methyl vinyl ketone in the presence of benzyltrimethylammonium hydroxide to yield the intermediate tetrahydropyranyl derivative of the hexahydrophenanthrene. The product XIX was liberated on treatment with acid. Although the yield of product was not greatly improved, the above method is more convenient in that the lengthy preparation of 4-diethylaminobutanone-2 methiodide is eliminated. In a similar fashion, the bistetrahydropyranyl derivative of 5,8-dihydroxy-1-methyltetralone-2 (XV) was converted into 5,8-dihydroxy-2-keto-4a-methyl-2,3,4,4a,9,10-hexahydrophenanthrene (XXI). The product was the same as that obtained by demethylating the methoxyhexahydrophenanthrene (XIX). 8-Acetoxy-2-keto-5-methoxy-4a-methyl-2,3,4,4a,9,10-hexahydrophenanthrene (XXII) was prepared by acetylating the 8-hydroxy compound XIX with acetic anhydride.

The structure of the hexahydrophenanthrene (XIX) was confirmed by its conversion to the known 5,8-dimethoxy-2-keto-4a-methyl-2,3,4,4a,-9,10-hexahydrophenanthrene (XVIII).[4]

Experimental[6]

β-(2-Hydroxy-5-methoxybenzoyl)-propionic Acid (II).—To an ice-cold mixture of 320 g. (2.32 moles) of hydroquinone dimethyl ether (I), 240 g. (2.40 moles) of succinic anhydride and 2 l. of nitrobenzene, 640 g. (4.81 moles) of anhydrous aluminum chloride was added. During this addition, which required one hour, the reaction mixture was stirred and cooled in an ice-bath. The temperature was maintained below 35°. The resulting solution was warmed slowly to 60° and stirred at this temperature for three hours. After cooling to 35°, the dark, viscous solution was poured into a mixture of 400 ml. of concentrated hydrochloric acid and 700 g. of ice. After removal of the nitrobenzene by steam distillation, the product crystallized when the mixture was cooled. The product was collected on a filter and dissolved in 6 l. of benzene by heating under reflux. The benzene solution was decanted from insoluble tars and then cooled to 5°. The crude product, 335 g. (62%), m.p. 128–135°, was collected on a filter. A solution of this material in 50% methanol–water was treated with Darco and filtered hot. After cooling, the yellow crystals, 275 g. (51%), m.p. 137–142°, were collected on a filter. After several crystallizations from ethyl acetate, the β-(2-hydroxy-5-methoxybenzoyl)-propionic acid melted at 145–146°.

Anal. Calcd. for $C_{11}H_{12}O_5$: C, 58.92; H, 5.39; CH_3O–, 13.8; neut. equiv., 224. Found: C, 59.46; H, 5.90; CH_3O–, 12.8; neut. equiv., 225.

γ-(2-Hydroxy-5-methoxyphenyl)-butyric Acid (III).—A mixture of 400 g. (1.8 moles) of β-(2-hydroxy-5-methoxybenzoyl)-propionic acid (II), 1 l. of 1.8 *N* potassium hydroxide and 50 g. of copper–chromium oxide catalyst was heated and shaken under a hydrogen pressure of 3,500 p.s.i. After two hours at 160°, the temperature was raised to 180° for several hours. The catalyst was removed by filtration. After acidification to *p*H 2 with concentrated hydrochloric acid, the solution was extracted several times with ether. The combined ether extracts were washed with saturated brine and dried over anhydrous sodium sulfate. After removal of the ether under reduced pressure, the residual oil was distilled. At 170–178° (0.1 mm.), 270 g. (71%) of a heavy oil was collected. The oil obtained by distillation was sufficiently pure for use directly in the next reaction. Crystallization and recrystallization of a small sample of this material from petroleum ether (b.p. 60–80°) afforded colorless prisms, m.p. 66–67°.

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.84; H, 6.72. Found: C, 62.06; H, 6.43.

Attempts to purify this product further were not successful and consistently low carbon values were obtained.

5-Hydroxy-8-methoxytetralone-1 (IV).—A solution of 260 g. (1.24 moles) of γ-(2-hydroxy-5-methoxyphenyl)-butyric acid (III) in 300 ml. of water and 940 ml. of concentrated sulfuric acid was heated at 98° for one hour. The dark solution then was poured into 8 l. of ice-water. After cooling at 0° overnight, the tan crystals were collected on a filter and washed thoroughly with cold water. This crude material was dissolved in 700 ml. of methanol and 1 l. of water, treated with Darco and filtered hot. The α-tetralone crystallized as yellow platelets, m.p. 155–160°, 200 g. (82%). Several recrystallizations from a mixture of benzene and methanol afforded material melting at 169–171°.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.67; H, 5.99.

