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Phenanthro[4,5-*bcd*]furan Derivatives. I. A Synthesis of 5-Hydroxy-1-methoxyphenanthro[4,5-*bcd*]furan

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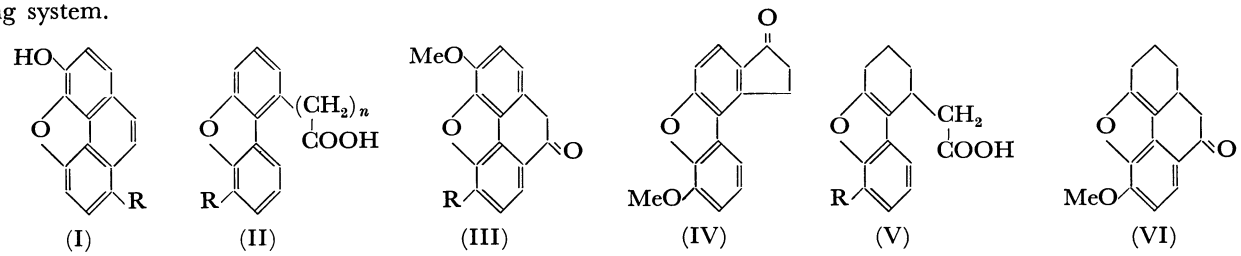
5-Hydroxy-1-methoxyphenanthro[4,5-*bcd*]furan(I;R=MeO) was synthesized by dehydrogenation with 20% palladium on charcoal from 5,6,7,7a,8,9-hexahydro-1-methoxy-5-oxophenanthro[4,5-*bcd*]furan(XVII), which had itself been prepared *via* a naphthofuran derivative (XVI) starting from 5,8-dimethoxy-1-tetralone (VII).

Morphine gives a variety of non-nitrogenous degradation products,[1] including morphenol (I;R=H), which has not yet been synthesized. Burger and Avakian[2] failed to cyclize the acid (II;R=H, n=1) to a phenanthrol derivative (III; R=H); similarly, the acid (II; R=MeO, n=2) was converted to the indenone (IV)[3] rather than to a phenahthro[4,5-*bcd*]-furan. Dendy *et al.*[4] succeeded in cyclizing it with a partially hydroaromatic precursor (V; R=MeO) into the ketone (VI), but the yield was too poor for them to continue the project further. They ascribed these difficulties of cyclization to a strain in the fused-

1) E. Mosettig and E. Meitzner, *J. Amer. Chem. Soc.*, **56**, 2738 (1934).
2) A. Burger and S. Avakian, *ibid.*, **62**, 226 (1940).
3) H. Gilman and L. C. Cheney, *ibid.*, **61**, 4149 (1938).
4) A. V. Dendy, J. H. P. Tyman, and W. B. Wahlley, *J. Chem. Soc.*, **1963**, 4040.

ring system.



