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1-Methyl-1*H*-2-pyrrolethiol and -Selenol. Synthesis, Tautomerism and Autotransformations.

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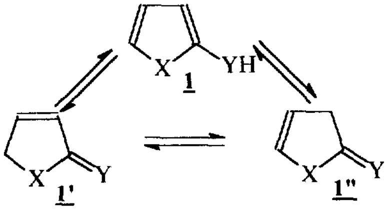
Abstract. Previously unknown 1-methyl-1*H*-2-pyrrolethiol and -selenol existing in solutions as equilibrium tautomeric mixtures with their thione (selone) forms have been synthesized. The reason for instability of the compounds was found to be their spontaneous dimerisation into 2-thio(seleno) lactams. © 1997 Elsevier Science Ltd.

Introduction

2-Pyrrolethiols 1 (X = NR, Y= S) as well as other compounds of the structure 1 (X, Y = O, S, Se, NR) are potentially tautomeric (**Scheme 1**). Only a few 2-pyrrolethiols, namely, those containing electron withdrawing (alkoxy- or alkylcarbonyl-) substituents and existing in the mercapto form, have been known before, while the simplest compound in this series and its alkyl derivatives are supposed to be extremely unstable and could not be obtained in spite of numerous efforts.[1-4] We failed to find any information published on the corresponding selenols.

Scheme 1



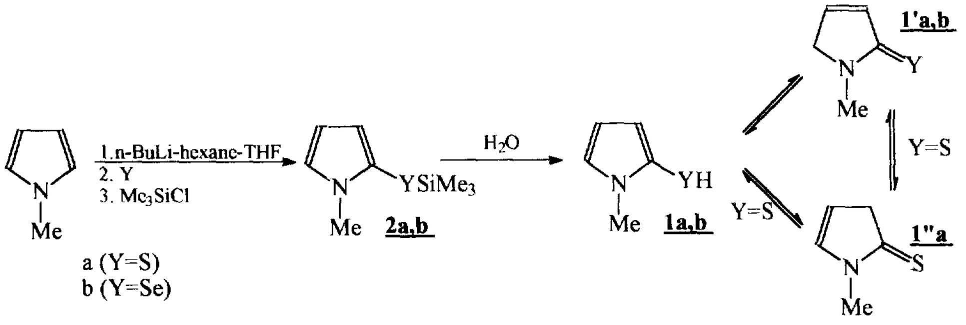
As a rule, potential hydroxy derivatives 1a (Y = O) exist in the oxo- form, while in the case of furan- and thiophene thiols 1 (X = O, S; Y = S), on the contrary, mercapto- forms prevail for the respective thiols.[5] Hence, there seems to be nothing surprising in the predominance of thiol tautomers in the 2-pyrrolthiols series. However, as known for hydroxythiophenes with their tautomerism studied in detail, the introduction of carbonyl containing substituents into the ring affords stabilization of hydroxy form 1 (X = S; Y = O) otherwise non- available in this series.[6] Thus, the question of the tautomeric structure of simple 2-pyrrolethiols has not been solved by the present time.

Previous attempts to synthesize alkyl substituted 2-pyrrolethiols, including N-methyl derivative **1a**, were based on obtaining the corresponding thiolates by alkaline hydrolysis of 2-pyrroleisothiuronium salts or pyrrole thiocyanates[4] followed by "precipitation" of the thiols with a 10% HCl solution.[1] No wonder, rather rough quenching conditions like these led to the failure of the experiment. The organolithium technique, quite common in the synthesis of various heteroarenethiols and, in principle, useful for the synthesis of N-substituted pyrrolethiols, has not been applied, most probably, because of difficulties in obtaining lithiopyrroles. However, at least 1-methylpyrrole, inert to BuLi in hexane or ether, is known to undergo lithiation in the presence of THF.[7]

Results and Discussion

In its classical way, the organolithium synthesis of thiols is finished with acid treatment. However, chloro trimethylsilane can also be used instead of acid to give trimethylsilyl sulfides (or selenides), stable in isolation and storage, from which the target thiols (or selenols) can easily be generated by mild hydrolysis (directly in an NMR tube, if needed). By this method, successfully applied before in our studies of unstable furanthiols and -selenols,[8] we could synthesise solutions of 1-methyl-1*H*-2-pyrrolethiol **1a** and selenol **1b** in solvents suitable for NMR spectroscopy (**Scheme 2**).

