A Synthesis of 3-Hydroxy-5-methoxyphenanthro[4,5-*bcd*]furan

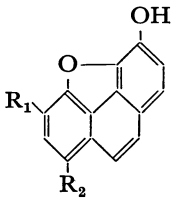
Takaaki HORAGUCHI and Takahachi SHIMIZU

Department of Chemistry, Faculty of Science, Niigata University, Igarashi, Niigata 950–21

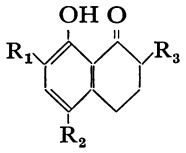
(Received May 1, 1974)

3-Hydroxy-5-methoxyphenanthro[4,5-*bcd*]furan (Ia) was synthesized by the dehydrogenation of 5-methoxy-3-oxo-1,2,3,8,9,9a-hexahydrophenanthro(4,5-*bcd*)furan (IVa), starting from 8-hydroxy-7-methoxy-1-tetralone (IIb).

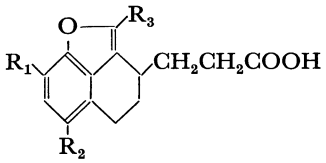
In previous papers,[1,2] the first synthetic route to phenanthro[4,5-*bcd*]furans which contain a ring strain[3] has been reported; by this method Ib and Ic (morphenol) were prepared starting from 8-hydroxy-1-tetralones (IIe and IIf respectively). In the syntheses, however, the yields were not satisfactory in two kinds of cyclization reactions, the formation of naphtho[1,8-*bc*]furans (IIIb and IIIc) from 8-hydroxy-1-tetralones (IIe and IIf) and ethyl bromoacetate, and the intramolecular cyclization of naphtho[1,8-*bc*]furans (IIIb and IIIc) to the corresponding phenanthro[4,5-*bcd*]-furans (IVb and IVc); on the other hand, a methoxyl group on the benzene ring in IIe and IIf served to increase the yield in the latter cyclizations (IIe,f→IIIe,f) and did not have any effect on the yield in the other cyclizations (IIIe,f→IVb,c). These results have required us to make a further attempt to prepare 3-hydroxy-5-methoxyphenanthro[4,5-*bcd*]furan (Ia), an isomer of Ib, starting from a 8-hydroxy-1-tetralone derivative (IId), which has a substituent at the *ortho*-position to the hydroxyl group.



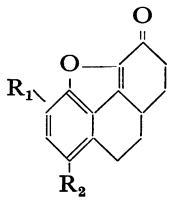
Ia: R_1=OMe, R_2=H
Ib: R_1=H, R_2=OMe
Ic: R_1=H, R_2=H



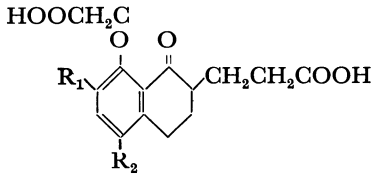
IIa: R_1=OMe, R_2=Cl, R_3=H
IIb: R_1=OMe, R_2=H, R_3=H
IIc: R_1=OMe, R_2=H, R_3=CHO
IId: R_1=OMe, R_2=H, R_3=CH_2CH_2COOH
IIe: R_1=H, R_2=OMe, R_3=CH_2CH_2COOMe
IIf: R_1=H, R_2=H, R_3=CH_2CH_2COOH



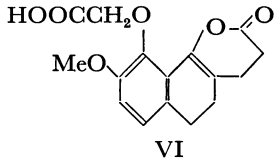
IIIa: R_1=OMe, R_2=H, R_3=COOH
IIIb: R_1=H, R_2=OMe, R_3=COOH
IIIc: R_1=H, R_2=H, R_3=COOH
IIId: R_1=OMe, R_2=H, R_3=H
IIIe: R_1=H, R_2=OMe, R_3=H
IIIf: R_1=H, R_2=H, R_3=H



IVa: R_1=OMe, R_2=H
IVb: R_1=H, R_2=OMe
IVc: R_1=H, R_2=H



V: R_1=OMe, R_2=H



VI

Fig. 1.

Results and Discussion

The tetralone (IId) was prepared from 3-(3,4-dimethoxybenzoyl)propionic acid through a series of intermediates (IIa), (IIb), and (IIc), as will be described in the Experimental section.

