Phenanthro[4,5-*bcd*]furan Derivatives. II. A Synthesis of 3-Hydroxyphenanthro[4,5-*bcd*]furan (Morphenol)

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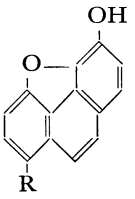
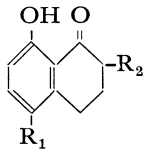
(Received September 28, 1973)

3-Hydroxyphenanthro[4,5-*bcd*]furan (I) was synthesized by the dehydrogenation, with 20% palladium on charcoal, of 3-oxo-1,2,3,8,9,9a-hexahydronaphtho[4,5-*bcd*]furan (XII), which had itself been prepared *via* a naphtho[1,8-*bc*]furan derivative (IX) starting from 8-hydroxy-1-tetralone (IV).

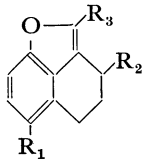
3-Hydroxyphenanthro[4,5-*bcd*]furan (I), which is a degradation product of morphine, had not been synthesized in spite of many attempts. These failures have been attributed to the presence of a ring strain[1] in the phenanthro[4,5-*bcd*]furan derivative which is the fundamental ring skeleton of morphenol. Recently, though, 5-hydroxy-1-methoxyphenanthro[4,5-*bcd*]furan (II) was synthesized,[2] as the first synthetic phenanthro[4,5-*bcd*]furan derivative, starting from methyl 3-(8-hydroxy-5-methoxy-1-oxo-1,2,3,4-tetrahydro-2-naphthyl)propionate (III), however, the product (II), unlike morphenol, has a methoxyl group at the 1-position. This paper will show that this synthetic course is applicable also to morphenol (I) and, therefore, would be useful for the preparation of general phenanthro[4,5-*bcd*]furan derivatives.



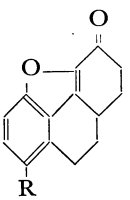
I: R=H
II: R=OMe



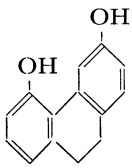
III: R_1=OMe, R_2=$(CH_2)_2CO_2Me$
IV: R_1=H, R_2=H
V: R_1=H, R_2=CHOH
VI: R_1=H, R_2=$(CH_2)_2CO_2Me$
VII: R_1=H, R_2=$(CH_2)_2COOH$



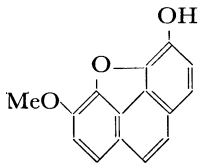
VIII: R_1=H, R_2=$(CH_2)_2COOH$, R_3=COOH
IX: R_1=H, R_2=$(CH_2)_2COOH$, R_3=H
X: R_1=OMe, R_2=$(CH_2)_2COOH$, R_3=COOH
XI: R_1=OMe, R_2=$(CH_2)_2COOH$, R_3=H



XII: R=H
XIII: R=OMe



XIV



XV

Fig.

Results and Discussion

8-Hydroxy-1-tetralone (IV) was condensed[3] with ethyl formate in the presence of sodium methylate to give 8-hydroxy-2-hydroxymethylidene-1-tetralone (V). When a mixture of V and methyl acrylate was heated under reflux in aqueous methanol containing triethylamine, methyl 3-(8-hydroxy-1-oxo-1,2,3,4-tetrahydro-2-naphthyl)propionate (VI) was obtained along with IV; the ester (VI) gave an absorption corresponding to the phenolic hydroxyl group at τ −2.04 in the nuclear magnetic resonance spectrum and a conjugated-carbonyl band at 1634 cm^{-1} in the infrared spectrum. The ester was saponified to the corresponding carboxylic acid (VII) for practical separation from IV.

When VII was treated with ethyl bromoacetate at 170 °C, followed by hydrolysis, the expected di- and monocarboxylic acids, 3-(2-carboxy-4,5-dihydro-3*H*-naphtho[1,8-*bc*]furan-3-yl)propionic acid (VIII) and 3-(4,5-dihydro-3*H*-naphtho[1,8-*bc*]furan-3-yl)propionic acid (IX), were obtained in yields of 34 and 2% respectively; on the other hand, the use of VI in place of VII gave slightly increased yields (42% and 6%), which were comparable to those of the corresponding carboxylic acid (X and XI) in the synthesis of II (43% and 8%).[2] The monocarboxylic acid (IX), which was also obtained from the dicarboxylic acid by decarboxylation (59%), was subjected to polyphosphoric acid-catalyzed intramolecular cyclization to give 3-oxo-1,2,3,8,9,9a-hexahydrophenanthro[4,5-*bcd* furan (XII) in a 45% yield.