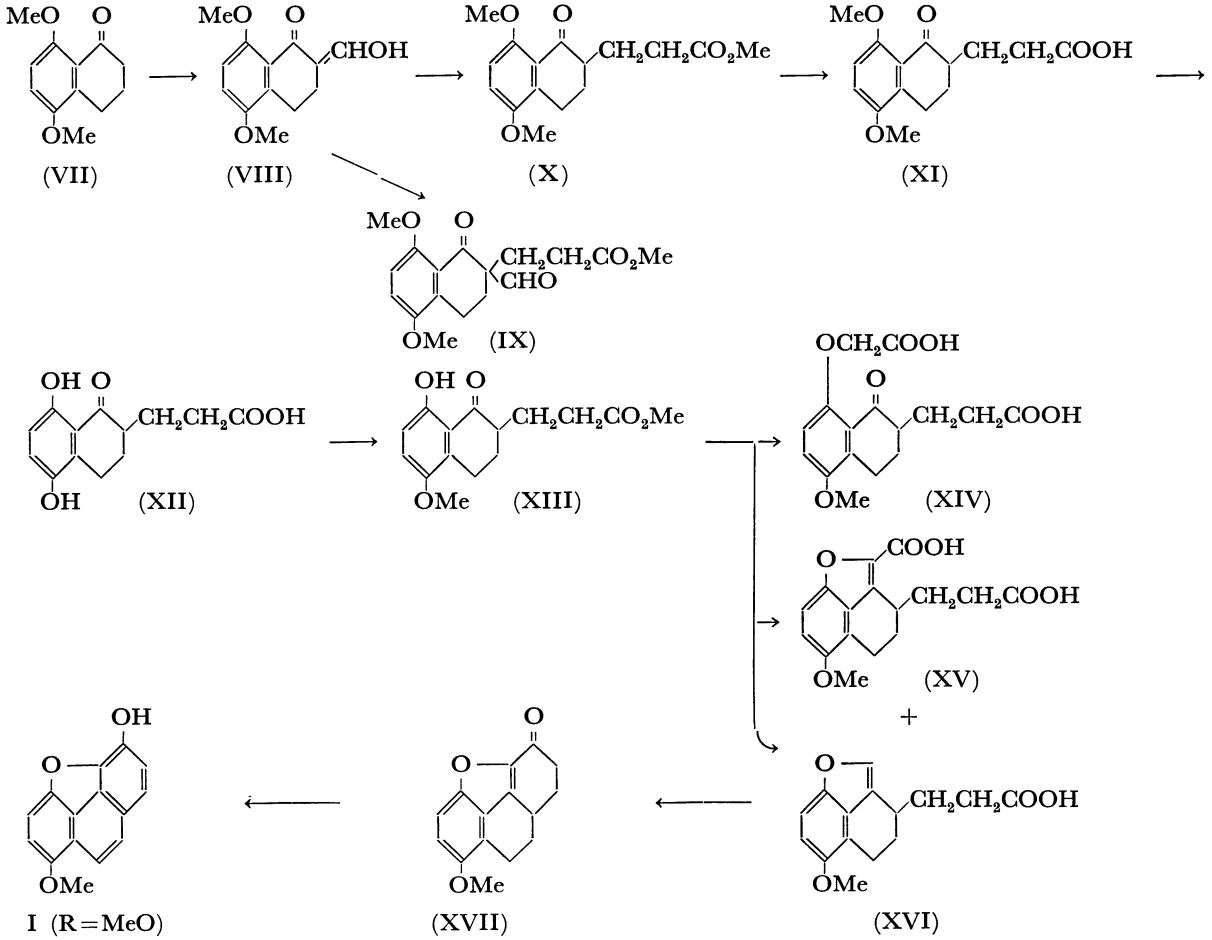
(I) (II) (III) (IV) (V) (VI)

An approach to the synthesis of morphenol, not from a dibenzofuran, but from the naphtho[1,8-*bc*]furan derivative (XVI), was planned. In this paper, the results of a model experiment will be reported, this experiment led to a successful synthesis of a kind of methoxymorphenol, 5-hydroxy-1-methoxyphenanthro-[4,5-*bcd*]furan(I; R=MeO).

Results and Discussion

The naphtho[1,8-*bc*]furan derivative (XVI) was prepared from 5,8-dimethoxy-1-tetralone (VII) *via* a series of intermediate, as is shown in scheme 1.

5,8-Dimethoxy-1-tetralone (VII) was prepared starting from 3-(2,5-dimethoxybenzoyl)propionic acid (*cf.* the Experimental section). VII was formylated[5] to give VIII, with ethyl formate on the methylene group adjacent to the carbonyl group, becasue the methylene was not expected to be active enough to react with methyl acrylate because of the electronic effect of two methoxy groups on the benzene ring.[6] The addition reaction of VIII with methyl acrylate was performed in a refluxing methanol solution containing a small amount of triethylamine; this gave X in a good yield rather than IX. The propionic acid derivative (XI) was prepared from X by saponification. The heating of XI with pyridinium chloride[7] afforded a dihydric phenol derivative (XII). XII showed a absorption due to OH stretching at 3400 cm^{-1} in the infrared absorption spectrum and reacted with ferric chloride.