4-Methoxy-5-methyl-7,8-dihydronaphthol-1 (V).—Methylmagnesium iodide was prepared by slowly adding 78 ml. (1.25 moles) of methyl iodide to 30 g. (1.25 moles) of magnesium in 400 ml. of dry ether. The Grignard reagent was added slowly to a cold solution of 48 g. (0.25 mole) of 5-hydroxy-8-methoxytetralone-1 (IV) in 400 ml. of dry pyridine. After the addition of Grignard reagent was completed, 750 ml. of dry ether was added to facilitate stirring of the solid complex. The resulting mixture was stirred at room temperature for approximately 18 hours, and the complex was then decomposed in ice containing 500 ml. of concentrated hydrochloric acid. After saturation with sodium chloride, the aqueous phase was extracted four times with ether. The combined ether extracts were washed with sodium carbonate solution and with water and dried over anhydrous

(6) We are indebted to Mr. R. N. Boos and his associates for microanalyses reported in this paper.

sodium sulfate. The crystalline material which remained after concentration weighed 38 g. Distillation of the residue (b.p. 115–130° (0.1 mm.)) yielded 34 g. (72%) of crystals, m.p. 80–84°. After several recrystallizations from petroleum ether (b.p. 90–100°), the dihydronaphthol melted at 85–86°.

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42; CH_3O–, 16.3. Found: C, 75.68; H, 7.22; CH_3O–, 15.2.

5,8-Dihydroxytetralone-1.—This product was formed when a pyridine solution of 5-hydroxy-8-methoxytetralone-1 (IV) was added to excess methylmagnesium iodide in ether. After decomposition of the Grignard addition compound, 5,8-dihydroxytetralone-1 was obtained in 30–40% yields. After several recrystallizations from 50% methanol and water, the dihydroxytetralone melted at 178–180°.[7] The only other product isolated from this reaction was starting material.

Anal. Calcd. for $C_{10}H_{10}O_3$: C, 67.50; H, 5.67. Found: C, 67.29; H, 5.45.

5-Benzyloxy-8-methoxytetralone-1 (XII).—A mixture of 44 g. (0.23 mole) of 5-hydroxy-8-methoxytetralone-1 (IV) and 43.2 g. (0.253 mole) of benzyl bromide was dissolved in 100 ml. of methanol and the solution was heated to reflux temperature. The solution was stirred and 15.1 g. (0.279 mole) of sodium methoxide in 100 ml. of methanol was added over a period of one hour. The reaction mixture was cooled and 400 g. of ice and water was added to it. The yield of 5-benzyloxy-8-methoxytetralone-1, m.p. 111–116°, was 61.3 g. (93%). A portion was recrystallized twice from methanol and once from benzene to yield an analytical sample, m.p. 116.5–117.5°.

Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43; CH_3O–, 10.99. Found: C, 76.50; H, 6.52; CH_3O–, 11.22.

1-Benzyloxy-4-methoxy-5-methyl-7,8-dihydronaphthalene (XI).—A mixture of 16.9 g. (0.089 mole) of 4-methoxy-5-methyl-7,8-dihydronaphthol-1 (V) and 12 ml. (0.998 mole) of benzyl bromide in 50 ml. of methanol was heated to reflux temperature under a nitrogen atmosphere. A solution of 7.8 g. (0.144 mole) of sodium methoxide in 50 ml. of methanol was added with stirring over a period of ten minutes. Refluxing was continued for 20 minutes and the mixture was cooled. To this mixture was added 25 ml. of 2.5 *N* hydrochloric acid and 250 ml. of water. The mixture was extracted several times with ether. The combined ethereal extracts were washed successively with dilute sodium hydroxide, with dilute hydrochloric acid and with water. They were dried and concentrated under reduced pressure. The residue was distilled at 149–152° at 0.1 mm. to yield 18 g. of an oil.

The distillate crystallized on standing at room temperature. A sample was recrystallized twice from a mixture of alcohol and water and twice more from alcohol to yield material melting at 53.5–54.5°. Although acceptable analyses were not obtained, the product was satisfactory for use in the preparation of 1,2-dibenzoxy-5-benzyloxy-8-methoxy-1-methyl-1,2,3,4-tetrahydronaphthalene (VIII).

Anal. Calcd. for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19. Found: C, 80.27; H, 7.16.

1-Acetoxy-4-methoxy-5-methyl-7,8-dihydronaphthalene (VI).—Twenty grams of 4-methoxy-5-methyl-7,8-dihydronaphthol-1 (V) was dissolved in a mixture of 100 ml. of pyridine and 20 ml. of acetic anhydride. This mixture was allowed to stand overnight at room temperature. It was poured slowly into one l. of water with stirring, whereupon the product separated as a crystalline solid. It was filtered, washed well with water, and was dried in air at room temperature. The yield of 1-acetoxy-4-methoxy-5-methyl-7,8-dihydronaphthalene was 23.7 g. (97%), m.p. 56–57°. A sample, recrystallized three times from a mixture of alcohol and water, melted at 59–60°.

Anal. Calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.56; H, 6.78.

