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Short Note

Cyclo[Tri(thiomethyl-1,2-phenylmethylene)]

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Abstract: During the purification of a reported compound named 1,3-dihydrobenzo[*c*]thiophene, we isolated an unexpected molecule in one of the chromatography fractions by serendipity. Structural elucidation using common techniques such as 1D and 2D NMR, and mass spectrometry revealed the nature of this novel product characterized as cyclo[tri(thiomethyl-1,2-phenylmethylene)].

Keywords: thia-crown-ether; macrocycle; thioether; thia cyclopentadecane; serendipity

1. Introduction

Macrocycles are an important group of compounds that have garnered great interest owing to their pharmaceutical activity and capacity to coordinate metallic atoms [1,2]. Indeed, some of these molecular rings can be found in living organisms, playing important roles in many biological processes [3]. Among the different macrocycles, crown ethers are one of the most famous types due to their ability to create host–guest complexes, which entailed significant advances in supramolecular chemistry and phase transfer catalysis in the last century [4]. As a result, Pedersen received the 1987 Nobel Prize in Chemistry, shared with Lehn and Cram, for his contribution to new synthetic routes for preparing this type of molecules [5].

Despite their notorious ability to complex transition metals, inter alia, the first generation of crown ether-based molecular hosts lack specificity and chelate diverse-sized cations indiscriminately. To tackle this issue, the community has introduced two main strategies: (i) the rigidification of the macrocycle skeleton to preserve a unique size for the host cavity and (ii) the use of different heteroatoms with higher attraction toward certain metallic centers [4,6,7]. In this sense, the first introductions of thioether groups into crown ether structures were performed to prepare more specific host systems, such as noble–metal complexes [8,9]. Nevertheless, the synthesis of pure thia crown ethers incorporating only sulfur as anchoring positions remains overlooked, with the exception of the more attractive cyclophanes [10–13] (Figure 1a,b).

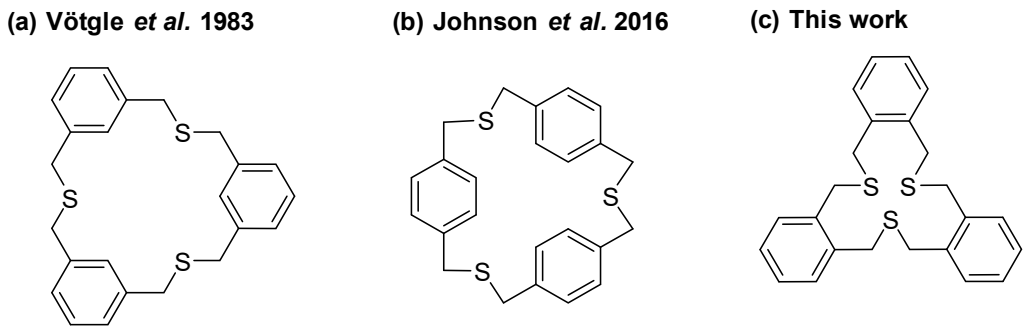

Figure 1. (**a**,**b**) Analog S3 thia crown ethers with C_3 symmetry [12,13] and (**c**) the new molecule highlighted in this short note.

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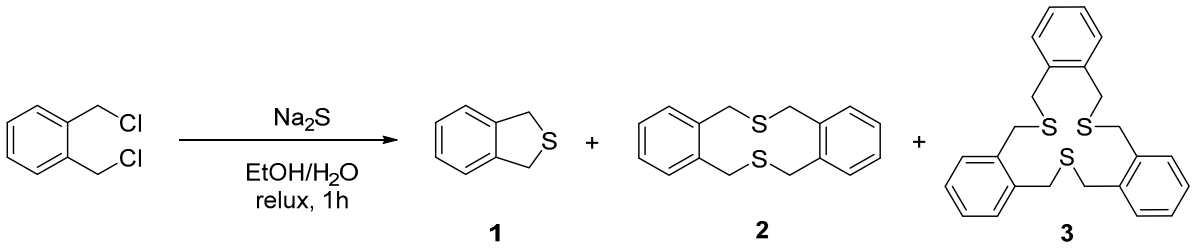
Herein, we prepared a new symmetric thia crown ether containing only sulfur atoms as chelating positions by serendipity. The 15-membered macrocycle presents a star shape with a C_3 axis of symmetry and enhanced structural rigidity endowed by the phenyl rings embedded in its backbone, leading to highly specific host–guest interactions.