Scheme 2



NMR studies of the resulting solutions reveal that compound **1a** exists in equilibrium with tautomeric forms **1"a** and **1'a**, with the latter, 1-methyl-2,5-dihydro-1*H*-2-pyrrolethione, predominating in all the solvents used. The time of equilibration decreases when polar solvents are used and varies from several days to several minutes. The following ratios of tautomers were observed after the hydrolysis in $CDCl_3$* solution with distilled water: 75:15:10 in 1 h, 25:70:5 in 24 h, and 14:85:1 in 80 h. The sample color changed from light-yellow to yellowish orange, typical of many thiocarbonyl compounds and particularly expected for the thione **1'a** containing a conjugated double bond system. In acetonitrile, the equilibrium of composition 5:90:5 established in 2 min. In similar studies of 1-methyl-1*H*-2-pyrroleselenol **1b** in CCl_4*, an analogous transformation of this compound to the

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* Acetone d_6 (about 10 vol. %) was added, otherwise the hydrolysis did not proceed.

corresponding selone **1'b** proceeded much faster than the transformation of the thiol **1a**. Thus, 1 minute after the addition of water, the ratio **1b**:**1b'** was 90:10, in 3 min 50:50, and in 220 min 10:90, after that the equilibrium remained unchanged for about 1 hour. Then, evolution of red selenium began with the ratio **1b**:**1'b** increasing to 30:70 indicating an exceptional, or at least, highly preferential decay of selone rather than selenol. 24 h later, 1-methylpyrrole was shown (GLC and ^{1}H NMR) to be the only product of selenium elimination. In polar solvents (acetone, or THF), the evolution of selenium can be observed immediately after the addition of water to the solution of **2b**.

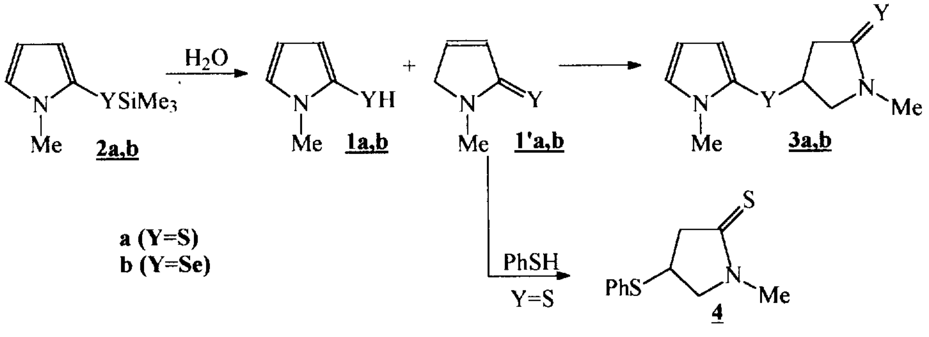
NMR spectra of the studied tautomers have the expected appearance. Thus, δ and J values for the thiol **1a** are very similar to the corresponding parameters of its trimethylsilyl ether **2a**, though an additional interaction of protons in the ring positions 3 and 5 with the SH group is observed in spite of the fact that the SH proton is exchanged with a small quantity of water and trimethylsilanol forming in the course of hydrolysis and appears as a broad signal. A similar interaction was previously observed for pyrrolethiols.[1] Moreover, if the position 3 is occupied with a methyl group the former is also coupled with the SH proton with J = 1.5 Hz.[1]

Multiplicity of the methylene proton signals is the most characteristic feature of the ^{1}H NMR spectra of thiones **1'a** and **1''a**. For example, for the compound **1''a**, one can observe the interaction of methylene protons with vinyl protons only and corresponding multiplicity (dd) at 3.57 ppm. On the other hand, CH_2 group of the thione **1'a** is directly bonded to the NMe fragment therefore its signal (ddq) is additionally coupled with the methyl group protons and appears as an octet due to similar J values. The recorded δ and J values are in good agreement with the corresponding data for 2,3- and 2,5-dihydro-1*H*-2-pyrrolones.[9] The signal at 195.23 ppm in the ^{13}C NMR spectrum of the compound **1'a** indicates the presence of thiocarbonyl group.

Thus, in diluted solutions the thiol **1a** and selenol **1b** predominantly exist as tautomeric 5H-thione and -selone correspondingly, with the latter being unstable and giving 1-methylpyrrole and selenium. Is it possible to isolate this compounds?