1,2,5-Trihydroxy-8-methoxy-1-methyl-1,2,3,4-tetrahydronaphthalene (VII).—A solution of 7.26 g. (0.028 mole) of osmium tetroxide in 100 ml. of dry diethyl ether was added to a solution of 4.9 g. (0.026 mole) of 4-methoxy-5-methyl-7,8-dihydronaphthol-1 (V) in 50 ml. of dry diethyl ether. An immediate separation of dark brown osmate ester occurred along with the evolution of considerable heat. After 18 hours at room temperature, the solid was removed by filtration. To the osmate ester, dissolved in 250 ml. of ethanol, a solution of 29 g. of sodium sulfite in 250 ml. of water was added. The mixture was heated under reflux for about two hours. The precipitate of reduced osmium and undissolved sodium sulfite was removed by filtration through Super-cel. The cake was washed with several portions of hot ethanol and hot water. The combined filtrates were concentrated under reduced pressure to a volume of about 250 ml. The residue was neutralized (*p*H 7) with 2.5 *N* hydrochloric acid and the product was extracted with five portions of diethyl ether. The combined ether extracts were dried over anhydrous sodium sulfate and the ether was removed by distillation under reduced pressure. Recrystallization of the residue from 20 ml. of chloroform by adding 5 ml. of petroleum ether (b.p. 30–60°) afforded 4 g. (64%) of the glycol, m.p. 133–135°. Several recrystallizations from chloroform and petroleum ether gave material melting at 147–148° with some softening at 135°.

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19; CH_3O–, 13.84. Found: C, 64.53; H, 6.91; CH_3O–, 14.48.

5-Hydroxy-8-methoxy-1-methyltetralone-2 (XIII). From VII.—A solution of 35 g. of 1,2,5-trihydroxy-8-methoxy-1-methyl-1,2,3,4-tetrahydronaphthalene (VII) in 135 ml. of water, 70 ml. of ethanol and 20 ml. of concentrated sulfuric acid was warmed on the steam-cone for one hour. Sixty milliliters of water was added and crystallization was allowed to proceed at room temperature for several hours and then at 0° overnight. The crystalline product was collected on a filter and washed with water. This procedure afforded 30 g. (93%) of 5-hydroxy-8-methoxy-1-methyltetralone-2, m.p. 135–138°. Several recrystallizations from alcohol and water gave a sample melting at 139–140°.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84; CH_3O–, 15.03. Found: C, 69.64; H, 6.74; CH_3O–, 14.92.

1,2,5-Triacetoxy-8-methoxy-1-methyl-1,2,3,4-tetrahydronaphthalene (IX).—A mixture of 200 g. of 4-methoxy-5-5-methyl-7,8-dihydronaphthol-1 (V), 2 g. of sodium acetate and 200 ml. of acetic anhydride was heated under reflux for one hour. After adding 1200 ml. of glacial acetic acid, the solution was cooled to 50°. The addition of 720 g. of red lead oxide was performed with stirring at a rate sufficient to maintain the temperature of the reaction mixture at 57–59°. After the temperature dropped below 50°, 600 ml. of acetic acid was removed by distillation under reduced pressure. The distillation residue was poured into 6 l. of water and stirred for 20 minutes. The triacetate was extracted with chloroform. After removal of the chloroform by distillation under reduced pressure, the residue was triturated with diethyl ether. The crystals were collected on a filter and washed with ether to give 202 g. (53% from V) of product, m.p. <140°. The *cis*- and *trans*-triacetates were separated by fractional crystallization from ethanol. One isomer (a) melted at 174–175°, the other (b) melted at 161–162°. Since each triacetate was converted easily to the same β-tetralone with acid, the crude mixture was used directly in the next step.

Anal. Calcd. for $C_{18}H_{22}O_7$: C, 61.70; H, 6.33. Found: (a) C, 62.10; H, 6.48. Found: (b) C, 61.20; H, 6.27.

5-Hydroxy-8-methoxy-1-methyltetralone-2 (XIII). From IX.—Nine hundred grams of 1,2,5-triacetoxy-8-methoxy-1-methyl-1,2,3,4-tetrahydronaphthalene (IX) was heated under reflux for 30 minutes in a solution of 1450 ml. of ethanol, 1950 ml. of water and 350 ml. of concentrated sulfuric acid. Fifty grams of Darco was added and the mixture was heated under reflux for an additional 30 minutes. After filtration, 1500 ml. of water was added and crystallization was allowed to proceed overnight at 3°. The crystalline 5-hydroxy-8-methoxy-1-methyltetralone-2 (XIII) was collected on a filter, washed with water and dried. This procedure afforded 522 g. (98%) of material melting at 135–138°.

5-Hydroxy-8-methoxy-1-methyltetralone-2 (XIII). By Monoperphthalic Acid Oxidation of V.—Five grams (0.027 mole) of 4-methoxy-5-methyl-7,8-dihydronaphthol-1 (V) was dissolved in 50 ml. of ether. To this solution 5.8 g. (0.032 mole) of monoperphthalic acid in 100 ml. of ether was added rapidly at 20–25° and the reaction mixture was maintained at this temperature for ten minutes. The greenish-colored solution was washed twice with an aqueous solution of sodium bicarbonate to remove the acidic components. It then was washed three times with a saturated

(7) R. H. Thomson, *J. Chem. Soc.*, 1822 (1952).

aqueous solution of ammonium sulfate, and was dried with anhydrous magnesium sulfate.