2. Results and Discussion

Enrolled in the synthesis of 1,3-dihydrobenzo[*c*]thiophene (**1**) via nucleophilic substitution of 1,2-bis(chloromethyl)benzene by a sulfur dianion (Scheme 1), we realized that the crude thin-layer chromatography (TLC) displayed two other spots below the one described in the literature for the desired product (F1: R_f = 0.82; F2: R_f = 0.53; F3: R_f = 0.29; eluent: Hep/AcOEt, 9/1) [14]. In addition to the benzothiophene derivative **1** (F1), we also isolated the two lower fractions via column chromatography in order to understand the side reactions and work on yield improvement. The two unexpected compounds resulted in poor yields compared to the 77% observed for **1**.



Scheme 1. Synthetic conditions for the synthesis of **1**, **2,** and **3**.

Analyzed by ^{1}H-NMR, the three compounds showcased two sets of peaks integrating by the same number of protons: two doublet of doublets (dd) in the aromatic region (7.70–7.20 ppm), presumably ascribed to ABB' systems, and a singlet (s) in the aliphatic region (4.40–3.40 ppm) from the benzyl mercaptan moiety (Figures 2 and S1–S6). These observations indicate that the three fractions share similar scaffolds with a high degree of symmetry. As expected, the signals of the less polar compound match perfectly with the ones reported for the desired product 1,3-dihydrobenzo[*c*]thiophene [14]. On the other hand, the compound isolated in F2 presents a deshielding effect in the aromatic signals and a singlet shielded compared with **1**. After an exhaustive investigation of the literature, we determined that the latter could be characterized as 2,9,11,18-tetrahydrodibenzo[c,h][1,10]dithiecine (**2**), as we found that Kreber et al. already reported in 1991 in the *Chemische Berichte* journal (only in Germany) the possible formation of **2** as a side product during the synthesis of benzo[*c*]thiophenes, due to the excess of Na_2S in the reaction media [15]. However, no clue about a third by-product was detected in old or modern journals. According to the NMR profiles and the nature of the F2, we started speculating that the unknown third fraction could be the product of the coupling between more than two bis(chloromethyl)benzenes, presumably three, bridged by the nucleophilic substitution of the same number of S^{2-}. Eventually, the structure was confirmed using mass spectrometry (TOF MS CI^+) (Figure S7), concluding that the 15-membered thia crown ether **3** is synthesized, in a poor 2% yield, as a minor side product during the preparation of **1**.

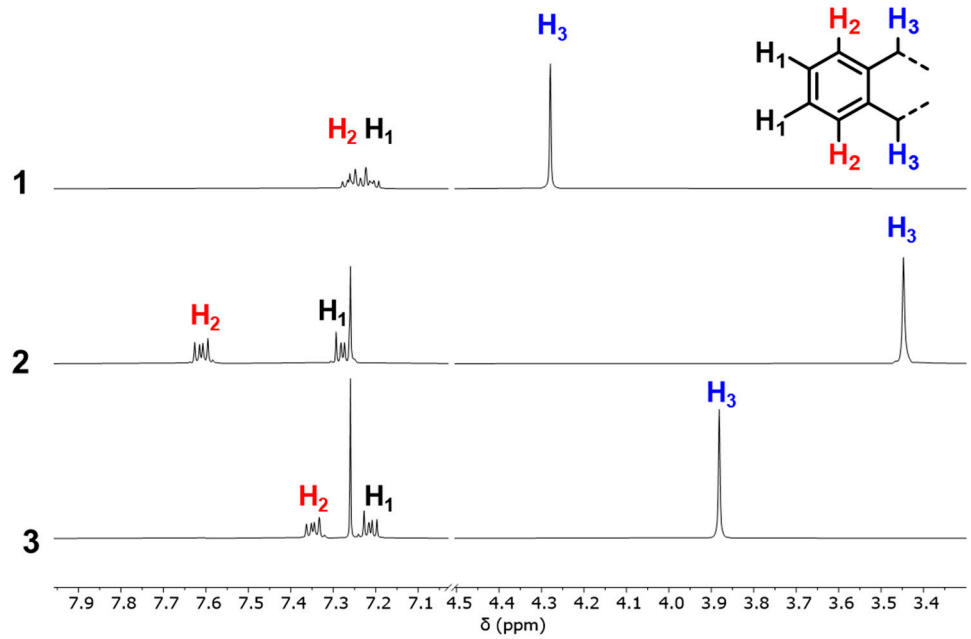


Figure 2. Aromatic and aliphatic stacked region of the ^{1}H-NMR spectra (300 MHz, $CDCl_3$, 25 °C) obtained from the three products purified during the synthesis of 1,3-dihydrobenzo[*c*]thiophene, **1**, **2** and **3**.