We made an attempt to concentrate the hydrolyzed samples under reduced pressure. However, instead of the target compounds **1a,b**, their "dimers" **3a,b** were isolated (**Scheme 2**).

Scheme 2

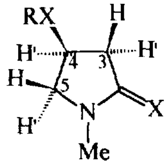


The result was not unexpected, for we had already observed the formation of similar products in our studies of autotransformations of 2-furan-, thiophene- and selenophene thiols and selenols[5]. However, in the earlier studies, the addition of thiol (selenol) to the corresponding 2,5-dihydrothione (selone) was postulated to explain the chemistry of these transformations, whereas here the existence of tautomeric forms of the compounds studied has directly been observed.

When carried out with 5 equivalents of thiophenol, the hydrolysis of the sulfide 2a gives thiolactam 4, the product of the addition of thiophenol to the thion 1'a. Obviously, the same method can be used for the introduction of other substituents into the thiolactam ring position 4. It is interesting to notice that recently a multistep synthesis of 4-organylthio-2-pyrrolidinethiones, to which compounds 2a and 4 also belong, was patented with its key step proposed to be the interaction of 3-organylthio-4- halogenobuturic acids with amines.[10]

Experimental

NMR spectra ($CDCl_3$) were recorded on a Bruker AC-300, 300 MHz instrument and analysed with WinNMR 950801.1 software; GLC-MS and MS spectra were recorded on LKB-2091 spectrometer, 70 eV. Structural fragments in the NMR spectra of the compounds 3a,b and 4 are numbered according to the scheme below.



3a, X = S, R = Het = 1-Me-1*H*-2-pyrrolyl
3b, X = S, R = Het = 1-Me-1*H*-2-pyrrolyl
4, X = S, R = Ph

2-(Trimethylsilylthio)-1-methyl-1*H*-pyrrole 2a. To a solution of 8.9 g (0.11 mol) 1-methylpyrrole in 70 ml THF at room temperature n-BuLi hexane solution (70 ml, 0.1 mol) was added. The solution temperature rose to 35°C within half an hour and was kept at this level for an additional period of 90 min. Then the solution was cooled to -20°C and 3.2 g of sulfur (0.1 mol) was added. After the sulfur dissolved 11.9 g (1.1 mol) of chloro trimethylsilane was added at -40 °C, the temperature was allowed to rise up to room temperature and the mixture was concentrated under reduced pressure. Distillation of the residue from a 250 ml flask (to prevent foaming) afforded 14.2 g (77%) of the compound 2a, b.p. 53°C (0.5 mm Hg); ^1H NMR spectrum, δ, ppm: 0.27s (9H, Me_3Si), 3.61s (3H, MeN), 6.01 dd (1H, H^4), 6.18 dd (1H, H^3), 6.71 dd (1H, H^5), $J_{3,4}$ = 3.60, $J_{3,5}$ = 1.86, $J_{4,5}$ = 2.86 Hz; ^{13}C NMR, δ, ppm: 0.72 ($SiMe_3$), 34.21 (MeN), 107.74 (C-4), 115.56 (C-3), 116.24(C-2), 123.57 (C-5). Anal. Calc. for $C_8H_{15}NSSi$: C 51.84, H 8.16, S 17.30, Si 15.15. Found: C 51.29, H 8.36, S 17.11, Si 14.89. Mass-spectrum, m/z (%): 185 (M^+, 43).

2-(Trimethylsilylseleno)-1-methyl-1*H*-pyrrole 2b. Was synthesised similarly to the compound **1a** (amorphous red selenium was used instead of sulfur) in yield 13.2 g (57%), b.p. 60°C (0.5 mm Hg), ^{1}H NMR spectrum, δ, ppm: 0.34 s (9H, Me_3Si), 3.60 s (3H, MeN), 6.11 dd (1H, H^4), 6.20 dd (1H, H^3), 6.73 dd (1H, H^5), $J_{3,4}$ = 3.57, $J_{3,5}$ = 1.93, $J_{4,5}$ = 2.47 Hz; mass-spectrum, m/z (%): 233 (M^+, 26). Anal. Calc. for $C_8H_{15}NSeSi$: C 41.38, H 6.51, Se 33.98, Si 12.10. Found: C 40.81, H 5.95, Se 33.41, Si 11.83.