The ether was removed under reduced pressure leaving an oily residue. This residue was dissolved in a mixture of benzene and ethyl acetate and chromatographed on a column of acid-washed alumina. The column was developed with the same solvent mixture and 1.7 g. (34%) of starting material was recovered from the eluate. Development of the column with acetone gave 0.4 g. (7%) of a crystalline product which proved to be 1,2,5-trihydroxy-8-methoxy-1-methyl-1,2,3,4-tetrahydronaphthalene (VII), m.p. 141–143°.

One hundred milligrams of this glycol VII was rearranged using sulfuric acid as described above. This procedure yielded 70 mg. (76%) of 5-hydroxy-8-methoxy-1-methyltetralone-2, m.p. 142–143°. The melting point of a mixture of this material with an authentic sample of the tetralone showed no depression.

5-Hydroxy-8-methoxy-1-methyltetralone-2 (XIII). By Perbenzoic Acid Oxidation of V.—Five grams (0.027 mole of 4-methoxy-5-methyl-7,8-dihydronaphthol-1 (V) was converted into 5-hydroxy-8-methoxy-1-methyltetralone-2 (XIII) in a manner identical with that described below using 1-acetoxy-4-methoxy-7,8-dihydronaphthalene (VI). Two crops of product (0.5 g. (9%), m.p. 140–141°, and 0.6 g. (10%), m.p. 137–139°) were obtained.

5-Hydroxy-8-methoxy-1-methyltetralone-2 (XIII). From VI.—Six and one-tenth grams (0.026 mole) of 1-acetoxy-4-methoxy-5-methyl-7,8-dihydronaphthalene (VI) was dissolved in 100 ml. of benzene. The solution was cooled to 5° and 4.4 g. (0.032 mole) of perbenzoic acid in 90 ml. of benzene was added dropwise with stirring over a period of 20 minutes. The temperature of the reaction mixture was maintained at 5°. The mixture was washed twice with an aqueous solution of sodium bicarbonate, then with water and was dried with anhydrous sodium sulfate. The solvent was removed under reduced pressure.

The residue was dissolved in a mixture of 60 ml. of ethanol, 80 ml. of water and 14 ml. of concentrated sulfuric acid, and the mixture was heated under reflux for 20 minutes. It was cooled, diluted to 500 ml. with water, and filtered through Super-cel to remove a dark, gummy precipitate. The filtrate on cooling yielded 1.8 g. (34%) of product, m.p. 140–141°.

The gummy material on the Super-cel was extracted several times with chloroform, and this chloroform in turn was used to extract the aqueous mother liquor of the first crop of material. The chloroform extracts were washed with sodium bicarbonate solution and with water. After drying, the solvent was removed under reduced pressure. The residue was crystallized from 5 ml. of benzene to yield 1.7 g. (33%) of product, m.p. 135–138°.

5-Benzyloxy-8-methoxy-1-methyltetralone-2 (XIV).—To a mixture of 16.2 g. (0.079 mole) of 5-hydroxy-8-methoxy-1-methyltetralone-2 (XIII) and 14.8 g. (0.087 mole) of benzyl bromide in 50 ml. of methanol was added slowly a solution of 4.86 g. (0.091 mole) of sodium methoxide in 50 ml. of methanol with stirring and refluxing. In about an hour the mixture was cooled and the product crystallized from solution. The yield of 5-benzyloxy-8-methoxy-1-methyltetralone-2, m.p. 79–81°, was 16.1 g. (69%). Two recrystallizations from methanol raised the melting point to 81–82°.

Anal. Calcd. for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80; CH_3O–, 10.47. Found: C, 77.01; H, 6.52; CH_3O–, 10.61.

1,2-Dibenzoxy-5-benzyloxy-8-methoxy-1-methyl-1,2,3,4-tetrahydronaphthalene (VIII).—Seven grams (0.025 mole) of 1-benzyloxy-4-methoxy-5-methyl-7,8-dihydronaphthalene (XI) was dissolved in 100 ml. of chloroform. The solution was cooled to −20° and 4.2 g. (0.031 mole) of perbenzoic acid in 60 ml. of chloroform was added over a period of 15 minutes with stirring. The temperature of the reaction mixture was maintained at −20°. The greenish-colored mixture was washed twice with sodium bicarbonate solution, with water and was dried with anhydrous magnesium sulfate. The solvent was removed under reduced pressure.

The oily residue was dissolved in a little benzene and petroleum ether was added until the solution became cloudy. This solution was chromatographed on acid-washed alumina and the column was developed with a benzene–petroleum ether mixture of the same composition as the starting solvents. On evaporation of the solvent, 3 g. (23%) of 1,2-dibenzoxy-5-benzyloxy-8-methoxy-1-methyl-1,2,3,4-tetrahydronaphthalene (VIII) was obtained from the eluate. It was recrystallized three times from benzene–petroleum ether to yield an analytical sample, m.p. 154.5–155.5°.

