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# EFFECT OF CROWN ETHER MACROCYCLE ON THE METHYLATION OF THE THIOAMIDE DERIVATIVES OF BENZO-15-CROWN-5 AND VERATROLE

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*It was shown that benzo-15-crown-5 ether has an effect on the methylation of the thioamide derivatives, leading to the formation of the nitriles of carboxylic acids.*

**Keywords:** benzo-15-crown-5, veratrole, methylation, thioamides, thioamidation.

Thioamides are convenient intermediates in organic synthesis, and their reactivity increases in the transition to S-alkyl-substituted thioimidic esters [1]. The latter are usually produced by methylation of the thioamides with methyl iodide in an alkaline medium. We tried to use this method to produce the methyl esters of thioveratrimidic and benzo-15-crown-5-thiocarboximidic acids. The initial thioamides of the acids were obtained by the reaction of veratrole and benzo-15-crown-5 (B15C5) respectively with potassium thiocyanate in polyphosphoric acid [2].

During the methylation of thioveratramide (**1**) in an alkaline medium the expected product methyl thioveratrimidate (**2**) was formed (Table 1, expt. 1). The structure was established on the basis of the $^1$H NMR spectrum. The doublet at 7.80, the singlet at 7.70, and the doublet at 7.13 ppm correspond to the protons of the benzene ring at positions 6, 2, and 5 respectively. The doublet at 3.93 ppm corresponds to the six protons of the methoxyl groups. The three-proton singlet at 3.0 ppm confirms the presence of the methyl group.

Contrary to our expectations, an attempt at the methylation of (benzo-15-crown-5)-4'-thiocarboxamide (**3**) under analogous conditions led to the formation of (benzo-15-crown-5)-4'-carbonitrile (**4**) (expt. 2).

The structure of compound **4** followed from the $^1$H NMR spectrum and IR and mass spectra. The $^1$H NMR spectrum contains signals for the aromatic protons at 7.2, 7.0, and 6.8 ppm, which correspond to the three protons at positions 5', 3', and 6' respectively, and the multiplet for the 16 protons of the macrocycle is at 3.60-4.17 ppm. There are no signals for the protons of a methyl group. In the IR spectrum there absorption bands at 3750 and 2230 cm$^{-1}$, characteristic of the CN group. The mass spectrum contains a molecular ion [M]$^+$ 293, confirming the structure of the nitrile **4**.

In an alkaline medium the thioamide derivatives are transformed into nitriles [3]. We therefore excluded methyl iodide from the reaction mixture and treated compound **3** only with potassium hydroxide (expt. 3). The reaction does not go at room temperature, but (benzo-15-crown-5)-4'-carboxylic acid (**5**) was formed on heating. The results demonstrate the effect of the crown ether on this reaction. In order to confirm the conclusion we

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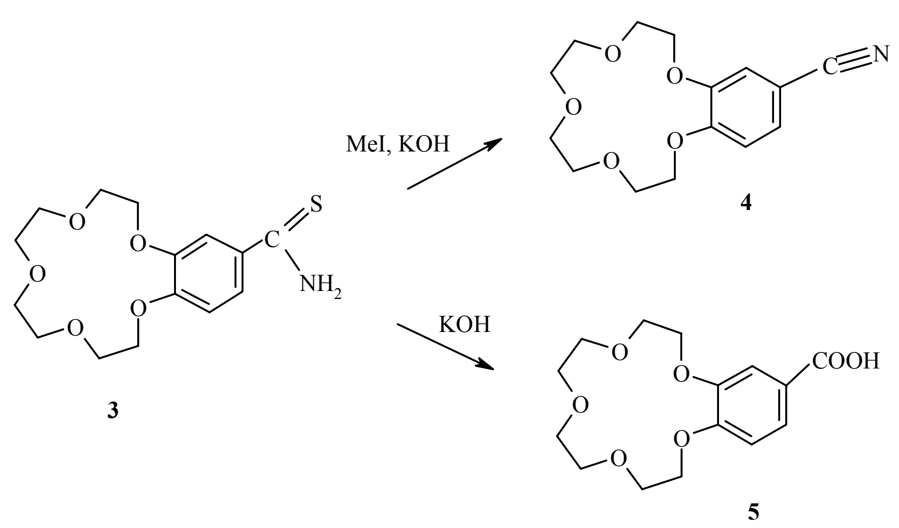