When IId was treated with ethyl bromoacetate at 170 °C, followed by hydrolysis, the expected di- and monocarboxylic acids, 3-(2-carboxy-8-methoxy-4,5-dihydro-3*H*-naphtho[1,8-*bc*]furan-3-yl)propionic acid (IIIa) and 3-(8-methoxy-4,5-dihydro-3*H*-naphtho[1,8-*bc*]furan-3-yl)propionic acid (IIId), were obtained in 39 and 1.5% yields respectively. An attempt to prepare IIId from V by treating it with a mixture of acetic anhydride and sodium acetate was unsuccessful; the reaction mixture gave a crystalline product. The infrared absorption spectrum of the product, unlike that of V, shows no bands corresponding to the conjugated-carbonyl group near 1660 cm^{-1} and to the carboxyl group of the propionic acid near 1700 cm^{-1}; instead, it has a new band at 1756 cm^{-1} which is characteristic of a γ,δ-unsaturated δ-lactone ring. Therefore, the compound is believed to have the lactone structure (VI).

The monocarboxylic acid (IIId), which was also obtained from the dicarboxylic acid (IIIa) by decarboxylation (58%), was subjected to a polyphosphoric acid-catalyzed intramolecular cyclization to give 5-methoxy-3-oxo-1,2,3,8,9,9a-hexahydrophenanthro[4,5-*bcd*]furan (IVa) in a 59% yield. For the aromatization of IVa to the phenol (Ia), palladium on charcoal was used as the catalyst; the yield was 10%.

The yields of the di- and monocarboxylic acids

(IIIa and IIId) were comparable to those of the corresponding carboxylic acids (IIIc and IIIf) from IIf in the synthesis of Ic (34 and 2%).[2] The results, combined with previously reported,[1,2] seem to indicate that the methoxyl groups of IId and IIe have no effect on the yields of the cyclizations. The yield of the ketone (IVa) was almost the same as that of IVb (67%)[1] and better than that of IVc (45%).[2] The results indicate that the methoxy groups of IIId and IIIe serve to increase the yields in the cyclizations. As the IVa–c are obtained in fairly good yields from IId–f under mild conditions, no large strain is introduced into the reactions. If the strain is present in phenanthro[4,5-*bcd*]furan derivatives (IV),[3] it is mainly present in the naphtho[1,8-*bc*]furan ring. The problem of the strain in naphtho[1,8-*bc*]furan derivatives will be further investigated later.

Experimental

All the melting points are uncorrected. The column chromatography was performed on silica gel (WAKOGEL C-200). The polyphosphoric acid was prepared from 85% phosphoric acid (100 ml) and phosphorus pentoxide (123 g) by heating them at 160—165 °C for 5 hr. Unless otherwise stated, anhydrous sodium sulfate was employed as the drying agent. The infrared absorption spectra were determined with a JASCO Model DS 402 G infrared spectrophothometer. The ultraviolet absorption spectra were determined with a Shimadzu Model UV-200 spectrophothometer. The nuclear magnetic resonance spectra were determined at 100 MHz with a JEOL Model 4H-100 NMR spectrometer, using tetramethylsilane as the internal standard.

4-(3,4-Dimethoxyphenyl)butyric Acid. A mixture of 3-(3,4-dimethoxybenzoyl)propionic acid (40 g) in acetic acid (150 ml), palladium chloride (520 mg) in 0.1M hydrochloric acid (30 ml), and charcoal (10 g) was shaken under a hydrogen atmosphere at room temperature.[4] After the usual treatment, the recrystallization of the resulting solid from chloroform–petroleum ether gave 30.3 g (85%) of 4-(3,4-dimethoxyphenyl)butyric acid as colorless plates; mp 60—61 °C (lit,[5] 58—59 °C).

4-(2-Chloro-4,5-dimethoxyphenyl)butyric Acid. This acid was prepared according to the method of Brown *et al.*[6] Colorless prisms; mp 106—108 °C (lit,[5] 112 °C).

5-Chloro-8-hydroxy-7-methoxy-1-tetralone (IIa). A mixture of 4-(chloro-4,5-dimethoxyphenyl)butyric acid (30.0 g) and polyphosphoric acid (390 g) was heated with stirring at 90 °C for 7 hr. The deep red mixture was decomposed with ice water, and the resulting precipitates were extracted with ether. The ethereal layer was washed with 1M potassium carbonate and then water, dried, and evaporated. The recrystallization of the residue from ethanol gave 22.7 g (86%) of IIa as yellow needles; mp 102—103 °C (lit,[5] 104—105 °C).

