Regioselective synthesis of pentathiepines fused with pyrrole, thiophene, or indole rings*

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Pentathiepines fused with pyrrole, thiophene, or indole rings were obtained by reactions of the corresponding heterocycles or their tetrahydro derivatives with a prepared mixture of sulfur monochloride and DABCO.

Key words: thiophenes, furans, indoles, sulfur monochloride, 1,2,3,4,5-pentathiepines, 1,4-diazabicyclo[2.2.2]octane.

1,2,3,4,5-Pentathiepines are important sulfur-containing heterocyclic compounds.[1] In recent years, 1,2,3,4,5-pentathiepines have attracted great interest as anticancer, antimycotic, and antiseptic drugs.[1—3] In addition, 1,2,3,4,5-pentathiepines can be used in engineering applications; for instance, 6-methyl-6*H*-[1,2,3,4,5]pentathiepino[6,7-*b*]indole we have synthesized earlier[4] is proposed as a cathodic material.[5] 1,2,3,4,5-Pentathiepines are also starting reagents for the synthesis of a variety of polysulfur-containing compounds such as 1,4-dithiines, 1,2,4,5-tetrathiocines, 1,3-dithioles, vicinal 1,2-dimercapto derivatives, *etc*.

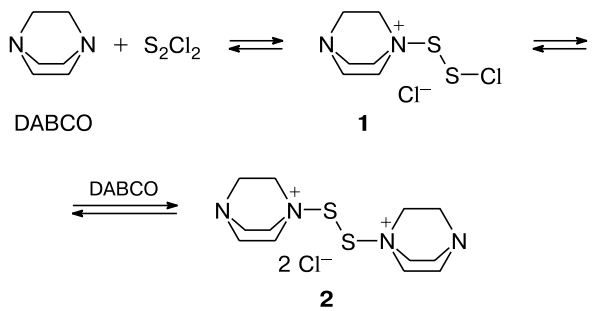
Among both natural and synthetic pentathiepines, benzopentathiepine and its derivatives are most familiar. Natural representatives (varacin, lissoclinotoxin A, and *N*,*N*-dimethyl-5-(methylthio)varacin) exhibit antiseptic and antimycotic properties, selectively inhibit kinase C, and have anticancer activity.[1] However, despite constant attention of the researchers to compounds of this class, one can state that the current methods for the synthesis of 1,2,3,4,5-pentathiepines, especially those fused with heterocycles, are underdeveloped.

Recently,[6,7] we have found that a wide range of pentathiepines fused with such nitrogen-containing heterocycles as pyrroles and indoles can be obtained by reactions of these five-membered nucleophilic heterocycles and their tetrahydro derivatives with sulfur monochloride and 1,4-diazabicyclo[2.2.2]octane (DABCO) in chloroform at 20 °C. However, if a nucleophilic heterocycle contains more than one bond for the formation of a pentathiepine ring, these reactions are not regioselective and their outcomes depend on the nature of the heterocycle and the reaction conditions.[6]

Earlier,[8] we have reported that the outcomes of the reactions can depend on the order of mixing the reagents. For instance, if a prepared mixture of sulfur monochloride and DABCO is kept for a while before addition of a heterocycle, then pyrrolidines and indoles selectively give β-annulated pentathiepine derivatives in moderate yields. Here we studied this reaction systematically to optimize its conditions and extend the range of suitable heterocycles for this transformation.

We assumed that the reaction of sulfur monochloride with DABCO gives rise to some reactive intermediates. To verify this assumption, we investigated mixtures of sulfur monochloride and DABCO with different concentrations and different ratios of the reagents by IR spectroscopy. We found that when sulfur monochloride (1 mol) and DABCO (1 mol) are mixed and kept at room temperature for 1 h, the band of the S—S bond shifts to the longer wavelengths (from 540 to 584 cm^{-1}), while the bands due to the S—Cl bond (436 and 452 cm^{-1}) remain unchanged. We attributed these changes to the formation of 1-(chlorodisulfanyl)-4-aza-1-azoniabicyclo[2.2.2]octane chloride (**1**) (Scheme 1). When the second mole of

Scheme 1



* Dedicated to Academician O. M. Nefedov on the occasion of his 75th birthday.

