Synthesis and properties of benzo[*b*]thiopheno[2,3-*d*]-1,3,2λ^5-diazaphosphinane-2-thione derivatives

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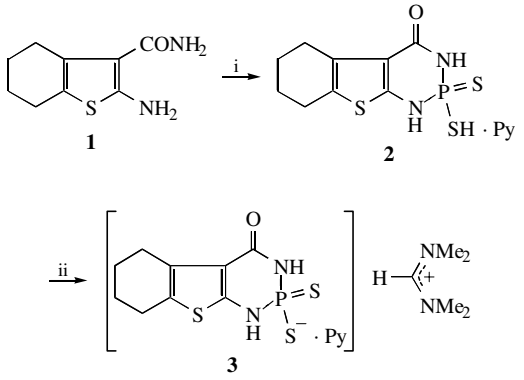
The treatment of 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid amide with phosphorus pentasulfide in the presence of pyridine yielded 4,5,6,7-tetrahydrobenzo[*b*]thiopheno[2,3-*d*]-1,3,2λ^5-diazaphosphinane-2-thione; the alkylation of its sodium salts was studied.

Recent studies[1–3] in the series of 1,3,2λ^5-diazaphosphinane-2-thiones demonstrated that their derivatives exhibit a wide range of biological activities.

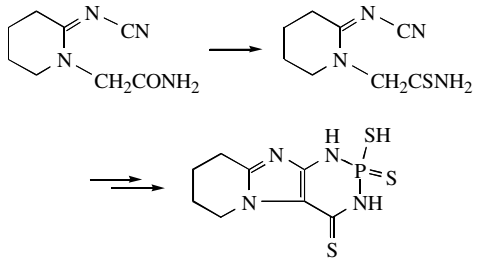
The aim of this work was to synthesise and characterise the derivatives of benzo[*b*]thiopheno[2,3-*d*]-1,3,2λ^5-diazaphosphinane, a new heterocyclic system, which are of biological interest. As a starting compound, we used 2-amino-3-carbamoyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene **1**, which was prepared by the condensation of cyclohexanone with cyanoacetamide and sulfur.[4] The reaction of compound **1** with phosphorus pentasulfide in the presence of pyridine afforded solvate **2** of 2-sulfanyl-4,5,6,7-tetrahydrobenzo[*b*]thiopheno[2,3-*d*]-1,3,2λ^5-diazaphosphinane-2-thion-4-one with pyridine in 84% yield. The solvates of other 1,3,2-diazaphosphinane derivatives with pyridine were described in considerable detail.[1,5–8] It was found that solvates with various pyridine contents were formed depending on reaction conditions; because of this, they are difficult to analyse and identify. Therefore, we performed the reaction of solvate **2** with dimethylformamide diethyl acetal in accordance with the published procedure.[1,9] As a result, we obtained stable tetramethylformamidinium salt **3**, the structure of which was confirmed using NMR spectroscopy, mass spectrometry and elemental analysis.† The mechanism of formation of salt **3** was described in detail elsewhere.[1,9]



1 **2** **3**

Scheme 1 *Reagents and conditions*: i, P_2S_5, pyridine, reflux, 10 min; ii, DMF diethyl acetal, EtOH, room temperature, 5 min.

It is interesting that in the above heterocyclization oxygen was not replaced by sulfur at the 4-position of the diazaphosphinane ring even with the use of a twofold excess of P_2S_5 and with an increase in the reaction time. This fact was observed in diazaphosphinanes for the first time; previously, only Shinde *et al.*[10] mentioned the presence of a 4-CO derivative of 1,3,2-diazaphosphinane as an impurity (according to mass-spectroscopic data). It is likely that the presence of a condensed alicyclic fragment in parent compound **1** and product **2** creates steric hindrance to the attack of phosphorus pentasulfide on the carbonyl oxygen. Note that 4-*cis*-substituted diazaphosphinanes, which contain a cycloalkane moiety as the third annelated ring, were obtained previously in the preparation of 7,8-polymethyleneimidazo-1,3,2λ^5-diazaphosphinanes. However, Nilov *et al.*[7] found that in this case thionation occurred at an early stage before the development of a bi- and tricyclic system:



Scheme 2

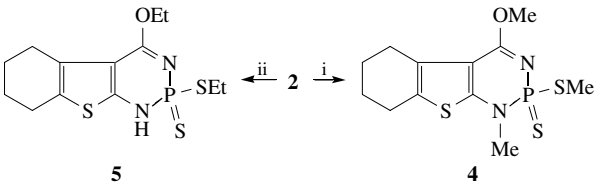
The dissolution of solvate **2** in an aqueous alkali solution gave a sodium salt, which readily reacted with dialkyl sulfates. With the use of dimethyl sulfate and diethyl sulfate, trimethyl derivative‡ **4** (40% yield) and diethyl derivative§ **5** (19% yield), respectively, were isolated from the reaction mixture and identified.

In both cases, it is likely that the entire set of alkyl derivatives was formed, of which only compounds **4** and **5** were isolated (the alkylation of the salts of other diazophosphinane

† *Spectroscopic data for* **3**: mp 194–196 °C (H_2O). ^{1}H NMR (400 MHz, [$^2H_6$]DMSO) δ: 1.65–1.72 (m, 4H, CH_2), 2.46–2.51 (m, 2H, CH_2), 2.57–2.73 (m, 2H, CH_2), 3.15 (s, 6H, 2NMe), 3.26 (s, 6H, 2NMe), 7.86 (d, 1H, NH, ^2J 12.7 Hz), 7.92 (s, 1H, CH), 8.99 (d, 1H, NH, ^2J 13.3 Hz). ^{13}C and DEPT NMR (100.6 MHz, [$^2H_6$]DMSO) δ: 22.17, 22.94, 23.84, 25.98 (–, s, cyclic CH_2), 38.50 (+, s, 2Me), 45.34 (+, s, 2Me), 110.62 (C_{quat}, d, J 2.2 Hz), 118.70, 132.17 (C_{quat}, s), 152.76 (C_{quat}, d, J 3.2 Hz), 161.31 (C_{quat}, d, CO, J 5.8 Hz). MS, *m/z*: 290 (44) [M$^+$], 256 (18) [M$^+$ – H_2S], 178 (45) [M$^+$ – PS_2H_2 – NH], 150 (100) [benzothiophene–NH]$^+$.

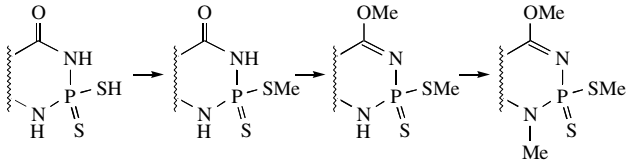
‡ *Spectroscopic data for* **4**: mp 104–105 °C (MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.73–1.86 (m, 4H, CH_2), 2.15 (d, 3H, SMe, ^3J 16.6 Hz), 2.59–2.63 (m, 2H, CH_2), 2.84–2.91 (m, 2H, CH_2), 3.29 (d, 3H, NMe, ^3J 10.9 Hz), 3.36 (d, 3H, OMe, ^5J 11.6 Hz). ^{13}C and DEPT NMR (100.6 MHz, $CDCl_3$) δ: 15.95 (+, d, SMe, J 5.0 Hz), 22.24, 23.02, 24.40, 26.20 (–, s, CH_2), 28.20 (+, d, NMe, J 8.2 Hz), 35.19 (+, d, OMe, J 7.4 Hz), 111.08, 123.70 (C_{quat}, s), 135.02 (C_{quat}, d, J 0.9 Hz), 154.21 (C_{quat}, d, J 2.2 Hz), 160.15 (C_{quat}, d, CO, J 1.9 Hz). IR (KBr, ν/cm^{-1}): 2939, 2859, 2362, 2335, 1658, 1511, 1432, 1351, 1290, 1215, 951. MS, *m/z*: 332 (88) [M$^+$], 285 (20) [M$^+$ – SMe], 253 (12) [M$^+$ – SMe – S].