8-Hydroxy-7-methoxy-1-tetralone (IIb). A mixture of charcoal (4.0 g), palladium chloride (500 mg) in 0.1 M hydrochloric acid (20 ml), and ethanol (50 ml) was shaken under a hydrogen atmosphere at room temperature until no hydrogen was consumed. After adding of IIa (30 g) in ethanol (200 ml), the mixture was then shaken at 40 °C until 2.3 l of hydrogen had been consumed.[6,7] After the usual subsequent treatment, the recrystallization of the resulting solid from hexane gave 15.2 g (60%) of IIb as yellow plates; mp 76—77 °C. IR(KBr): 1625 (C=O), 829 (OH), and 811 cm^{-1} (two adjacent aromatic hydrogen atoms). NMR(CD_3COCD_3): δ 12.67 (s, OH), 3.82 (s, OCH_3), 7.15 (d, 1H, J=8 Hz, Ar–H), and 6.70 (d, 1H, J=8 Hz, Ar–H).

Found: C, 68.81; H, 6.28%. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29%.

8-Hydroxy-2-hydroxymethylidene-7-methoxy-1-tetralone (IIc). To a mixture of sodium methoxide (8.0 g, from 4.3 g of sodium and absolute methanol) and benzene (50 ml), we added ethyl formate (14.5 ml) under a nitrogen atmosphere at room temperature, after which the mixture was stirred for 30 min. To the mixture we then added IIb (8 g) in benzene (50 ml), drop by drop, over a 30min period under cooling with ice water, after which the mixture was stirred for an additional 4 hr at room temperature. The resulting green-yellow mixture was decomposed with 1 M sulfuric acid (120 ml) and extracted with benzene. The benzene layer was extracted with a 1 M potassium carbonate solution. The alkaline solution thus obtained was acidified with 6 M hydrochloric acid, and the resulting precipitates were recrystallized from 60% aqueous ethanol to give 7.7 g (84%) of IIc as yellow plates; mp 110—111 °C. IR(KBr): 1625 (C=O), 832 (OH), and 800 cm^{-1} (two adjacent aromatic hydrogen atoms). NMR(CD_3COCD_3): δ 13.36 (broad s, Ar–OH+ =C–OH), 11.98 (s, –C–OH), 2.00 (broad s, =CH–O–), 2.43 (broad s, =CH–O–), 7.10 (d, 1H, J=8 Hz, Ar–H), 6.68 (d, 1H, J=8 Hz, Ar–H), and 3.84 (s, OCH_3). UV(EtOH): λ_{max} 225 (ε 14500) and 315—356 nm, (10500).

Found: C, 65.33; H, 5.54%. Calcd for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49%.

3-(Hydroxy-7-methoxy-1-oxo-1,2,3,4-tetrahydro-2-naphthyl)-propionic Acid (IId). A mixture of IIc (15.0 g), methyl acrylate (75.0 g), triethylamine (7.5 g), and 80% aqueous methanol (120 ml) was refluxed at 115 °C for 1 hr. The reaction mixture was then concentrated under reduced pressure, and the resulting oil was extracted with ether. The ethereal layer was washed with 2 M hydrochloric acid, a 1 M potassium carbonate solution, and then water, and dried, after which the ether was evaporated. The residue was heated in a water-bath under reduced pressure to remove any unreacted methyl acrylate. The residue was then dissolved in a small amount of ethanol and hydrolyzed with a 3 M potassium hydroxide solution. The alkaline solution was acidified with 6M hydrochloric acid. The resulting precipitates were collected and recrystallized from 70% aqueous ethanol to give 15.2 g (85%) of IId as orange yellow needles; mp 157—158.5 °C. IR(KBr): 1708 (COOH), 1625 (C=O), and 812 cm^{-1}, (two adjacent aromatic hydrogen atoms). NMR(CD_3COCD_3): δ 12.67 (s, OH), 7.14 (d, 1H, J=8 Hz, Ar–H), and 6.70 (d, 1H, J=8 Hz, Ar–H). UV (EtOH): λ_{max} 227 (ε 16300), 267 (10200), and 353 nm (3100).

Found: C, 63.66; H, 6.13%. Calcd for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10%.