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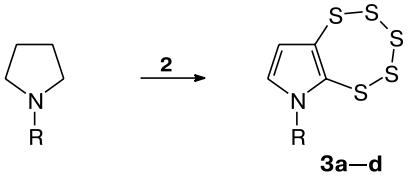
DABCO is added, the bands of the S—Cl bond disappear; this suggests the formation of a new compound, namely, bis(4-aza-1-azoniabicyclo[2.2.2]oct-1-yl) disulfide dichloride (**2**). It should be noted that compounds **1** and **2** are unstable, decomposing into sulfur and DABCO hydrochloride on attempted isolation from their solutions in chloroform and upon storage of these solutions at room temperature for several days. Obviously, compound **2**, in contrast to sulfur monochloride and compound **1**, should mainly exhibit the sulfurating rather than chlorinating ability; for this reason, we used only compound **2** in subsequent transformations.

Indeed, the reactions of all the *N*-alkylpyrrolidines we studied with a fivefold excess of compound **2** selectively gave monopentathiepines **3a**—**d** in moderate yields (Scheme 2); no chlorinated products were detected in any of the reactions.

Scheme 2



3a—d

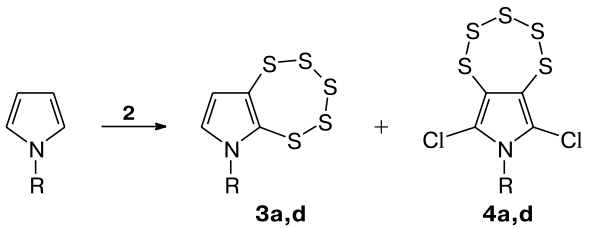
Conditions: 48 h, 20 °C.

Compound	R	Yield (%)	Compound	R	Yield
a	Me	29	**c**	Pr^i	30
b	Et	31	**d**	Bu^t	61

The new compounds obtained were characterized by data from elemental analysis and physicochemical methods (NMR spectroscopy, mass spectrometry, and high-resolution mass spectrometry). The location of the pentathiepine ring was determined from the presence of the classic AB system (J = 2.6—3.0 Hz) in the ^{1}H NMR spectra. The highest yield was reached for *tert*-butyl derivative **3d**; this is probably due to steric hindrances that prevent electrophilic species from attacking the α-position of the pyrrole ring (which is shared by the pentathiepine fragment) to decompose such compounds.

N-Methyl- and *N*-*tert*-butylpyrroles under the conditions optimized for pyrrolidines (fivefold excess of reagent **2**, 48 h, ~20 °C) yielded two types of products: pentathiepines **3a,d** and chlorinated products **4a,d**. Apparently, the formation of dichloropentathiepines **4a,d** is favored by the excess of reagent **2**. To verify our assumption, we carried out reactions with a lower amount of reagent **2** (threefold excess) and selectively obtained monopentathiepines **3a** and **3d** (Scheme 3). Their yields were comparable with the yields of these products from pyrrolidines.

Scheme 3



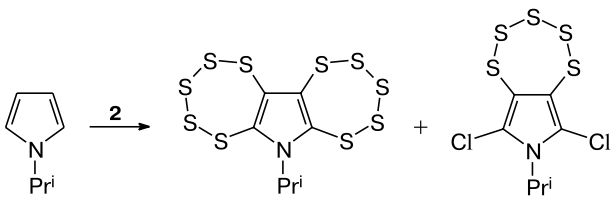
3a,d **4a,d**

Conditions: 48 h, 20 °C. R = Me (**a**), Bu^t (**d**)

Excess	Yields of the products
Fivefold	23% (**3a**) + 6% (**4a**) 14% (**3d**) + 17% (**4d**)
Threefold	33% (**3a**) 44% (**3d**)

A room-temperature reaction of *N*-isopropylpyrrole with reagent **2** gave a mixture of bispentathiepine **5** and dichloropentathiepine **4c** in an approximately equal proportions, while the same reaction at 0 °C selectively afforded bispentathiepine **5**, the total yield remaining virtually unchanged (Scheme 4).

