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# Synthesis of Crowned Phenoxazine Derivatives

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**Summary.** 16 *H*-2,5,8,11,14-Pentaoxacyclopentadecano[2,3-a]phenoxazin-16-one, its 17-bromo analogue and 16-hydroxy-2,5,8,11,14-pentaoxacyclopentadecanophenoxazine were prepared by the reaction of 1,4-quinone of benzo[15]crown-5 or its dibromide with 2-aminophenol. Dehalogenation of the bromophenoxazinone was also investigated.

**Keywords.** 16 *H*-2,5,8,11,14-Pentaoxacyclopentadecano[2,3-a]phenoxazin-16-one; 16-Hydroxy-2,5,8,11,14-pentaoxacyclopentadecanophenoxazine; 17,18-Dibromo-16,19-dioxo-2,5,8,11,14-petaoxabiclo[13.4.0]-$1^{15}$,$17^{18}$-nonadecadien; 17-Bromo-16 *H*-2,5,8,11,14-pentaoxacyclopentadecano[2,3-a]phenoxazin-16-one.

**Synthese von Kronen-Phenoxazin-Derivaten (Kurze Mitt.)**

**Zusammenfassung.** 16 *H*-2,5,8,11,14-Pentaoxacyclopentadecano[2,3-a]phenoxazin-16-on, sein Brom-Analog und 16-Hydroxy-pentaoxacyclopentadecanophenoxazin wurden mittels der Reaktion des 1,4-Chinons von Benzo[15]krone-5 oder dessen Dibromid mit 2-Aminophenol hergestellt. Die Dehalogenierung von Bromphenoxazinon wurde ebenfalls untersucht.

## Introduction

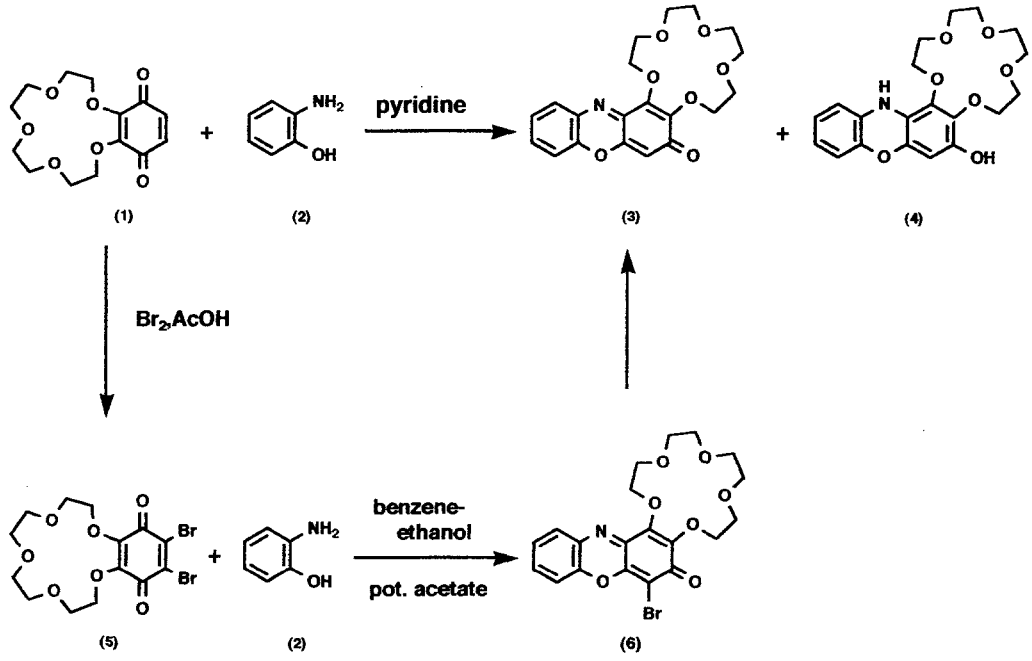
Phenoxazinone and Phenothiazinone derivatives containing the iminoquinone system have been studied for biological and pharmaceutical activities and to obtain useful pigments [1–6]. In continuation of our interest in the synthesis and usage of these compounds [7–9], we now report the preparation of crowned phenoxazine derivatives.