Scheme 1.

5) R. B. Turner, D. E. Nettleton, J. R. and R. F. Ferebee, *J. Amer. Chem. Soc.*, **76**, 5923 (1956).

6) R. E. Juday, *ibid.*, **75**, 4071 (1953).

7) M. S. Newman and R. L. Childers, *J. Org. Chem.*, **32**, 62 (1967).

The reaction mixture changed in color from blue to brown in time. The reaction of XII with dimethyl sulfate afforded a good yield of a monohydric phenol, which then reacted with ferric chloride to result in a blue color. In spite of the color reaction, XIII did not manifest any OH stretching absorption in the infrared absorption spectrum above 3000 cm^{-1}; such a phenomenon is, though, often observed for *O*-acyl phenols.[8]

Let us turn now to a consideration of the building of the strained fused-ring; our first effort involved the transformation of XIII into the naphtho[1,8-*bc*]furan derivative (XVI). The reaction of the tetralone (XIII) with a mixture of ethyl bromoacetate and potassium carbonate in acetone at 100 °C, followed by saponification, afforded the dicarboxylic acid (XIV), which was then heated with a mixture of acetic anhydride and sodium acetate in the expectation that the naphthofuran would be formed. However, no evolution of carbon dioxide was observed, indicating no reaction, that these was not even under the above reaction conditions.

In the course of further studies of the formation of a furan ring, a convenient method for the direct synthesis of naphtho[1,8-*bc*]furan from 8-hydroxy-1-tetralone was discovered by accident: the heating of the tetralone in ethyl bromoacetate at 170 °C, followed by saponification, gave two crystalline products, 3-(4,5-dihydro-6-methoxy-3*H*-naphtho[1,8-*bc*]fur-3-yl)propionic acid (XVI) and 3-(2-carboxy-4,5-dihydro-6-methoxy-3*H*-naphtho[1,8-*bc*]fur-3-yl)propionic acid (XV), but XIV was not detected. The structures of XV and XVI were discussed on the basis of their spectral properties and subsequent transformations. The infrared spectrum for XV shows a conjugated-carbonyl band at 1693 cm^{-1} in addition to an unconjugated-carbonyl band at 1710 cm^{-1}. XV was transformed into XVI by heating with a mixture of quinoline and copper. The ultraviolet spectrum of XVI shows λ_{max}^{EtOH} 253 nm (ε 9300) and 292 nm (ε 3600), similar to those of the benzofurans, and the nuclear magnetic resonance absorption spectrum shows a sharp singlet at τ 2.43 which might be ascribed to a methine hydrogen on the furan ring. The acid (XVI), when heated at 90 °C in polyphosphoric acid, was transformed into the expected ketone (XVII) in a good yield; this substance showed an absorption band due to a conjugated-carbonyl group at 1660 cm^{-1} in the infrared absorption spectrum.

For aromatization[9] of XVII to the phenol I (R=MeO), palladium on charcoal was used as the catalyst; the yield was 20%. The resulting phenol decomposes at 187—191 °C and gives an intense blue fluorescence in an alkaline solution, much like morphenol I (R=H). The structure of I (R=MeO) was established on the basis of its spectral properties. The nuclear magnetic absorption spectrum showed the existence of a methoxyl group at τ 5.49 (s), two equivalently-situated hydrogens on the phenanthrene ring at τ 2.13 (s), four hydrogens on the phenanthrene ring at τ 2.23—2.82 (oct), and a hydroxyl group at τ 0.59 (s); moreover, the band at τ 2.23—2.82 (oct) could be explained as an assembly of two kinds of AB-type resonances. The ultraviolet absorption spectrum of I (R=MeO) is very similar to that of morphenol methyl ether.[10] The infrared absorption spectrum of I (R=MeO) posseses bands corresponding to three kinds of two adjacent hydrogens on the phenanthrene ring at 800 and 826 cm^{-1}—one of the three expected absorptions is overlapped with one of the two residual absorptions—and a broad band corresponding to the hydroxyl group at 3250 cm^{-1}.