§ *Spectroscopic data for* **5**: mp 151–154 °C (Pr^{i}OH). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.28 (t, 3H, SMe, ^3J 7.5 Hz), 1.43 (t, OMe, ^3J 7.1 Hz), 1.73–1.88 (m, 4H, cyclic CH_2), 2.60–2.63 (m, 2H, cyclic CH_2), 2.76–2.96 (m, 4H, cyclic CH_2 and SCH_2), 3.68 (qdd, 1H, OCH_2, ^3J 7.0 Hz, ^5J 12.7 Hz, ^2J 15.0 Hz), 3.99 (qdd, 1H, OCH_2, ^3J 7.3 Hz, ^5J 15.5 Hz, ^2J 15.0 Hz), 7.27 (br. s, 1H, NH). ^{13}C and DEPT NMR (100.6 MHz, $CDCl_3$) δ: 14.04 (+, d, SCH_2*Me*, J 1.1 Hz), 15.41 (+, d, OCH_2*Me*, J 7.1 Hz), 22.19, 23.05, 24.38, 25.94 (–, s, cyclic CH_2), 28.52 (–, d, S*C*H_2Me, J 4.5 Hz), 43.97 (–, d, O*C*H_2Me, J 8.0 Hz), 112.49, 124.26 (C_{quat}, s), 134.63 (C_{quat}, d, J 0.9 Hz), 154.71 (C_{quat}, d, J 3.4 Hz), 159.68 (C_{quat}, d, CO, J 6.3 Hz). IR (KBr, ν/cm^{-1}): 3076, 2947, 2769, 1655, 1498, 1439, 1446, 1278, 1155, 997, 690. MS, *m/z*: 346 (100) [M$^+$], 285 (19) [M$^+$ – SCH_2Me], 253 (12) [M$^+$ – SCH_2Me – S].



Scheme 3 *Reagents and conditions*: i, $NaOH/H_2O$, Me_2SO_4, 20 °C, 1 h; ii, $NaOH/H_2O$, Et_2SO_4, 20 °C, 1 h.

derivatives with the formation of tri- and dialkyl derivatives was described[1,3,6–8,10]). To confirm this, we studied the reaction mixture obtained upon the action of dimethyl sulfate on solvate **2** in an alkaline medium. A mass-spectrometric study demonstrated that monomethyl derivative **6** ([MH^+] 319), dimethyl derivative **7** ([MH^+] 305) and trimethyl derivative **4** ([MH^+] 333) were present in the mixture. The assignment of these peaks to three individual compounds followed from a comparison of their ion chromatograms. Taking into account published data,[10] the sequence of reactions that occur in the methylation can be represented as follows:



Scheme 4

A study of the same mixture by ^{1}H NMR spectroscopy exhibited the occurrence of three doublet signals ascribed to PSMe groups. The ratio between these signals depended on the conditions of alkylation. In our particular case, these were 77% trimethyl derivative **4** (δ 2.15 ppm), 14% (δ 2.42 ppm) and 9% (δ 2.07 ppm) (di- and monosubstituted products). Note that the ^{1}H NMR spectrum of compound **4** exhibited the spin–spin interactions of protons of all the three methyl groups with the asymmetric phosphorus atom, δ/ppm: 2.15 (d, 3H, ^3J 16.6 Hz, SMe), 3.29 (d, 3H, ^3J 10.9 Hz, NMe) and 3.36 (d, 3H, ^4J 11.6 Hz, OMe). This effect was not observed previously in compounds with the SMe group at the 3-position of the diazaphosphinane ring.[1,3,6–8,10]

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