Scheme 4

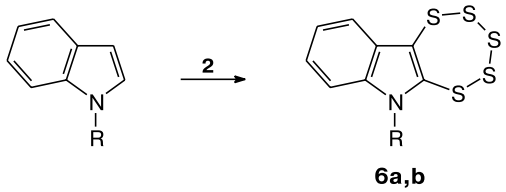


5 **4c**

T/°C	Yields of the products
20	15% (**5**) + 18% (**4c**)
0	33% (**5**)

N-Methyl- and *N*-ethylindoles reacted with a fivefold excess of reagent **2** to give pentathiepines **6** in 51 and 62% yields, respectively (Scheme 5), while the reaction with a mixture of sulfur monochloride and DABCO gives dichloroindoles.[6]

Scheme 5



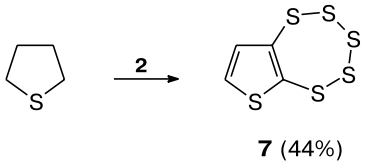
6a,b

R = Me (**a**), Et (**b**)

Conditions and yields: 48 h, 20 °C; 51% (**6a**), 62% (**6b**).

We studied reactions of reagent **2** with other heterocyclic compounds. Thiophene, furan, or benzo[*b*]thiophene did not react with compound **2**. Tetrahydrothiophene reacted with reagent **2** to give pentathiepine **7** in rather good yield (Scheme 6).

Scheme 6



Conditions: 48 h, 20 °C.

To estimate the reactivity of reagent **2**, we used heterocyclic compounds in the reaction with S_2Cl_2 and DABCO (1 : 1) in chloroform at 20 °C without preliminary mixing and keeping of the reagents. These reactions with *N*-alkylpyrrolidines gave dichloropentathiepines **4** in slightly lower yields along with pentathiepine **3a**, chloropentathiepine **8**, and bispentathiepine **5** (Scheme 7).[6] It has also been demonstrated that pentathiepines **3**, **5**, and **8** are intermediates in the synthesis of final dichloropentathiepines **4**.

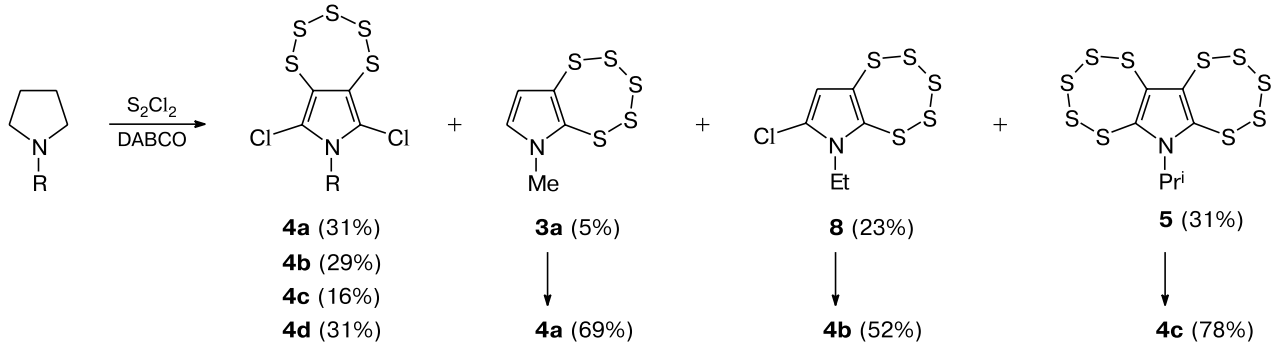
As noted above, *N*-alkylindoles react with a mixture of S_2Cl_2 and DABCO to give only the corresponding dichloroindoles in high yields, while thiophene and tetrahydrothiophene yield an inseparable mixture of oligomers.[6]

Thus, the reaction with reagent **2** we synthesized is more selective than the reaction with a mixture of S_2Cl_2 and DABCO.

Let us consider a possible mechanism of this reaction with *N*-methylpyrrolidine as an example. The key steps are aromatization of the saturated heterocycle and the formation of a β-annulated pentathiepine ring.