Anal. Calcd. for $C_{33}H_{30}O_6$: C, 75.84; H, 5.79. Found: C, 75.44; H, 6.19.

5-Benzyloxy-8-methoxy-1-methyltetralone-2 (XIV).—Five hundred milligrams of the dibenzoate VIII was dissolved in a mixture of 20 ml. of ethanol, 10 ml. of water and 2 ml. of concentrated sulfuric acid, and the mixture was heated under reflux for 25 minutes. The solution was cooled, diluted with 25 ml. of water and extracted with chloroform. The chloroform was removed under reduced pressure; the residue was dissolved in a mixture of benzene and petroleum ether and chromatographed on a column of acid-washed alumina. After being washed with benzene–petroleum ether to remove 50 mg. of an oily fraction, the column was washed with benzene. On evaporation of the benzene eluate, 0.3 g. of 5-benzyloxy-8-methoxy-1-methyltetralone-2 was obtained. It was crystallized three times from a mixture of alcohol and water to give an almost quantitative yield of product, m.p. 80.5–81°. The melting point of a mixture of this material with a sample of known composition showed no depression.

5,8-Dihydroxy-1-methyltetralone-2 (XV).—A mixture of 2 g. (0.01 mole) of 5-hydroxy-8-methoxy-1-methyltetralone-2 (XIII) and 6 g. (0.05 mole) of pyridine hydrochloride was heated under nitrogen at 155° for five hours. The reaction mixture was cooled, dissolved in water and extracted with ether. The ether layer was washed with 1 *N* hydrochloric acid and dilute sodium bicarbonate solution, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated to yield a 1.77-g. residue. This material was distilled and a fraction (0.6 g.) boiling at a bath temperature of 220° (0.2 mm.) was obtained. The distillate was crystallized from benzene to give 0.42 g. (22%) of 5,8-dihydroxy-1-methyltetralone-2, m.p. 139–140°. Two recrystallizations from ethylene dichloride produced a purified sample, m.p. 142–143°.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.73; H, 6.30. Found: C, 68.54; H, 6.02.

The melting point of a mixture of the product and starting tetralone, m.p. 139–140°, was 110–119°.

5,8-Dibenzyloxy-1-methyltetralone-2 (XVI).—A solution of 1.4 g. (0.06 mole) of sodium in 40 ml. of methanol was added to a refluxing (under nitrogen) solution of 3.2 g. (0.017 mole) of 5,8-dihydroxy-1-methyltetralone-2 (XV) and 4.8 ml. of benzyl bromide in 20 ml. of methanol. After 0.5 hour, the cooled reaction solution was acidified (*p*H 2.5) with 2.5 *N* hydrochloric acid and extracted with three portions of ether. The ether extracts were washed with 2.5 *N* sodium hydroxide, 2.5 *N* hydrochloric acid and aqueous sodium bicarbonate. The ether solution was dried over anhydrous sodium sulfate, filtered and concentrated at reduced pressure to yield a 5.98-g. residue. The product, b.p. 230 ± 10° (5–10 μ), was distilled. The distillate was dissolved in methanol and cooled in Dry Ice and methanol. The crystals which formed were separated from the methanol by using a filter-stick. The product was recrystallized to yield 5,8-dibenzyloxy-1-methyltetralone-2, a low melting (*ca.* −20°) solid.

Anal. Calcd. for $C_{25}H_{24}O_3$: C, 80.62; H, 6.50. Found: C, 80.42; H, 6.26.

8-Hydroxy-2-keto-5-methoxy-4a-methyl-2,3,4,4a,9,10-hexahydrophenanthrene (XIX). Using Diethylaminobutanone-2 Methiodide.—Three hundred and eighty milliliters of 4-diethylaminobutanone-2[8] was stirred at 5° in 1200 ml. of dry ether during the dropwise addition of 150 ml. of methyl iodide. The resulting suspension of crystalline methiodide was kept under reduced pressure. The ice-bath was removed and stirring was continued until most of the ether was removed by distillation. Three liters of ethanol and 400 g. of 5-hydroxy-8-methoxy-1-methyltetralone-2 (XIII) were added and the flask was flushed with nitrogen. The solution was stirred and cooled at 5–10° during the dropwise addition of a solution of 436 g. of potassium hydroxide in 3 l. of water. An atmosphere of nitrogen was maintained during the addition of alkali, which required two hours. The solution was heated under reflux for 30 minutes. After cooling in an ice-bath the solution was stirred vigorously and acidified to *p*H 2 with 4 *N* sulfuric acid. During

(8) A. L. Wilds and C. H. Shunk, THIS JOURNAL, **65**, 469 (1943)

the acidification, the temperature of the solution remained below 15°. The solid precipitate was collected on a filter and washed thoroughly with 7 l. of water. The filter-cake was dissolved in 2 l. of hot benzene. The aqueous layer was discarded. The benzene solution was concentrated almost to dryness, and then one l. of ether and 100 ml. of methanol were added to the residue. Crystallization was allowed to proceed at 3° overnight. This procedure afforded 240 g. (53%) of the crystalline hexahydrophenanthrene melting at 177–179°. Several recrystallizations from methanol afforded a sample melting at 181–183°.[9]

Anal. Calcd. for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 74.69; H, 6.98.