In this work, 1,4-quinone of benzo[15]crown-5 (**1**) [10, 11], was treated with 2-aminophenol (**2**) in pyridine to afford 16 *H*-2,5,8,11,14-pentaoxacyclopentadecano[2,3-a]phenoxazin-16-one (**3**) and 16-hydroxy-2,5,8,11,14-pentaoxacyclopentadecanophenoxazine (**4**). The structures of these compounds were determined on the basis of spectroscopic data. The structure of **3** was also confirmed by direct comparison with a sample prepared by an alternate route. **1**, on treatment with bromide in acetic followed by addition of sodium acetate, provided dibromide **5**, as evident from the disappearance of vinylic proton signals in its NMR spectrum.

The reaction of **5** with **2** in benzene-ethanol in the presence of anhydrous potassium acetate furnished 17-bromo-2,5,8,11,14-pentaoxacyclopentadecano[2,3-a]phenoxazin-16-one (**6**), which on dehalogenation in presence of sodium hydrosulfite dissolved in aqueous pyridine gave compound **3**. This compound was found to be identical with the compound prepared in pyridine (mixed melting point, co-tlc and spectroscopic data).

## Experimental Part

Meltingpoints were determined on a Yanagimoto micromelting apparatus and are uncorrected. The infrared spectra were recorded on a Jasco A-102 spectrometer, the UV spectra with a Jasco Ubest-30 instrument. The $^1$H-NMR spectra were measured on a Joel JNM-PMX 60 SI NMR spectrometer using tetramethylsilane as internal reference. Mass spectra were obtained with a Hitachi M-2000 spectrometer. Microanalysis was carried out with a Yanaco MT-3 CHN corder.




*Reaction of 16,19-Dioxo-2,5,8,11,14-pentaoxabiclo[13.4.0]-1$^{15}$,17$^{18}$-nonadecadien (1,4-Quinone of Benzo[15]crown-5)* (**1**) *with 2-Aminophenol* (**2**)

Crown quinone **1** (298.3 mg, 1.0 mmol) was dissolved in pyridine (5 ml) and 2-aminophenol (**2**) (327.39 mg, 3.0 mmol) was added. The mixture was stirred at room temperature for 5 h. After evaporation of pyridine under reduced pressure, the residue was extracted with chloroform and washed with 1 *N* hydrochloric acid and water. The extract, after evaporation of the solvent, was passed down a column of silica gel using chloroform : ethanol (99 : 1) as an eluent.

The first fraction gave compound **3** (15.5 mg, 3.9%) recrystallised from chloroform-hexane, m.p. 83–86°C; IR (KBr): 1610 (C=O), 1585 (C=N) cm$^{-1}$; $^1$H-NMR ($CDCl_3$): δ 7.8 (m, 1H, arom.), 7.25 (m, 3H, arom.), 6.2 (s, 1H, arom.), 4.5 (m, 4H, crown-H), 3.8 (m,12H, crown-H); UV (chloroform): $\lambda_{max}$, nm (log ε), 397.0 (4.5); MS calcd. for $C_{20}H_{21}NO_7$: 387.39; found *m/e*: 387.0 ($M^+$); analyt. calcd. C 62.00, H 5.46, N 3.61; found C 61.63, H 5.63, N 3.40.

The second fraction afforded compound **4** (22.0 mg, 5.6%) recrystallized from chloroform-hexane, m.p. 195–196°C; IR (KBr): 3440 (NH, OH) cm$^{-1}$; $^1$H-NMR (*DMSO-$d_6$* + $CDCl_3$): δ 9.09 (br, 1H,

NH, exchangeable with $D_2O$), 7.59 (m, 1 H, −OH, exchangeable with $D_2O$), 7.09 (s, 1 H, arom.), 6.89 (m, 3 H, arom.), 5.89 (m, 1 H, arom.), 4.49 (m, 2 H, crown-H), 4.33 (m, 2 H, crown-H), 3.73 (m, 12 H, crown-H); UV (chloroform): $\lambda_{max}$, nm (log ε), 420.5 (3.59), 340.5 (4.21), 325.5 (4.25); MS calcd. for $C_{20}H_{23}NO_7$: 389.40; found *m/e*: 389.0 ($M^+$); analyt. calcd. C 61.68, H 5.95, N 3.59; found C 61.12, H 5.75, N 3.38.