Finally, the aromatization[3,4] of XII with 20% palladium on charcoal afforded two phenolic compounds with different melting points, 142.5—143 °C and 175—179 °C (dec.), in 16 and 10% yields respectively. The lower-melting product was identified as 3-hydroxyphenanthro[4,5-*bcd*]furan (I) from its physical and spectral properties. It showed a purple fluorescence in a potassium hydroxide solution and a green fluorescence in concentrated sulfuric acid. The infrared spectrum gave absorptions at 3220 (OH) and at 814 and 822 cm^{-1} (2H), the ultraviolet spectrum was almost concordant with that of methyl morphenol,[5] and the nuclear magnetic resonance spectrum corresponded to the structure of I.

The other phenolic product, although it has not been subjected to elemental analysis, is perhaps 3,5-dihydroxyphenanthrene (XIV) in view of the following facts: (i) the nuclear magnetic resonance spectrum exhibited absorptions corresponding to two phenolic hydroxyl groups at τ 0.58 and 1.23, (ii) an isomeric 3,4-dihydroxyphenanthrene has been known to have a melting point of 143 °C,[6] (iii) the infrared spectrum is similar to that of morphenol in the 700—900 cm^{-1} region, showing the existence of two and three neighboring hydrogen atoms on the aromatic ring system.

Our synthetic course leading to 5-hydroxy-1-methoxyphenanthro[4,5-*bcd*]furan (II) is applicable also to morphenol. This suggests that the synthetic course would be generally useful for phenanthro[4,5-*bcd*]furan derivatives. It seemed that almost no effects of a methoxyl group appeared except in the intramolecular cyclization reaction (IX→XII). The yield (45%) of XII from IX was considerably lower than that (67%) of XIII. The cause of the difference in yields might be due to the steric effect of a methoxyl group; however, it is not yet clear. The effect of a methoxyl group will be further investigated by preparing 3-hydroxy-5-methoxyphenanthro[4,5-*bcd*]furan (XV).

Experimental

All the melting points are uncorrected. The column chromatography was performed over silica gel (WAKOGEL C-200, Wako Pure Chemical Industries, Ltd.). The polyphosphoric acid was prepared from 85% phosphoric acid (100 ml) and phosphorus pentoxide (123 g) by heating it 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 402G infrared spectrophotometer. The ultraviolet spectra were determined with a Shimadzu Model UV-200 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.

8-Hydroxy-2-hydroxymethylidene-1-tetralone (V). Ethyl formate (14.5 ml) was added to a mixture of sodium methylate (8.0 g) and benzene (50 ml) over a 5-min period, with stirring and cooling at 0 °C in nitrogen atmosphere; the stirring was then continued for one more hr. To the solution, IV (10 g) in benzene (50 ml) was added over a 30-min period at 0 °C, after which the mixture was stirred for an additional 4.5 hr at room temperature. The viscous mixture was then decomposed with 80 ml of 1 M sulfuric acid and extracted with benzene. The benzene layer was extracted with seven 55-ml portions of aqueous 1 M potassium carbonate. The alkaline solution thus obtained was acidified with 6 M hydrochloric acid, and the resulting precipitates were collected by filtration and recrystallized from *n*-hexane to give 5.35 g (76%) of V as yellow needles; mp 63—64 °C. IR(KBr): 1622 cm^{-1} (C=O). NMR($CDCl_3$): τ −3.45, −3.32 (d, C=CHOH), −1.90 (ϕ-OH).

Found: C, 69.65; H, 5.34%. Calcd for $C_{11}H_{10}O_3$: C, 69.83; H, 5.33%.

3-(8-Hydroxy-1-oxo-1,2,3,4-tetrahydro-2-naphthyl)propionic Acid (VII). A mixture of V (4.0 g), methyl acrylate (20.0 g), triethylamine (1.8 g), and 80% methanol (50 ml) was heated under reflux at 112 °C for 8 hr. The solution was then extracted with ether, and the ether layer was washed with four 30 ml-positions of aqueous 1 M potassium carbonate and with water, and dried. The ether was then evaporated, and the residue was hydrolyzed with a 3 M potassium hydroxide solution. The alkaline solution was acidified with 6 M hydrochloric acid, and the resulting precipitates were collected by filtration. They were then recrystallized from aqueous ethanol to give 3.7 g (75%) of VII as colorless needles; mp 164—165 °C. IR(KBr): 1717 (COOH), 1630 cm^{-1}(C=O).

Found: C, 66.78; H, 6.02%. Calcd for $C_{13}H_{14}O_4$: C, 66.68; H, 6.03%.

3-(2-Carboxy-4,5-dihydro-3H-naphtho[1,8-bc]furan-3-yl)propionic Acid (VIII) and 3-(4,5-Dihydro-3H-naphtho[1,8-bc]furan-3-yl)propionic Acid (VIII) and 3-(4,5-Dihydro-3H-naphtho[1,8-bc]furan-3-yl)propionic Acid (IX). A mixture of VII (2.0 g), ethyl bromoacetate (18.6 g) and potassium carbonate (12.8 g) was heated slowly up to 170 °C and then refluxed for 7 more hr at this temperature. The dark brown mixture was extracted with acetone, and then the acetone was evaporated. The residue was then separated after saponification with a 3 M potassium hydroxide solution into two moieties, one of which is insoluble in benzene. The benzene-insoluble moiety was recrystallized from tetrahydrofuran-benzene to give 0.8 g (34%) of VIII as colorless needles; mp 219—220 °C. IR (KBr): 1700 cm^{-1} (COOH).