5-Hydroxy-1-(3-ketobutyl)-8-methoxy-1-methyltetralone-2 (XVII).—Three and one-half grams of 4-diethylaminobutanone-2 was converted to the methiodide as described above, using 3.5 g. of methyl iodide. The solvent was removed under reduced pressure. To the methiodide was added a solution of 5 g. (0.025 mole) of 5-hydroxy-8-methoxy-1-methyltetralone-2 (XIII) in 50 ml. of ether under a nitrogen atmosphere. A solution of 7.6 g. (0.09 mole) of potassium ethoxide in ethanol was added all at once, while the reaction mixture was being cooled. The resulting solution, which was dark red in color, was kept cold overnight and then was acidified to about *p*H 1 with 100 ml. of 2 *N* sulfuric acid which had been deoxygenated with nitrogen.

The mixture was diluted with 250 ml. of water and extracted with ether. The ether extract was washed with water, dried and concentrated under reduced pressure. The residue was recrystallized from a mixture of carbon tetrachloride and chloroform to yield 2.8 g. (40%) of crystalline material, m.p. 197–198°. A sample recrystallized first from ether and then from chloroform melted at 208–209°.

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.51; H, 7.14.

8-Hydroxy-2-keto-5-methoxy-4a-methyl-2,3,4,4a,9,10-hexahydrophenanthrene (XIX). From XVII.—Eight-tenths of a gram of 5-hydroxy-1-(3-ketobutyl)-8-methoxy-1-methyltetralone-2 (XVII) was dissolved in a mixture of 95 ml. of acetic acid and 20 ml. of concentrated hydrochloric acid. The mixture was heated under reflux for one hour. The mixture was concentrated to dryness under reduced pressure and the residue was taken up in ether. The ether extract was washed with water, dried and concentrated to a small volume. On cooling, 0.35 g. (47%) of 8-hydroxy-2-keto-5-methoxy-4a-methyl-2,3,4,4a,9,10-hexahydrophenanthrene (XIX), m.p. 146°, was obtained.

8-Benzyloxy-2-keto-5-methoxy-4a-methyl-2,3,4,4a,9,10-hexahydrophenanthrene (XX). From XIV.—Two and one-tenth grams (0.015 mole) of 4-diethylaminobutanone-2 was converted to the methiodide as described above, using 2.1 g. of methyl iodide. A solution of 4.4 g. (0.015 mole) of 5-benzyloxy-8-methoxy-1-methyltetralone-2 (XIV) in 150 ml. of methanol was added with cooling under nitrogen to the diethylaminobutanone methiodide. Similarly, a solution of 1.43 g. (0.017 mole) of potassium ethoxide in 50 ml. of ethanol was added. The reaction mixture was kept cold for one hour and then was heated under reflux for one-half hour. It was cooled and acidified with 2 *N* sulfuric acid. Enough water was added to dissolve the inorganic salts and the mixture was extracted with ether. The ether extract was washed with water, dried and concentrated under reduced pressure. The yield of residue was 5.3 g. Distillation at 0.01 mm. and a bath temperature of 200–215° yielded 3.8 g. of product which did not crystallize.

A 2,4-dinitrophenylhydrazone was prepared by the reaction of 3.6 g. of the oil with 2 g. of 2,4-dinitrophenylhydrazine in ethanol in the presence of 2 ml. of concentrated hydrochloric acid. The derivative was recrystallized from ethyl acetate to give a product melting at 208–210°.

Anal. Calcd. for $C_{29}H_{28}N_4O_6$: C, 65.90: H, 5.34; N, 10.60. Found: C, 66.37; H, 5.51; N, 11.08.

Reaction of 8-hydroxy-2-keto-5-methoxy-4a-methyl-2,3,4,4a,9,10-hexahydrophenanthrene (XIX) with benzyl bromide in methanolic sodium methoxide gave the corresponding 8-benzyl ether. Conversion of this product to a 2,4-dinitrophenylhydrazone (m.p. 207–208°) identical with that described above, confirms the proposed structure.