*17,18-Dibromo-16,19-dioxo-2,5,8,11,14-pentaoxabicyclo[13.4.0]-1$^{15}$,17$^{18}$-nonadecadien* (**5**)

Crown quinone **1** (298.29 mg, 1 mmol) was dissolved in acetic acid (4 ml) under protection from light. Bromide (191.76 mg, 1.2 mmol) was added. The mixture was stirred in dark for 4 h, then during 1 h a stream of argon was passed through to sweep out excess of bromide. Sodium acetate (318 mg, 3.87 mmol) was added and the mixture stirred over night. Then it was poured into cold water and extracted with chloroform, washed with 10% sodium bicarbonate solution and water. The solvent was evaporated and the residue was passed down a column of silica gel using ethyl acetate : hexane (9 : 1) as an eluent. 220 mg of **5** were obtained on recrystallization from chloroform and hexane, m.p. 70 − 70.5°C; IR (KBr): 1 660 (C=O), 1 620 (C=C) $cm^{-1}$; $^1$H-NMR ($CDCl_3$): 4.5 (m, 4 H, crown-H), 3.73 (m, 12 H, crown-H); MS for $C_{14}H_{16}O_7Br_2$: 456.04, found *m/e*: 455.7 ($M^+$).

*Reaction of Dibromo Quinone* **5** *with 2-Aminophenol* (**2**)

To a suspension of **5** (228.03 mg, 0.5 mmol) and anhydrous potassium acetate (58.88 mg, 0.6 mmol) in 1 ml of benzene, an alcoholic solution (1.5 ml) of 2-aminophenol (54.56 mg, 0.5 mmol) was added dropwise under refluxing. After refluxing for additional 3 h with stirring, the mixture was evaporated in vacuo. The residue was washed with water and column chromatographed on silica gel using ethyl acetate : hexane (9 : 1) as an eluent, affording 40 mg of **6** (17.1%), recrystallised from chloroform-hexane, m.p. 143 − 145°C; IR (KBr): 1 630 (C=O), 1 590 (C=N) $cm^{-1}$; $^1$H-NMR ($CDCl_3$): δ 7.97 (m, 1 H, arom.), 7.45 (m, 3 H, arom.), 4.5 (m, 4 H, crown-H), 3.9 (m, 12 H, crown-H); UV (chloroform): $\lambda_{max}$, nm (log ε), 400 (4.46); MS for $C_{20}H_{20}NO_7Br$: 466.24; found *m/e*: 467.1 ($M^+$); analyt. calcd. C 51.52, H 4.32, N 3.0; found C 50.85, H 4.32, N 2.71.

*Dehalogenation of 17-Bromo-16 H-2,5,8,11,14-pentaoxacyclopentadecano[2,3-a]phenoxazin-16-one* (**6**)

A mixture of **6** (50 mg, 0.107 mmol), sodium hydrosulfite (186.28 mg, 1.07 mmol), benzene (0.4 ml) and water (0.5 ml) was bubbled with nitrogen for 20 min. After reduction of the starting material, the mixture was heated to reflux, then 0.25 ml pyridine was added and the resulting mixture was refluxed for 3 h under nitrogen atmosphere. After cooling to room temperature the mixture was evaporated in vacuo, the residue was extracted in chloroform and washed with water. Then the residue was colum chromatographed over silica gel using chloroform : ethanol (98 : 2) as an elluent, affording 12 mg of **3** (28%).

## References

[1] Hollstein U. (1974) Chem. Rev. **74**: 625
[2] Brockmann H., Muxfeldt H. (1956) Angew. Chem. **68**
[3] Motohashi N. (1983) Yakugaku Zasshi **103**: 364
[4] Butenandt A., Schiedt U., Biekert E., Cromartie R. J. T. (1654) Ann. Chem. **590**: 75
[5] Agarwal N. L., Schafer W. (1980) J. Org. Chem. **45**: 5144
[6] Agarwal N. L., Schafer W. (1980) J. Org. Chem. **45**: 2155
[7] Nan'ye S., Maekawa E., Hayokawa H., Kitaguchi Y., Ueno Y. (1985) J. Heterocyclic Chem. **22**: 1488

[8] Hayakawa H., Nan'ye S., Yamamoto T., Maekawa E., Ueno Y. (1986) J. Heterocyclic Chem. **23**: 1737
[9] Sakakibara M., Nagai W. Hasegawa K., Ueno Y. (1991) Pharmazie **46**: 28
[10] Hayakawa K., Kido K., Kanematsu K. (1986) J. Chem. Soc. Chem. Commun.: 268
[11] Dietl F., Gierer G., Merz A. (1985) Synthesis: 626

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