3. Materials and Methods

The solvents were purchased from commercial suppliers. 1,2-bis(chloromethyl)benzene was purchased from BLDpharm (Shanghai, China) and Na_2S from Merck (Darmstadt, Germany).

NMR spectroscopy and mass spectrometry were performed by the appropriate services of the Toulouse Institute of Chemistry (ICT–UAR 2599).

^{1}H and ^{13}C-NMR spectra were recorded on Bruker Avance III HD 400 MHz (probe 5 mm TBO ATMA) and Avance NEO 300 MHz (probe 5 mm BBFO ATM) spectrometers (Billerica, MA, USA). Chemical shifts (δ) are reported in ppm. Coupling constants (*J*) are given in Hz, and the following abbreviations have been used to describe the signals: singlet (s); doublet (d); and multiplet (m). Full assignments of ^{1}H and ^{13}C NMR spectra were made with the assistance of HMBC, HSQC, and NOESY spectra. High-resolution mass spectra (HR-MS) were performed with a Waters GCT Premier spectrometer (Milford, MA, USA) for desorption chemical ionization (DCI-CH_4). The melting point was measured using a Kofler hot bench. IR spectra were run using KBr pellet samples in the 400–4000 cm^{-1} range on an FTIR spectrometer Spectrum 100 from Perkin-Elmer (Wellesley, MA, USA).

The density functional theory (DFT) single-point geometry optimization was carried out with Guassian16 at PBE1PBE/6-311+g(d,p) level, applying the D3 version of Grimme's dispersion.

*Synthesis of Cyclo[tri(thiomethyl-1,2-phenylmethylene)] (**3**)*

To a refluxed solution of sodium sulfide (2.34 g, 29.98 mmol) in EtOH (68 mL) and water (14 mL), 1,2-bis(chloromethyl)benzene (2.5 mL, 19.34 mmol) was added through a Soxhlet extractor with the help of the refluxing solvent. After the total addition of the reagent, the reaction was refluxed for an additional 40 min. Thereafter, the reaction was cooled down to room temperature, and the solvent evaporated. The residual oil was extracted with dichloromethane, washed with water, and the organic layer dried over $MgSO_4$. The solvent was evaporated under vacuum, and the crude was purified by column chromatography (eluent: heptane/EtOAc, 9:1). The first fraction (**1**) was obtained as a yellowish oil (2.02 g, 77% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.30–7.18 (m, 4H), 4.28 (s, 4H), according to the literature [14]. The second fraction (**2**) was

recovered as a crystalline white solid (400 mg, 8% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.61 (dd, *J* = 5.8, 3.5 Hz, 4H), 7.28 (dd, *J* = 5.8, 3.5 Hz, 4H), 3.45 (s, 8H), as reported in the literature [15]. Eventually, the macrocycle **3** was isolated in the third fraction as a white powder (81 mg, 2%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.35 (dd, J = 5.6, 3.5 Hz, 6H), 7.21 (dd, J = 5.7, 3.4 Hz, 6H), 3.88 (s, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 136.1, 130.6, 127.7, 34.8. HRMS (MALDI-TOF-CI+): *m*/*z* calcd for $C_{24}H_{24}S_3$: 408.1040, found: 408.1032 [M^+] and 409.1116 [$M+H^+$]. IR (KBr): 3063–3016 cm^{-1} (C_{sp2}-H, Ar), 2946–2859 cm^{-1}(C_{sp3}-H), 1609-1427 cm^{-1} (C=C, Ar + -CH_2-), 743–722 (C-H, *o*-Ar + C-S-C). Melting Point: decomposes at 200 °C.

4. Conclusions

Herein, we have reported the synthesis and purification of a 15-membered thia crown ether obtained as a side product in the preparation of 1,3-dihydrobenzo[*c*]thiophene. The chemical structure was elucidated using NMR and MS spectrometry, adding a new compound to this rare family of macrocycles with potential application in coordination chemistry and pharmacology.

Supplementary Materials: NMR spectroscopy, MS spectrometry, IR spectroscopy, and DFT.

Author Contributions: Methodology, validation, investigation, writing—original draft preparation and funding acquisition, P.S.M.; investigation and writing—review and editing, N.B.; validation, supervision, writing—review and editing, funding acquisition, C.K. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: Not applicable.

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Conflicts of Interest: The authors declare no conflicts of interest.

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