8-Hydroxy-2-keto-5-methoxy-4a-methyl-2,3,4,4a,9,10-hexahydrophenanthrene (XIX). Using Methyl Vinyl Ketone.—A solution of 100 g. (0.49 mole) of 5-hydroxy-8-methoxy-1-methyltetralone-2 (XIII) in 150 ml. of dihydropyran was treated with four drops of concentrated hydrochloric acid. The solution was warmed for 45 minutes, cooled and washed with 2.5 *N* sodium hydroxide and saturated sodium chloride solution. The organic phase was concentrated under reduced pressure. The residual 5-(2-tetrahydropyranyl)-8-methoxy-1-methyltetralone-2 was dissolved in 400 ml. of ethanol and treated with a solution of 28 g. of benzyltrimethylammonium hydroxide in 400 ml. of ethanol. The solution was cooled to about 0° and protected with an atmosphere of nitrogen. A solution of 40 ml. of methyl vinyl ketone (85% azeotrope) in 400 ml. of ethanol was added with stirring over a period of one hour. Stirring was continued an additional hour and then the solution was refluxed for 0.5 hour. The reaction solution was acidified with 4 *N* sulfuric acid and refluxed for one hour. While hot, the solution was diluted with 1800 ml. of water. The reaction mixture was cooled to 0° and 200 ml. of ether was added. The crystalline product separated[10] while stirring and cooling were continued for 0.5 hour. The mixture was filtered. The product was washed with water and ether and dried to yield 64 g. (51%) of 8-hydroxy-2-keto-5-methoxy-4a-methyl-2,3,4,4a,9,10-hexahydrophenanthrene, m.p. 179–181°. From the mother liquors and ether washes an additional 2 g. (2%) of product, m.p. 174–177°, was obtained.

5,8-Dihydroxy-2-keto-4a-methyl-2,3,4,4a,9,10-hexahydrophenanthrene (XXI). From XIX.—A mixture of 2 g. (0.008 mole) of 8-hydroxy-2-keto-5-methoxy-4a-methyl-2,3,4,4a,9,10-hexahydrophenanthrene (XIX) and 6 g. (0.05 mole) of pyridine hydrochloride was heated under nitrogen at 155° for five hours. The residue was partially soluble in 30 ml. of water. The water extract was saturated with sodium chloride and extracted with ether. The combined ether extracts were dried and concentrated to yield a 0.4-g. residue. Several crystallizations of the residue from ethylene dichloride and benzene–methanol yielded 0.04 g. of 5,8-dihydroxy-2-keto-4a-methyl-2,3,4,4a,9,10-hexahydrophenanthrene, m.p. 248–250°.

Anal. Calcd. for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.89; H, 6.17.

5,8-Dihydroxy-2-keto-4a-methyl-2,3,4,4a,9,10-hexahydrophenanthrene (XXI). From XV.—A mixture of 12.7 g. (0.066 mole) of 5,8-dihydroxy-1-methyltetralone-2 (XV) and 22 g. (25 ml.) of dihydropyran was treated with 1 drop of concentrated hydrochloric acid and 2 drops of water. The mixture was stirred under nitrogen for six hours. The excess dihydropyran was removed under reduced pressure and the residue was dissolved in ether. The ether solution was washed twice with 2.5 *N* sodium hydroxide and washed immediately with aqueous sulfuric acid and water. The ether layer was dried over anhydrous potassium carbonate, filtered and concentrated at reduced pressure to yield 23 g. of 5,8-di-(2-tetrahydropyranyl)-1-methyltetralone-2.

A solution of 23 g. (0.064 mole) of the tetrahydropyranyl derivative in 200 ml. of ethanol was added to 4-diethylaminobutanone-2 methiodide (prepared in the usual manner from 8.9 g. (0.064 mole) of 4-diethylaminobutanone-2 and 4 ml. of methyl iodide). The mixture was cooled and stirred under nitrogen while 14.5 g. of potassium hydroxide in 10 ml. of water and 200 ml. of ethanol were added. The mixture was stirred at room temperature for 1.5 hours and at the reflux temperature for 0.5 hour. The reaction mixture was cooled and diluted with 600 ml. of water. The product was extracted with ether and the ether extracts were washed with dilute acetic acid. The ether solution was dried and concentrated under reduced pressure to yield a residue (26.2 g.) of 5,8-di-(2-tetrahydropyranyl)-2-keto-4a-methyl-2,3,4,4a,9,10-hexahydrophenanthrene.

The tetrahydropyranyl derivative was dissolved in 600 ml. of ethanol and treated with 8 drops of concentrated hydrochloric acid and 8 drops of water. The solution was kept under nitrogen at room temperature for 16 hours, and concentrated at reduced pressure. The 18.5-g. residue was

(9) 8-Hydroxy-2-keto-5-methoxy-4a-methyl-2,3,4,4a,9,10-hexahydrophenanthrene (XIX) exists in two crystalline modifications, one melting at 146–147°, the other melting at 180–181°. When the two forms were mixed, the melting point was 180–181°.

(10) Crystallization was initiated by adding a few pieces of Dry Ice. In many cases this expedient was unnecessary.

crystallized from a small amount of acetone to yield 6.3 g. (40%) of 5,8-dihydroxy-2-keto-4a-methyl-2,3,4,4a,9,10-hexahydrophenanthrene, m.p. 241–245°.