This phenolic compound is believed to be the never-before-synthesized phenanthro[4,5-*bcd*]furan. The ketone (XVII) must be as strained as the ketone (VI) prepared by Dendy *et al.*,[4] since the two ketones are very similar to each other in fused-ring structure. From this point of view, it is surprising that we unexpectedly obtained good yields in two cyclizations, from XIII to a mixture of XV and XVI, and from XVI to XVII. However, that the latter cyclization proceeded under mild reaction conditions suggests that the strain was dominantly introduced in the former cyclization, in which a drastic reaction condition was required to give a lower yield. This suggestion is surported by the experiments of Royer *et al.*[11]

Experimental

All the melting point are uncorrected. The chromatography was performed over silica gel (WAKOGEL C-200, Wako Pure Chemical Industries, Ltd.). The polyphosphoric acid was prepared from 85% phosphoric acid (470 g) and phosphorus pentoxide (516 g) by heating at 160—165 °C for 5 hr. Unless otherwise stated, sodium sulfate was employed as the drying agent. The infrared spectra were determined with a JASCO Model DS 402 G infrared spectrophotometer. The ultraviolet spectra were determined with a Shimadzu Model MR-31 spectrophotometer. The nuclear magnetic resonance spectra were determined at 100 MHz with a JEOL Model 4H-100 NMR spectrometer, using tetramethylsilane as the internal standard. Their chemical shifts are presented in terms of the τ value.

4-(2,5-Dimethoxyphenyl)butyric Acid. In a vessel for reduction we placed a solution of 3-(2,5-dimethoxybenzoyl)-propionic acid (40 g) in acetic acid (120 ml), a solution of palladium chloride (0.25 g) in 0.1 M hydrochloric acid (32 ml), and active charcoal (12.0 g). The hydrogenation[12] was carried out at room temperature and at atmospheric pressure until the hydrogen uptake had ceased. The catalyst was then filtered out, and the filtrate was evaporated under

8) "Documentation of Molecular Spectroscopy" (D.M.S.), Butterworth and Co. (Publishers) Ltd., Lomdon, No. 5522, 6755, 9300; L. J. Bellamy, "The infrared Spectra of Complex Molecules," 2nd ed., John Wiley & Sons, Inc., New York, (1958), pp. 103-104.

9) R. B. Turner, D. E. Nettleton, *J. Amer. Chem. Soc.*, **76**, 5923 (1956); E. Mosettig and H. M. Duvoll, *ibid.*, **59**, 367 (1937).

10) H. Rapoport, A. D. Batchs, and J. E. Gordon, *ibid.*, **80**, 5767 (1958).

11) R. Royer, E. Bisagni, and G. Menichi, *Bull. Soc. Chim. Fr.*, **1964** (9), 2112; *Chem. Abstr.*, **62**, 1618h (1965). They obtained 2-acetyl{or 2-(*p*-methoxybenzoyl)}-6-methoxy-4,5-dihydro-3*H*-naphtho[1,8-*bc*]furan by condensation of 8-hydroxy-5-methoxy-1-tetralone with chloromethyl methyl (or *p*-methoxyphenyl) ketone; however, the yields are poor (2.5% or 17%, respectively).

12) S. Mitsuo, H. Saito, and H. Mamuro, *Nippon Kagaku Zasshi*, **81**, 292 (1960); *Chem. Abstr.*, **59**, 437f (1962).

reduced pressure to leave a viscous oil. Trituration with ice-cold water, followed by the washing of the resulting crystals with water, gave a crude solid in a 76.5% yield (57.5 g). Recrystallization from 30% aqueous ethanol afforded the pure 4-(2,5-dimethoxyphenyl)butyric acid as colorless plates; mp 66—68 °C. The mixed melting point with an authentic sample[11] did not depressed.