3-(2-Carboxy-8-methoxy-4,5-dihydro-3H-naphtho[1,8-bc]furan-3-yl)propionic Acid (IIIa) and 3-(8-Methoxy-4,5-dihydro-3H-naphtho-[1,8-bc]furan-3-yl)propionic Acid (IIId). A mixture of IId (2.0 g), ethyl bromoacetate (18.6 g), and potassium carbonate (12.8 g) was gradually heated to 170 °C and then refluxed for an additional 6 hr at this temperature. The dark brown mixture was extracted with hot acetone, and then the acetone was evaporated. The residue was dissolved in a small amount of ethanol and hydrolyzed with a 3 M potassium hydroxide solution. The alkaline solution was acidified with 6M hydrochloric acid, and the resulting precipitates were extracted with ether. The ethereal solution was washed with water and dried, and then the solvent was evaporated. The residue was divided into soluble and insoluble portions with benzene. The benzene-insoluble portion (0.9 g, 39%) was recrystallized from 60% aqueous

ethanol to give IIIa as colorless needles; mp 213—214 °C. IR(KBr): 1705 and 1690 cm^{-1} (COOH). UV(EtOH): λ_{max} 234 (ε 22500) and 277 nm (14500).

Found: C, 63.20; H, 5.37%. Calcd for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30%.

The benzene-soluble portion was chromatographed on silica gel and eluted with benzene–ether (9 : 1). A yellow fraction was collected to give crystals. Recrystallization from benzene–*n*-hexane gave 30 mg (1.5%) of IIId as colorless plates; mp 136—138 °C. IR(KBr): 1705 cm^{-1} (COOH). NMR(CD_3COCD_3): δ 7.60 (d, 1H, J=1 Hz, furan H), 6.91 (d, 1H, J=8 Hz, Ar–H), 6.76 (d, 1H, J=8 Hz, Ar–H), and 5.97 (s, OCH_3). UV(EtOH): λ_{max} 216 (ε 30700), 247 (10000), 255 (9200), 280 (1900), and 290 nm (1700).

Found: C, 69.22; H, 6.22%. Calcd for $C_{15}H_{16}O_4$: C, 69.92; H, 6.20%.

Decarboxylation of IIIa. A mixture of IIIa (1.0 g), copper powder (1.0 g), and quinoline (10 g) was heated at 160 °C for 1 hr. The reaction mixture was extracted with ether and acidified with 2M hydrochloric acid. The ethereal layer was washed with 2M hydrochloric acid and then water, dried, and then evaporated. The residue was chromatographed on silica gel and eluted with benzene–ether (9 : 1). A yellow fraction was collected, and after the removal of the solvent the residue was recrystallized from benzene–*n*-hexane to give 500 mg (58%) of IIId as colorless plates; mp 137—138 °C.

5-Methoxy-3-oxo-1,2,3,8,9,9a-hexahydrophenanthro[4,5-bcd]-furan (IVa). A mixture of IIId (2.0 g) and polyphosphoric acid (260 g) was heated while being stirred at 80 °C for 4 hr. The green reaction mixture was then decomposed with ice water, and the resulting precipitates were extracted with ether. The ethereal layer was washed with a 1M potassium carbonate solution and then water, and dried. The ether was evaporated, and the residue was recrystallized from ethanol to give 1.1 g (59%) of IVa as colorless needles; mp 161—162 °C. IR(KBr): 1659 cm^{-1} (C=O). NMR ($CDCl_3$): δ 6.97 (d, 1H, J=8 Hz, Ar–H), 6.86 (d, 1H, J=8 Hz, Ar–H), and 4.06 (s, OCH_3). UV(EtOH): λ_{max} 240 (ε 16500) and 294 nm (20200).

Found: C, 74.06; H, 5.85%. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82%.