Found: C, 68.37; H, 5.49%. Calcd for $C_{15}H_{14}O_5 \cdot 0.43\ C_6H_6$: C, 68.37; H, 5.40%.

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*-hxeane to give 40 mg (2%) of IX as colorless plates; mp 98—99 °C. IR(KBr): 1705 cm^{-1} (COOH). NMR ($CDCl_3$): τ −1.13 (COOH), 2.55 (H on the furan ring). UV: λ_{max}^{EtOH} 250 nm (ε 9500).

Found: C, 73.16; H, 6.10%. Calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13%.

When 1.3 g of the ester (VI) was used in place of the acid (VII), 0.6 g (41%) of VIII and 80 mg (6%) of IX were obtained.

Decarboxylation of VIII. A mixture of 10.0 g of quinoline, 1.0 g of VIII, and 1.0 g of copper powder was heated at 155 °C for 1.5 hr and then at 160 °C for 10 more min. The mixture was acidified with 1 M hydrochloric acid and extracted with ether. The ether extract was washed with four 30-ml portions of 2 M hydrochloric acid and with water, and dried, and then the ether was evaporated. The residue was crystallized from benzene-*n*-hexane to give 0.5 g (59%) of IX as colorless plates; mp 98—99 °C.

3-Oxo-1,2,3,8,9,9a-hexahydrophenanthro[4,5-bcd]furan (XII). A mixture of 0.5 g of IX and 69 g of polyphosphoric acid was stirred at 75 °C for 4 hr. The reaction mixture was poured onto ice and extracted with ether. The ether was washed with water, with four 45-ml portions of 1M aqueous potassium carbonate, and with water, and then dried. The ether was evaporated to give crystals. Recrystallization from ethanol–*n*-hexane gave 0.21 g (45%) of XII as colorless needles; mp 109—110 °C. IR(KBr): 1670 cm^{-1} (C=O). NMR($CDCl_3$): τ 2.45—2.90 (multiplet, ϕ-H), 6.57—7.03 (m, $-CH_2-$, $-CH-$), 7.40—7.72 (m, $-CH_2-$), 7.95—8.73 (m, $-CH_2-$).

Found: C, 79.13; H, 5.67%. Calcd for $C_{12}H_{12}O_2$: C, 79.23; H, 5.70%.

3-Hydroxyphenanthro[4,5-bcd]furan (I). A mixture of XII (0.2 g), 20% palladium on charcoal (0.4 g), and α-methylnaphthalene (3.5 g) was heated at 230 °C for 30 hr under nitrogen atmosphere. The reaction mixture was filtered, and the filtrate was extracted with ether. The ether layer was extracted with five 45 ml-portions of a 1 M potassium hydroxide solution, and the alkaline solution thus obtained was washed with three 30 ml-portions of carbon tetrachloride and then made acidic with 6 M hydrochloric acid. The resulting precipitates were extracted with ether, and the ether extract was washed with water, dried, and then concentrated. The residue was chromatogtaphed over silica gel and eluted with benzene-ether (9 : 1) to give colorless crystals from the first fraction. Recrystallization from benzene gave 32 mg (16%) of I as colorless needles; mp 142.5—143 °C. IR(KBr): 3220 (OH), 822, 813 (2H), 760 cm^{-1} (3H). NMR($CDCl_3$): τ 0.49(OH), 2.0—2.56 (ϕ-H). UV: λ_{max}^{EtOH} 234 (ε 47500), 240 (ε 49300), 257 (ε 23900), 269 (ε

17500), 317 (ε 13400), 335 (ε 4300), 353 nm (ε 6100).

Found: C, 80.75; H, 3.96%. Calcd for $C_{14}H_8O_2$: C, 80.76; H, 3.87%.

The latter fraction was also collected to give a phenolic compound. Recrystallization from benzene gave 20 mg (10 %) of colorless needles, which may be 3,5-dihydroxyphenanthrene (XIV) judging from the following spectral properties. IR(KBr): 3240 (OH), 840, 814 (2H), 762 cm^{-1} (3H). NMR(CD_3COCD_3): τ 0.58, 0.78 (d, ϕ-H), 1.23 (OH), 2.24—2.96 (m, ϕ-7H). UV: λ_{max}^{EtOH} 235 (ε 38700), 252 (ε 61400), 285 (ε 9800), 310 (ε 10900), 328 (ε 2600), 345 (ε 6000), 365 nm (ε 8300).

The authors wish to thank Mr. Y. Takahashi for the elemental analyses, Mr. H. Saisu for the infrared analyses, and Mr. T. Ono for the nuclear magnetic resonance analyses.

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