5,8-Dimethoxy-1-tetralone (VII). A mixture of γ-(2,5-dimethoxyphenyl)butyric acid (25 g) and polyphosphoric acid (325 g) was stirred at 50 °C for 8.5 hr. The resulting yellow mixture was diluted with ice-cold water and extracted with ether. The ether was washed with 1M aqueous potassium carbonate and with water, and then dried. After the removal of the solvent the extract was crystallized from *n*-hexane–ether to give 13.4 g (58.2%) of VII as colorless needles; mp 62—63 °C (lit,[11] mp 61 °C).

Found: C, 69.82; H, 6.74%. Calcd for $C_{12}H_{14}O_3$: C, 69.90; H, 6.84%.

2-Hydroxymethylidene-5,8-dimethoxy-1-tetralone (VIII). In a 500-ml flask equipped with a stirrer and a dropping funnel we placed sodium methylate powder (from 6.6 g of sodium metal and 70 ml of absolute methanol) and benzene (200 ml). Into the suspension ethyl formate (36 ml) was stirred over a 5-min period under cooling in ice-cold water; the stirring was then continued for 1 more hr. The tetralone (VII, 15 g) in benzene (120 ml) was added, drop by drop, over 50-min period, during which the reaction temperature was kept below room temperature. The ice-bath was then removed, and the stirring was continued for an additional 2.5 hr. The reaction mixture was then acidified with 2 M hydrochloric acid (150 ml) to give crystals of VIII. Recrystallization from 60% ethanol afforded 13.7 g of the pure VIII as colorless needles; mp 85—86 °C. IR(KBr): 3270 cm^{-1} (OH), 1263 cm^{-1}(C=O). NMR($CDCl_3$): τ 1.67 (OH).

Found: C, 66.61; H, 6.08%. Calcd for $C_{13}H_{14}O_4$: C, 66.74; H, 6.03%.

Methyl 3-(1,2,3,4-Tetrahydro-5,8-dimethoxy-1-oxo-2-naphthyl)-propionate (X). To 20.0 g of VIII we added 12.0 g of methyl acrylate, 27.0 g of triethylamine, and 80% methanol (80 ml), after which the mixture was refluxed for 7.5 hr. The reaction mixture was then extracted with ether. To remove the triethylamine and the acidic compounds, the ether (800 ml) was washed with five 100-ml portions of 0.5 M hydrochloric acid and then with four 50-ml portions of 2 M aqueous patossium carbonate, and washed with water. The ether, after drying, was evaporated to an oil, which was warmed on a steambath under reduced pressure to remove the unreacted methyl acrylate. Crystallization from methanol gave 14.3 g (57.2%) of X as colorless needles; mp 64—65 °C. IR(KBr): 1737 ($COOCH_3$), 1692 cm^{-1} (C=O). NMR (CCl_4): τ 6.45 ($COOCH_3$, s).

Found: C, 65.88; H, 6.91%. Calcd for $C_{16}H_{20}O_5$: C, 65.75; H, 6.81%.

3-(1,2,3,4-Tetrahydro-5,8-dimethoxy-1-oxo-2-naphthyl)propionic Acid (XI). Into a saturated alcoholic solution of X (20 g) we stirred, drop by drop, 3 M aqueous potassium hydroxide until the last few drops no longer induced instantaneous milky turbidity. After standing for 30 min, the reaction mixture was diluted with water and acidified with 6 M hydrochloric acid to give precipitates of XI. Recrystallization from 60% ethanol afforded 15.8 g (83.0%) of the pure XI as colorless needles; mp 139—140.5 °C. IR (KBr): 1716 (COOH), 1685 cm^{-1} (C=O).

Found: C, 64.76; H, 6.55%. Calcd for $C_{15}H_{18}O_5$: C, 64.74; H, 6.47%.