NMR Studies of tautomers 1a, 1'a and 1"a mixture. Several drops of freshly distilled sulfide 2a, $CDCl_3$ (0.8 ml), acetone-d_6 (0.1 ml) and a drop of water were vigorously shaken under nitrogen, $MgSO_4$ added, the mixture shaken again and filtered directly into the NMR tube scavenged with nitrogen.

1-Methyl-1*H*-2-pyrrolethiol 1a. ^{1}H NMR spectrum, δ, ppm: 3.0 br.s (1H, SH), 3.60d (3H, Me), 5.98 dd (1H, H^4), 6.23 dd (1H, H^3), 6.70 dddq (1H, H^5), $J_{3,4}$ = 3.62, $J_{3,5}$ = 1.86, $J_{4,5}$ = 2.86, $J_{3,SH}$ = 1.70, $J_{5,SH}$ = 1.15, $J_{5,Me}$ = 0.3 Hz; ^{13}C NMR, δ, ppm: 34.10 (MeN), 107.72 (C-4), 115.42(C-2), 117.28 (C-3), 124.68 (C-5).

1-Methyl-2,5-dihydro-1*H*-2-pyrrolethion 1'a. ^{1}H NMR spectrum, δ, ppm: 3.35t (3H, Me), 6.39 dt (1H, H^3), 7.00 dt (1H, H^4), 4.30 ddq (2H, H^5), $J_{3,4}$ = 5.7, $J_{3,5}$ = -1.76, $J_{4,5}$ = 1.72, $J_{5,Me}$ = 1.0 Hz; ^{13}C NMR, δ, ppm: 33.85 (Me), 62.71 (C-5), 137.61 (C-3), 139.25 (C-4), 195.23(C-2).

1-Methyl-2,3-dihydro-1*H*-2-pyrrolethion 1"a. ^{1}H NMR spectrum, δ, ppm: 3.36 s (3H, Me), 5.68 dt (1H, H^4), 3.57 dd (2H, H^3), 6.58 dt (1H, H^5), $J_{3,4}$ = 2.61, $J_{3,5}$ = -2.0, $J_{4,5}$ = 4.16.

NMR Studies of tautomers 1a, 1'a and 1"a mixture (carried out on a Varian VXR90, 90 MHz instrument). Into an NMR tube constantly scavenged with a slow nitrogen current, CCl_4 (0.5 ml) containing about 10% of acetone-d_6, compound 2b (50 µl) and water (10 µl) were introduced, the tube closed, vigorously shaken and spectra recorded without removing the rest of unreacted water. The δ and J values for compounds 1b and 1'b were equal, within the limits of experimental error, to those of sulfur containing analogues 1a and 1'a.

1-Methyl-4-[(1-methyl-1*H*-2-pyrrolyl)thio]-2-pyrrolidinethione 3a. To a solution of sulfide 2a (9.25 g, 0.05 mol) in THF (10 ml) 0.001 N HCl (0.5 ml) was added, the mixture was concentrated under reduced pressure, allowed to stay for 48 h, the resulting viscous dark oil was dissolved in a small amount of chloroform and purified by flash chromatography (neutral Al_2O_3, pentane-ether, 3:1) to give yellow crystals of dimer 3a (4.97 g, 88%), m.p. 75 °C; ^{1}H NMR spectrum, δ, ppm: 2.92 ddq (1H, H^3, $J_{3'}$ = 18.1, $J_{4'}$ = 4.8, J_{Me} = 0.5 Hz), 3.2 dd (3H, Me, $J_{3'}$ = 1.1 Hz), 3.26 ddq (1H, $H^{3'}$, $J_{4'}$ = 7.9 Hz), 3.52 m (1H, $H^{4'}$), 3.65 dd (1H, H^5; $J_{5'}$ = 12.0, $J_{4'}$ = 4.3 Hz), 3.69 s (3H, Me_{Het}) 3.91 dd (1H, $H^{5'}$, $J_{4'}$ = 7.1 Hz); ^{13}C NMR, δ, ppm: 33.87 (Me_{Het}), 34.94 (Me), 40.46 (C-4), 50.10 (C-3), 61.52 (C-5), 108.08 (C-4_{Het}), 117.27 (C-2_{Het}), 119.35 (C-3_{Het}), 125.89 (C-5_{Het}), 198.30 (C-2). Mass-spectrum, m/z (%): 226 (M^+, 59), 114 ($C_5H_8NS^+$, 87), 81 ($C_4H_4N^+$, 100). Anal. Calc. for $C_{10}H_{14}N_2S_2$: C 53.06, H 6.23, N 12.38, S 28.33. Found: C 53.25, H 6.46, N 12.0, S 29.11.