attempted the methylation of the amide of compound **1** in the presence of a small amount of B15C5 (expt. 4). Here veratric acid (**7**) and its nitrile **6** were obtained, while the methylation product was not detected. We assumed that the benzo-15-crown-5 combines the methyl iodide molecule into a complex and methylation does not occur. The formation of the same products – the acid **7** and its nitrile **6** – was observed when the reaction was conducted in the absence of methyl iodide (expt. 5). The results confirm that methylation does not take place in the presence of the crown ether exchanger and the usual alkaline hydrolysis of thioamides occurs.

We then studied the reaction of compound **2** with potassium hydroxide with and without the presence of benzo-15-crown-5 (expts. 6 and 7). In the first case a mixture of the nitrile **6** and the acid **7** was obtained. In the second (in the absence of the crown ether) only the nitrile **6** was formed. Consequently, the alkaline hydrolysis of compound **2** takes place more vigorously in the presence of the crown ether.

It can be concluded on the basis of the obtained data that methylation does not occur in the presence of the crown ether, and the products from alkaline hydrolysis (the nitriles and carboxylic acids) are formed. Such an effect from the benzo-15-crown-5 can be explained by its complex formation both with the methyl iodide, leading to the formation of the nitrile, and with the potassium hydroxide, resulting in the formation of the active "bare" OH anion, which promotes more extensive hydrolysis with the formation of the nitrile and then the acid.

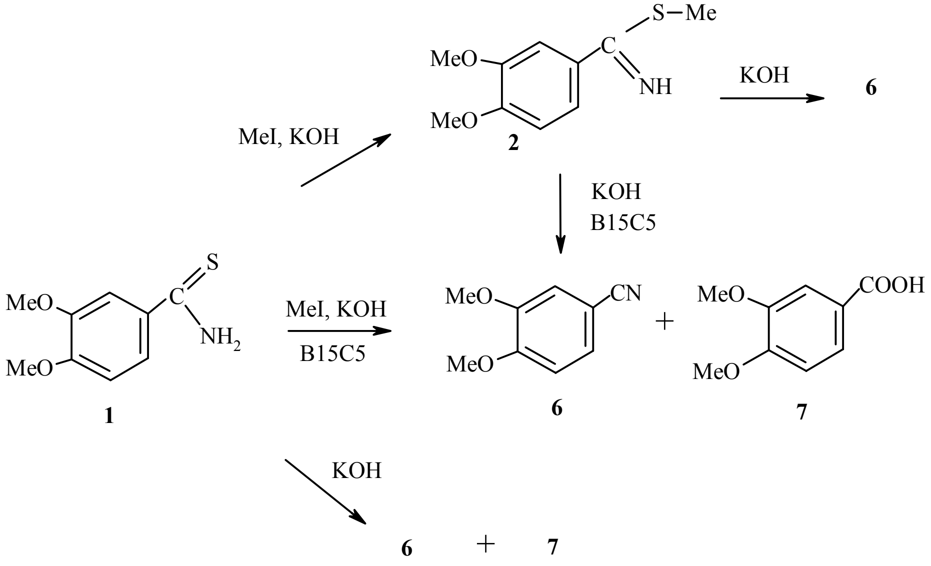

TABLE 1. Methylation of the Amides of Thioveratric and (Benzo-15-crown-5)-4'-thiocarboxylic acids

| Expt. | Reagents | Molecular ratios | Reaction time, °C | Reaction time, h | mp of product, °C | Reaction products |
|---|---|---|---|---|---|---|
| 1 | **1**,<br>KOH,<br>MeI | 1:4:4 | 20-25 | 4.5 | 175-179 | **2** |
| 2 | **3**,<br>KOH,<br>MeI | 1:4:4 | 20-25 | 2 | 86-87 | **4** |
| 3 | **3**,<br>KOH | 1:4 | 20-25 | 3 |  | No Reaction<br>(TLC data) |
|  |  |  | 80-83 | 2 | 178-184 | **5** |
| 4 | **1**,<br>KOH,<br>MeI,<br>B15C5 | 1:4:4:0.5 | 20-25 | 3 | Product not isolated | **7**,<br>**6**,<br>(TLC data) |
| 5 | **1**,<br>KOH | 1:4 | 20-25 | 3 | Product not isolated | **7**,<br>**6**<br>(TLC data) |
| 6 | **2**,<br>KOH,<br>B15C5 | 1:4:0.5 | 40-45 | 3 | 63-65<br>173-180 | **6**,<br>**7** |
| 7 | **2**,<br>KOH | 1:4 | 40-45 | 3 | 63-65 | **6** |