3-(1,2,3,4-Tetrahydro-5,8-dihydroxy-1-oxo-2-naphthyl)propionic Acid (XII). A mixture of XI (10.0 g) and pyridinium chloride (45 g) was heated at 220 °C (bath temp.) for 2.5 hr. The reaction mixture was dissolved in 2 M aqueous sodium hydroxide and filtered. The filtrate was acidified with 6 M hydrochloric acid and then extracted with ether. The ether was washed with three 80-ml portions of 1 M hydrochloric acid to remove the pyridine; then it was further washed with water and dried. The ether was evaporated to yellow crystals. Recrystallization from 25% ethanol gave 7.8 g (86.8%) of XII as yellow needles; mp 125—126 °C. IR(KBr): 3390 (OH), 1722 (COOH), 1625 cm^{-1}(C=O).

Found: C, 62.02; H, 5.70%. Calcd for $C_{13}H_{14}O_5$: C, 62.40; H, 5.60%.

Methyl 3-(1,2,3,4-Tetrahydro-8-hydroxy-5-methoxy-1-oxo-2-naphthyl)propionate (XIII). A mixture of XII (10.0 g), dimethyl sulfate (18.5 g), potassium carbonate (22.5 g) and acetone (33.5 g) was heated under reflux for 2 hr. The reaction mixture was refluxed with water (150 ml) for 15 min and then extracted with ether. The ether extract was washed with water, dried, and evaporated to a yellow solid. Recrystallization from methanol gave 8.5 g (76.3%) of XIII as yellow needles; mp 66.5—67.5 °C. IR(KBr): 1728 ($COOCH_3$), 1638 cm^{-1} (C=O).

Found: C, 64.75; H, 6.11%. Calcd for $C_{15}H_{18}O_5$: C, 64.74; H, 6.47%.

3-(1,2,3,4-Tetrahydro-8-carboxymethoxy-5-methoxy-1-oxo-2-naphthyl)propionic Acid (XIV). A mixture of XIII (1.0 g), ethyl bromoacetate (3.1 g), potassium carbonate (3.4 g), and methyl ethyl ketone (50 ml) was heated under reflux for 3 hr; ethyl bromoacetate (2.0 g) was then added to the mixture, and the refluxing was continued for an additional 3 hr. The reaction mixture was filtered and thoroughly washed with hot acetone, and then the filtrate and washings were combined and evaporated to dryness. The residue was treated much as has been described in connection with the preparation of XI to give 150 mg of XIV (13% based on XIII) as colorless prisms; mp 179—185 °C (decomp.). IR(KBr): 1780 (OCH_2COOH), 1705 (COOH), 1659 cm^{-1} (C=O).

Found: C, 59.39; H, 5.70%. Calcd for $C_{16}H_{18}O_7$: C: 59.70; H, 5.59%.

3-(2-Carboxy-4,5-dihydro-6-methoxy-3H-naphtho[1,8-bc]fur-3-yl)propionic Acid (XV) and 3-(4,5-Dihydro-6-methoxy-3H-naphtho[1,8-bc]fur-3-yl)propionic Acid (XVI). A mixture of XIII (2.0 g), ethyl bromoacetate (6.2 g), potassium carbonate (2.3 g), and methyl ethyl ketone (2.2 g) was heated at 170 °C (bath temp.) for 3 hr; ethyl bromoacetate (2.0 g) was then added to the mixture, and the refluxing was continued for an additional 3 hr. The dark brown and almost dry reaction mixture thus obtained was extracted with hot acetone, and the acetone was evaporated. The residue was hydrolyzed much as has been described in connection with the preparation of XI, and the resulting alkaline solution was acidified with 6 M hydrochloric acid and extracted with ether. The ether was washed with water, dried, and evaporated to dryness. The solid mass was separated into two moieties, one of which is insoluble in benzene. The benzene-insoluble moiety was crystallized from tetrahydrofuran–benzene to give 0.95 g (43.5%) of XV as colorless needles; mp 195—196 °C. IR (KBr): 1710, 1693 cm^{-1} (COOH).

Found: C, 63.11; H, 5.43%. Calcd for $C_{16}H_{16}O_6$: C, 63.16; H, 5.26%.