1-Methyl-4-|(1-methyl-1*H*-2-pyrrolyl)seleno|-2-pyrrolidineselone **3b**. Selenide **2b** (2.34 g, 0.01 mol) was hydrolysed under nitrogen with 0.001 *N* HCl (0.1 ml) in THF (2 ml), the mixture was immediately concentrated under reduced pressure, allowed to stay for 48 h under normal pressure of N_2 and finally in vacuum (0.5 mm Hg) for 3 hours at 35 °C to give **3b** (3.2 g, 100%) as a brown oil which was analysed without additional purification (under the chromatography conditions similarly to those for compound **3a**, an evolution of Se was observed). ^{1}H NMR spectrum, δ, ppm: 3.01 ddq (1H, H^3, $J_{3'} = 19.0$, $J_{4'} = 4.8$, $J_{Me} = 1.1$ Hz), 3.2 m (3H, Me, $J_{3'} = 1.3$ Hz), 3.30 ddq (1H, $H^{3'}$, $J_{4'} = 7.6$ Hz), 3.5-3.74 m (2H, $H^{4'}$, H^5), 3.68 s (3H, Me_{Het}) 3.89 dd (1H, $H^{5'}$, $J_{4'} = 6.9$, $J_5 = 12.2$ Hz), 6.13 dd (1H, $H^4{}_{Het}$), 6.40 dd (1H, $H^3{}_{Het}$), 6.89 dd (1H, $H^5{}_{Het}$), $J_{Het} = J_{3,4} = 3.62$, $J_{3,5} = 1.78$, $J_{4,5} = 2.82$ Hz; ^{13}C NMR, δ, ppm: 33.44, 35.50, 37.85, 55.69, 63.99, 108.77 (C-4_{Het}), 112.25(C-2_{Het}), 120.93 (C-3_{Het}), 126.22 (C-5_{Het}), 200.61 (C-2). Mass-spectrum, m/z (%): 322 (M^+, 14). Anal. Calc. for $C_{10}H_{14}N_2Se_2$: C 37.53, H 4.41, Se 49.31 Found: C 38.76, H 4.47, Se 47.73.

1-Methyl-4-(phenylthio)-2-pyrrolidinethione **4**. To a solution of sulfide **2a** (4.62 g, 0.025 mol) in THF (10 ml) 0.001 *N* HCl (0.25 ml) and thiophenol (5.5 g, 0.05 mol) was added, the mixture was refluxed for 4 hours, concentrated under reduced pressure and distilled in vacuum to yield the compound **4** (4.35 g, 78%) as a viscous brown oil, b.p. 170-180 °C (0.5 mm Hg) containing, according to NMR data, an admixture of dimer **3a** (about 5%); ^{1}H NMR spectrum, δ, ppm: 3.03 ddq (1H, H^3, $J_{3'} = 18.2$, $J_{4'} = 4.9$, $J_{Me} = 1.0$ Hz), 3.2 dd (3H, Me, $J_{3'} = 1.1$ Hz), 3.40 ddq (1H, $H^{3'}$, $J_{4'} = 8.2$ Hz), 3.91 m (1H, $H^{4'}$), 3.66 dd (1H, H^5; $J_{5'} = 11.8$, $J_{4'} = 4.3$ Hz), 4.05 dd (1H, $H^{5'}$, $J_{4'} = 7.3$ Hz), 7.2 - 7.5 m (5H, Ph); ^{13}C NMR, δ, ppm: 34.87 (Me), 38.71 (C-4), 50.62 (C-3), 62.36 (C-5), 127.37 (C-4_{Ph}), 128.91 (C-3_{Ph}), 131.39 (C-2_{Ph}), 132.88 (C-1_{Ph}), 198.20 (C-2). Mass-spectrum, m/z (%): 223(M^+, 68). Anal. Calc. for $C_{11}H_{13}NS_2$: C 59.15, H 5.87, N 6.27, S 28.71. Found: C 58.86, H 5.26, N 6.67, S 27.95

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