## EXPERIMENTAL

The $^1$H NMR spectra were recorded in deuterochloroform and hexadeuteroacetone on a Tesla BS-567 spectrometer (100 MHz). The IR spectra were obtained in tablets with potassium bromide on a Perkin-Elmer Fourier spectrophotometer. The mass spectra were obtained on a Kratos MS25RF instrument. The reactions and the purity of the products were monitored on aluminum oxide of II activity and on Silufol UV-254 plates.

The methylation of thioveratramide (**1**) to methyl thioveratramidate (**2**) (expt. 1) and the production of the nitrile of (benzo-15-crown-5)-4'-carboxylic acid (**4**) from the amide **3** (expt. 2) were realized in dioxane by the methods in [4].

**Hydrolysis of (Benzo-15-crown-5)-4'-thiocarboxamide (3) (Expt. 3).** To a solution of the amide **3** (0.07 g, 0.2 mmol) in dioxane (5 ml) we added dropwise a solution of potassium hydroxide (0.04 g, 0.8 mmol) in water (1 ml). The mixture was heated at 80°C for 2 h, and 5 ml of water was added to the reaction mass. The mixture was acidified with HCl and extracted with chloroform. After evaporation of the extract we obtained 0.02 g (33%) of compound **5**; mp 178-184°C (186°C [5]). The acid **5** dissolves readily in aqueous sodium bicarbonate solution.

**Reaction of Compound (1) with Methyl Iodide in the Presence of Benzo-15-crown-5 (Expt. 4).** A mixture of the amide **1** (0.1 g, 0.5 mmol) and benzo-15-crown-5 (0.067 g, 0.25 mmol) was rubbed and was then dissolved in dioxane (5 ml). To the obtained solution while stirring we added methyl iodide (0.12 ml, 2 mmol) and a solution of potassium hydroxide (0.1 g, 2 mmol) in water (1 ml). The mixture was kept at ~20°C for 3 h. According to TLC on aluminum oxide (eluent 3:1 benzene–acetone) the reaction products were the acid **7** and its nitrile **6** (~1:1).

**Hydrolysis of Compound (1) (Expt. 5).** Amide **1** (0.1 g, 0.5 mmol) was dissolved in dioxane (4 ml), and a solution of potassium hydroxide (0.11 g, 2 mmol) in water (2 ml) was added with stirring on a magnetic stirrer. The mixture was kept at ~20°C for 3 h. According to TLC on aluminum oxide (eluent 3:1 benzene–acetone) the acid **7** and its nitrile **6** were formed (~1:1).

**Hydrolysis of Compound 2 (Expt. 6).** Ester **2** (0.1 g, 0.5 mmol) and benzo-15-crown-5 (0.67 g, 0.25 mmol) were dissolved in dioxane (5 ml) at 40-45°C, and potassium hydroxide (0.11 g, 2 mmol) in water (1 ml) was added with stirring. The solution here became colorless. The stirring was continued for 3 h, and the reaction mixture was then diluted with water and extracted successively with chloroform and benzene. After removal of the benzene the residue was crystallized from hexane, and 0.33 g (yield 34%) of compound **6** was obtained; mp 63-65 (mp 67-68°C [6]). From the water–dioxane mother solution by acidification we obtained 0.22 g (yield 27%) of compound **7**; mp 173-180°C (mp 180°C [6]).

**Reaction of Compound 2 with Potassium Hydroxide (Expt. 7).** The reaction was carried out similarly to expt. 6 but without the addition of benzo-15-crown-5, and 0.05 g (yield 65%) of compound **6** was obtained; mp 63-65°C.

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