The other moiety in benzene was chromatographed over silica gel and eluted with benzene–ether (97 : 3). A yellow fraction was collected, and the solvent was evaporated. The residue was crystallized from benzene–*n*-hexane to give 0.1 g (8.8%) of XVI as colorless needles; mp 123—124 °C. IR (KBr): 1705 cm^{-1} (COOH). NMR(CD_3COCD_3): τ 2.43

(H on the furan ring. UV: λ_{max}^{EtOH} 253 (ε 9300), 292 (ε 3600), 302 nm (ε 3200).

Found: C, 68.88; H, 6.10%. Calcd for $C_{15}H_{16}O_4$: C, 69.21; H, 6.15%.

Decarboxylation of XV. A mixture of 8.0 g of quinoline, 0.6 g of XV, and 0.6 g of copper powder was heated at 150 °C for 1.5 hr, during which carbon dioxide was evolved, and then at 155 °C for 10 more min. The mixture was acidified with 1 M hydrochloric acid and extracted with ether. The ether extract (500 ml) was washed four 50-ml portions of 2 M hydrochloric acid, and with water, and then dried, after which the ether was evaporated. The residue in benzene was chromatographed over silica gel and eluted with benzene–ether (93 : 7). An orange fraction was collected, and the solvent was evaporated. The residue was crystallized from benzene–*n*-hexane to give 0.23 g (44.9%) of XVI as colorless needles; mp 123—124 °C.

5,6,7,7a,8,9-Hexahydro-1-methoxy-5-oxophenanthro[4,5-bcd]furan (XVII). A mixture of 0.4 g of XVI and 36.5 g of polyphosphoric acid was stirred at 80 °C for 3.5 hr. The violet reaction mixture was poured onto ice and extracted with ether. The ether (500 ml) was washed with water, with four 70-ml portions of 1 M aqueous potassium carbonate, and with water, and then dried. The ether was evaporated to give crystals. Recrystallization from ethanol gave 0.25 g (67.1%) of XVII as colorless needles; mp 170—170.5 °C. IR(KBr): 1660 cm^{-1}(C=O).

Found: C, 74.03; H, 5.83%. Calcd for $C_{15}H_{14}O_3$: C, 74.37; H, 5.79%.

5-Hydroxy-1-methoxyphenanthro[4,5-bcd]furan (I: R=MeO). A mixture of 0.1 g of XVII, 0.2 g of 20% palladium on charcoal, and 2.0 g of α-methylnaphthalene was heated at 240 °C for 30 hr in a nitrogen atmosphere. The catalyst was then filtered out and washed with ether. The filtrate and washings were combined, and the ether was extracted with five 50-ml portions of 1 M potassium hydroxide. The alkaline solution was washed with two 30-ml portions of carbon tetrachloride and acidified with 6 M hydrochloric acid, and the resulting precipitates were extracted with ether. The ether extract was washed with water and dried, and the ether was evaporated. The residue was dissolved in benzene containing a little ether, chromatographed over silica gel, and eluted with benzene–ether (9 : 1). A yellow fraction was collected, and the solvent was evaporated to give crystals. Recrystallization from benzene gave 0.02 g (20.3%) of I (R=MeO) as colorless needles; mp 187—191 °C (decomp.). IR(KBr): 3240 (OH), 825, 800 cm^{-1} (2H). NMR(CD_3COCD_3): τ 4.59 (MeO, s), 2.82, 2.73, 2.31, 2.23 (q, 2H), 2.58, 2.53, 2.49, 2.44 (q, 2H), 2.13 (2H), 0.59 (OH). UV: λ_{max}^{EtOH} 242 (ε 56300), 265 (ε 23500), 313 (ε 11300), 327 (ε 15700), 351 (ε 8120), 370 nm (ε 14700).

Found: C, 75.45; H, 4.29%. Calcd for $C_{15}H_{10}O_3$: C, 75.76; H, 4.26%.

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