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Short Communication

Synthesis of Crowned Phenothiazine Derivatives

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Summary. The reaction of 1,4-quinone of benzo[15]crown-5 with 2-aminothiophenol in an acidic medium afforded 16-hydroxy-2,5,8,11,14-pentaoxacyclopentadecanophenothiazine and 16*H*-2,5,8,11,14-pentaoxacyclopentadecano[2,3-a]phenothiazin-16-one. The oxidation of the alcohol to the corresponding ketone was also investigated.

Keywords. 16-Hydroxy-2,5,8,11,14-pentaoxacyclopentadecanophenothiazine; 16*H*-2,5,8,11,14-Pentaoxacyclopentadecano[2,3-a]phenothiazin-16-one.

Synthese von Kronenether-Phenothiazin-Derivaten (Kurze Mitt.)

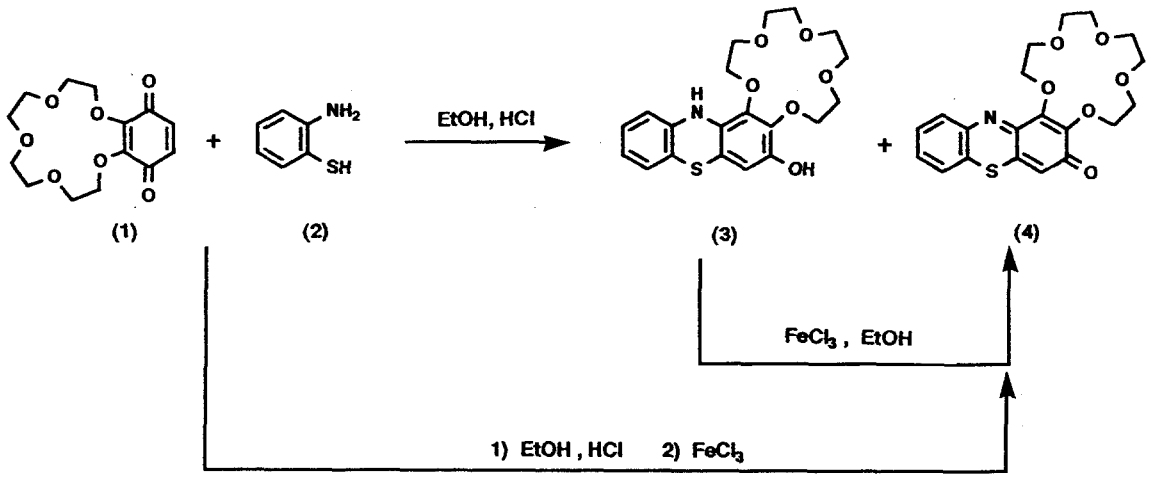
Zusammenfassung. Die Reaktion des 1,4-Chinons von Benzo[15]krone-5 mit 2-Aminophenol ergab in saurem Medium 16-Hydroxy-2,5,8,11,14-pentaoxacyclopentadecanophenothiazin und 16*H*-2,5,8,11,14-pentaoxacyclopentadecano[2,3-a]phenothiazin-16-on. Die Oxidation des Alkohols zum entsprechenden Keton wurde ebenfalls untersucht.

Introduction

The scope of interest in phenothiazine derivatives covers a wide assortment of areas. Many of them have remarkable pharmaceutical activities and are extensively used as enzyme inhibitors, antioxidants, dyestuffs and indicators in titrimetry [1–7]. Some of them are synthesized for IR dyes [8]. Our interest in the chemistry and pharmaceutical usage of these compounds has allowed us to prepare some of phenothiazines [9–11]. We now report the preparation of crowned phenothiazine derivatives.

Recent reports [12, 13] on the synthesis of the crowned benzoquinone **1** has prompted us to prepare it and to carry out its reaction with 2-aminothiophenol. This reaction was performed in alcoholic solution in the presence of hydrochloric acid, which resulted in the formation of 16-hydroxy-2,5,8,11,14-pentaoxacyclopentadecanophenothiazine (**3**) and 16*H*-2,5,8,11,14-pentaoxacyclopentadecano[2,3-a]phenothiazin-16-one (**4**). Oxidation of **3** with ferric chloride gave **4**. In another experiment ferric chloride was added in situ, which resulted in the isolation of compound **4** only. The stability of **3** may be attributed to the electron withdrawing

field effect of crowned oxygens, which favours aromatization, resulting in the predominate formation of **3**.



(1) (2) (3) (4)

Experimental Part

Melting points were determined on a Yanagimoto micromelting apparatus and are uncorrected. The infrared spectra were recorded on a Jasco A-102 spectrometer, and UV spectra with a Jasco Ubest-30 instrument. The ^{1}H-NMR spectra were measured on a Varian XL-200 spectrometer using tetramethylsilane as internal reference. Mass spectra were obtained with a Hitachi M-2000 spectrometer. Microanalysis was carried out by a Yanaco MT-3 CHN corder.