3-Hydroxy-5-methoxyphenanthro[4,5-bcd]furan (Ia). A mixture of IVa (200 mg), 20% palladium on charcoal (400 mg), and α-methylnaphthalene (3.5 g) was heated under a nitrogen atmosphere at 240 °C for 30 hr.[8,9] The reaction mixture was then filtered, and the filtrate was extracted with ether. The ethereal layer was extracted with a 1 M potassium hydroxide solution. The alkaline solution thus obtained was washed with carbon tetrachloride and then acidified with 6M hydrochloric acid. The resulting precipitates were extracted with ether. The ethereal layer was washed with water, dried, and then evaporated. The residue was chromatographed on silica gel and eluted with benzene–ether (9 : 1). A yellow fraction was collected, and after the removal of the solvent the residue was recrystallized from benzene to give 40 mg (10%) of Ia as colorless needles; mp 127—128 °C. IR(KBr): 3250 (Ar–OH) and 816 cm^{-1} (two adjacent aromatic hydrogen atoms). NMR(CD_3COCD_3): δ 9.61 (s, OH), 7.75 (s, 2H, Ar–H), 2.25—2.60 (m, 6H, Ar–H), and 5.65 (s, OCH_3). UV(EtOH):[10] λ_{max} 232 (ε 38200), 245 (48300), 258 (25300), 268 (24600), 315 (14000), 327 (14100), and 356 nm (23000).

Found: C, 75.76; H, 4.25%. Calcd for $C_{15}H_{10}O_3$: C, 75.62; H, 4.23%.

3-(8-Carboxymethoxy-7-methoxy-1-oxo-1,2,3,4-tetrahydro-2-naphthyl)propionic Acid (V). A mixture of IId (1.0 g), ethyl bromoacetate (3.7 g), potassium carbonate (6.0 g), and dioxane (15 ml) was refluxed for 6.5 hr at 115 °C. The reaction mixture was then extracted with acetone, and the acetone was evaporated. The residue was dissolved in ethanol and hydrolyzed with a 3M potassium hydroxide solution. The alkaline solution was acidified with 6M hydrochloric acid, and the resulting precipitates were extracted with ether. The ethereal layer was washed with water, dried, and then evaporated. The residue was washed with benzene to give 650 mg (53%) of V; mp 183—185 °C. Recrystallization from acetone–tetrahydrofuran gave colorless prisms; mp 185—187 °C. IR(KBr): 1750 (COOH), 1698 (COOH), 1658 (C–O), and 815 cm^{-1} (two adjacent aromatic hydrogen atoms). UV(EtOH): λ_{max} 219 (ε 18700), 253 (6000), and 320 nm (2300).

Found: C, 59.62; H, 5.63%. Calcd for $C_{16}H_{18}O_7$: C, 59.53; H, 5.82%.

Lactone (VI). A mixture of V (1.0 g), sodium acetate (4.6 g), and acetic anhydride (15 ml) was heated for 1 hr at 145 °C and then for 5 min at 150 °C. The reaction mixture was poured into water to decompose the acetic anhydride and then extracted with ether. The ethereal layer was washed with water, dried, and then evaporated. The residue was washed with benzene to give 500 mg (53%) of VI; mp 168—169 °C. Recrystallization from acetone gave colorless needles; mp 169—170 °C. IR(KBr): 1756 (lactone), 1736 (COOH), and 816 cm^{-1} (two adjacent aromatic hydrogen atoms).

Found: C, 62.97; H, 5.34%. Calcd for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30%.

The authors wish to thank Mr. Hideo Saisu for the infrared analyses and Mr. Hideo Ōno for the nuclear magnetic resonance analyses.

References

1) T. Shimizu, T. Horaguchi, and A. Watanabe, This Bulletin, **46**, 1772 (1973).
2) T. Horaguchi and T. Shimizu, *ibid.*, **47**, 485 (1974).
3) A. V. Dendy, J. H. P. Tyman, and W. B. Whalley, *J. Chem. Soc.*, **1963**, 4040.
4) M. Seki, H. Saito, and H. Mamuro, *Nippon Kagaku Zasshi*, **81**, 292 (1960).
5) R. Ghosh and Sir Robert Robinson, *J. Chem. Soc.*, **1944**, 508; R. D. Haworth and C. R. Mavin, *ibid.*, **1932**, 1486.
6) A. G. Brown, J. C. Lovie, and R. H. Thomson, *ibid.*, **1965**, 2348.
7) D. B. Bruce and R. H. Thomson, *ibid.*, **1955**, 1089.
8) R. B. Turner, D. E. Nettleton, J. R., and R. F. Ferebee, *J. Amer. Chem. Soc.*, **76**, 5923 (1956); W. S. Johnson and H. Posvic, *ibid.*, **69**, 1361 (1947).
9) E. Mosettig and H. M. Duvoll, *ibid.*, **59**, 367 (1939).
10) H. Rapoport, A. D. Batchs, and J. E. Gordon, *ibid.*, **80**, 5767 (1958).