8-Acetoxy-2-keto-5-methoxy-4a-methyl-2,3,4,4a,9,10-hexahydrophenanthrene (XXII).—A mixture of 5.2 g. (0.02 mole) of 8-hydroxy-2-keto-5-methoxy-4a-methyl-2,3,4,4a,9,-10-hexahydrophenanthrene (XIX), 6 ml. of acetic anhydride and a small amount of sodium acetate was refluxed for two hours. The reaction mixture was cooled and poured into water. The water solution was extracted with ether and the ether extract was washed with aqueous sodium bicarbonate and water. The ether layer was dried over anhydrous sodium sulfate, filtered and concentrated at reduced pressure. The product, 4.2 g. (67%), m.p. 117–119°, crystallized from the concentrate. A sample was recrystallized twice from chloroform to yield the purified acetoxy compound, m.p. 120–121°.

Anal. Calcd. for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.93; H, 6.47.

2-Keto-5,8-dimethoxy-4a-methyl-2,3,4,4a,9,10-hexahydrophenanthrene (XVIII).—Twenty milligrams of 8-hydroxy-2-keto-5-methoxy-4a-methyl-2,3,4,4a,9,10-hexahydrophenanthrene (XIX) was dissolved in 1.5 ml. of 2.5 *N* sodium hydroxide solution and treated with two drops of dimethyl sulfate. The mixture was stirred for 30 minutes at room temperature and then warmed at 60° for 15 minutes. After cooling the mixture to 0°, the colorless needles were collected on a filter and recrystallized from methanol. This procedure afforded the dimethoxy compound, m.p. 120–120.5° (lit. m.p. 120–121°[4]). The dimethoxyhexahydrophenanthrene was converted to a crystalline 2,4-dinitrophenylhydrazone melting at 218–220° with sintering at 215° (lit. m.p. 219–221°, sintered at 215°[4]).

RAHWAY, N. J.

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

Metabolite Analogs. IV. Preparation of Some Sulfur-containing Benzimidazoles with Substituents on the 4(7)- and 6(5)-Positions[1]

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Benzimidazoles, containing in addition to a nitro or amino group, a sulfonic acid, sulfonamido, mercapto or methylmercapto grouping on the 4(7)- and 6(5)-positions, have been prepared as potential metabolite (purine, vitamin B_{12}, folic acid) inhibitors.

In a preceding communication[3] the preparations of benzimidazoles with substituents on the 4(7)- and 6(5)-positions were described. Continuing the search for benzimidazoles possessing potential antimetabolite activity (purine, vitamin B_{12}, folic acid) a number of sulfur-containing derivatives have been added to this group. These compounds, in addition to a nitro or amino group, also contain a sulfonic acid, sulfonamido, mercapto or methylmercapto grouping. To cast some light on the effect of substituent and position upon the activity, reversed isomers have been prepared, where possible, with those compounds containing the latter two of the groupings mentioned above.

4-Nitrobenzimidazole-6-sulfonic acid and its amino analog were prepared by the partial (ammonium sulfide) and complete (stannous chloride) reduction of 3,5-dinitro-4-aminobenzenesulfonic acid, followed by formation of the imidazole ring. The ring closure with 3,4,5-triaminobenzenesulfonic acid was readily accomplished in 4 *N* hydrochloric acid according to Phillips' conditions.[4] This procedure, and others using formic acid or ethyl orthoformate, failed with 3,4-diamino-5-nitrobenzenesulfonic acid, probably because of interaction between the sulfonic acid group and one of the two amino groupings required for the ring closure. Under basic conditions, *i.e.*, on heating with formamide, the imidazole ring was formed, as evidenced by analytical data and the disappearance of the N–H absorption bands in the infrared at 2.84 and 2.92 μ (the product displayed a single band at 3.12 μ).

The sulfonic acids were prepared as possible intermediates for obtaining the sulfonamides and especially the divalent sulfur derivatives. Because of the anomalous behavior of heterocyclic sulfonic acids,[5] a route involving conversion of the sulfonic acid grouping before forming the imidazole ring was utilized instead.

Treatment of 4-chloro-3,5-dinitrobenzenesulfonyl chloride with ammonia in dioxane gave the corresponding 4-amino-3,5-dinitrobenzenesulfonamide. In benzene solution, in addition to the aminosulfonamide, a product was obtained in which only one chlorine atom had been replaced. This material was identical with 4-amino-3,5-dinitrobenzenesulfonyl chloride, prepared by the action of phosphorus pentachloride on 4-amino-3,5-dinitrobenzenesulfonic acid.

The reduction of 4-amino-3,5-dinitrobenzenesulfonamide. With ammonium sulfide resulted in 3,4-diamino-5-nitrobenzenesulfonamide. Stannouschloride in hydrochloric acid reduced both nitro groups, but did not affect the sulfonamido grouping at room temperature. With 3,5-dinitro-4-aminobenzenesulfonyl chloride, the sulfur moiety was also reduced under the latter conditions giving 3,4,5-triaminothiophenol. The mercapto grouping of this compound was readily methylated under alkaline conditions by methyl iodide giving methyl 3,4,5-triaminophenyl sulfide.

Formation of the benzimidazoles from these compounds was accomplished using modifications of the Phillips procedure with the exception of 4-nitro-6-sulfonamidobenzimidazole, which was prepared by heating the corresponding diamine with anhydrous formic acid.

The synthesis of the 6-nitro-(or amino)-4-mer-

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