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

Crown quinone (100 mg, 0.335 mmol) was dissolved in ethanol (14 ml); then 2-aminothiophenol (50.4 mg, 0.402 mmol) was added with stirring. Then hydrochloric acid (6*N*, 2 ml) was added dropwise in 15 min. The mixture was then allowed to stir at room temperature for 10 h. Then the reaction mixture was neutralized by saturated sodium bicarbonate solution. After removal of the solvent by distillation, the organic material obtained was extracted with chloroform. The extract, after evaporation of the solvent, was passed down a column of silica gel using chloroform : ethanol (98 : 2) as an eluent. Recrystallization from chloroform and hexane gave 92 mg of **3** (68%) and 12 mg of **4** (7.3%).

Compound **3** had a m.p. of 170–172°C. IR (KBr): 3350 (NH, OH), 745 (C–S) cm^{-1}. ^{1}H-NMR (*DMSO-d*$_6$): δ 9.02 (br, 1 H, NH, exchangeable with D_2O), 7.5 (s, 1 H, OH, exchangeable with D_2O), 7.04 (s, 2 H, arom.), 6.95 (d, J=4 Hz, 1 H, arom.), 6.78 (s, 1 H, arom.), 6.3 (s, 1 H, arom.), 4.06 (s, 4 H, crown-H), 3.98 (s, 2 H, crown-H), 3.8 (s, 2 H, crown-H), 3.6 (m, 8 H, crown-H). UV (chloroform): λ_{max}, nm (log ε), 421 (2.49), 400 (3.16), 341 (3.47), 317 (3.64), 257 (4.37). MS calcd. for $C_{20}H_{23}NO_6S$: 405.47; found m/e 405.1 (M^+). $C_{20}H_{23}NO_6S$: calcd. C 59.24, H 5.71, N 3.45; found C 58.83, H 5.59, N 3.08.

Compound **4** had a m.p. of 107–107.5°C. IR (KBr): 1600 (C=O), 1590 (C=N), 755 (C–S) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 8.01 (m, 1 H, arom.), 7.5 (m, 3 H, arom.), 6.67 (s, 1 H, vinylic), 4.58 (m, 4 H, crown-H), 4.06 (t, J=2 Hz, 2 H, crown-H), 3.9 (m, 2 H, crown-H), 3.75 (m, 8 H, crown-H). UV (chloroform): λ_{max}, nm (log ε), 403.5 (4.17), 293 (4.28), 285 (4.28), 246 (4.41), 241.5 (4.40), 240.5 (4.40), 239.0 (4.42). MS calcd. for $C_{20}H_{21}NO_6S$: 403.46; found m/e 403.1 (M^+). $C_{20}H_{21}NO_6S$: calcd. C 59.54, H 5.25, N 3.47; found C 59.36, H 5.25, N 3.02.

Ferric Chloride Oxidation of 16-Hydroxy-2,5,8,11,14-pentaoxacyclopentadecanophenothiazine (**3**)

Alcohol **3** (30 mg) (30 mg, 0.74 mmol) was dissolved in ethanol (10 ml), and 1 ml of an aqueous solution of ferric chloride hexahydrate (80 mg, 0.296 mmol) was added. The mixture was allowed to stir at room temperature for 3 h. Then the reaction mixture was neutralized by saturated sodium bicarbonate solution. Solvent was evaporated, and the orgnaic material was extracted with chloroform; after evaporation of the solvent the residue was passed through a column of silica gel, using ethyl acetate : hexane (9 : 1) as an eluent. About 22 mg of **4** (73.6%) were obtained after recystallization from chloroform and hexane.

Preparation of 16H-2,5,8,11,14-Pentaoxacyclopentadecano[2,3-a]phenothiazin-16-one (**4**) *by in situ Ferric Chloride Oxidation*

Crown quinone (50 mg, 0.168 mmol) was dissolved in ethanol (7 ml), then 2-aminothiophenol (25.2 mg, 0.201 mmol) was added with stirring. Afterwards hydrochloric acid (6*N*, 1 ml) was added dropwise within 15 min. The mixture was allowed to stir at room temperature for 10 h. Ferric chloride hexahydrate (181 mg, 0.669 mmol) was added and the mixture was stirred for additional 5 h, followed by neutralization with saturated sodium bicarbonate solution. The substance was evaporated to dryness and the residue was chromatographed on a column of silica gel using ethyl acetate : hexane (9 : 1) as an eluent. About 35 mg of **4** (51%) were obtained after recrystallization from chloroform and hexane.

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