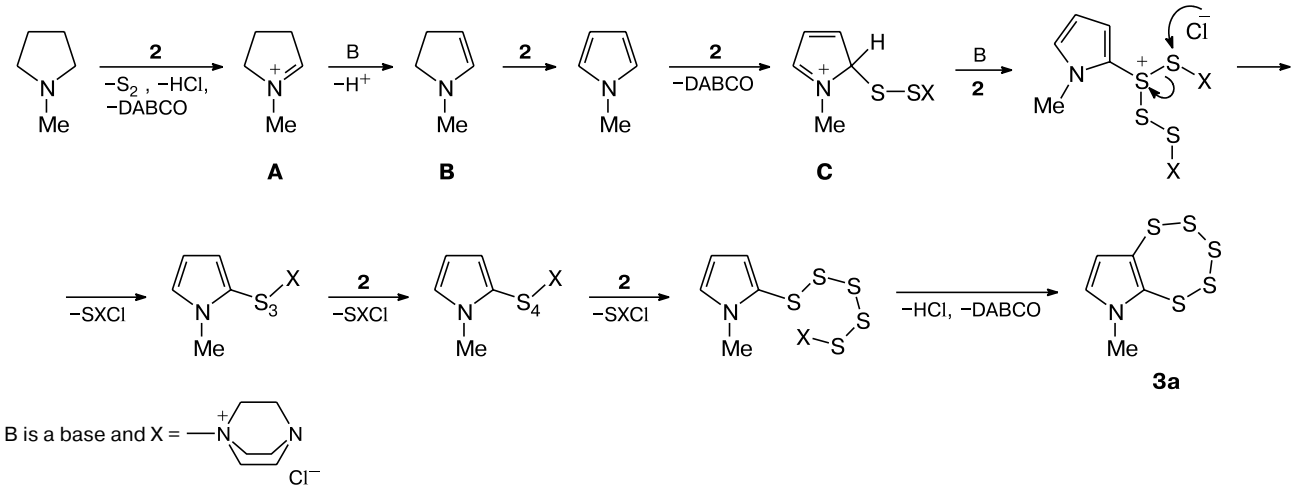
According to the mechanism we proposed (Scheme 8), *N*-methylpyrrolidine is first oxidized with reagent **2**

Scheme 7



R = Me (**a**), Et (**b**), Pr^i (**c**), Bu^t (**d**)

Scheme 8



into immonium salt **A**, which then is transformed into enamine **B** under the action of a base.[9] When repeated, this process yields *N*-methylpyrrole. This is followed by electrophilic addition of reagent **2** to position 2 of the heterocycle, giving rise to cation **C**. Then, the chain $-S_nX$ can be extended, through addition of reagent **2** and the loss of SXCl, to the chain $-S_{(n+1)}X$ and, finally, to the thermodynamically stable pentathiepine ring in compound **3a**.

Experimental

^{1}H NMR spectra were recorded on Bruker WM-250 and Bruker AM-300 instruments (250 and 300 MHz, respectively) in $CDCl_3$. Chemical shifts are given on the δ scale with reference to Me_4Si. Melting points were determined on a Kofler instrument and are given uncorrected. Mass spectra were recorded on a Finnigan MAT INCOS 50 instrument (EI); high-resolution mass spectra were recorded on a VG Autospec Q instrument.

Bis(4-aza-1-azoniabicyclo[2.2.2]oct-1-yl) disulfide dichloride (2). Sulfur monochloride (2 mL, 25 mmol) was added dropwise under argon at −35 to −25 °C to a solution of DABCO (5.6 g, 50 mmol) in chloroform (150 mL). The reaction mixture was stirred at ~20 °C for 1 h.

IR (5% solution of compound **2** in $CHCl_3$, $d = 0.058$, KBr), ν_{max}/cm^{-1}: 2960, 2892, 2744, 2504, 2316, 1484, 1464, 1436, 1320, 1244, 1210, 1056, 836, 792, 724, 664, 596.

Synthesis of pentathiepines (general procedure). A solution of a heterocycle (5 mmol; for *N*-methyl- or *N*-*tert*-butylpyrrole, the charge was 16.6 mmol) in chloroform (20 mL) was added dropwise at −25 to −10 °C to the solution of reagent **2**. The reaction mixture was kept under argon at ~20 °C (for *N*-isopropylpyrrole, at 0 °C) for 48 h and filtered. The precipitate was washed with CH_2Cl_2. The combined mother liquor was concentrated under reduced pressure and the residue was chromatographed on silica gel 60 (Merck) with CH_2Cl_2—light petroleum as an eluent.

The spectroscopic characteristics of compounds **3a**, **4a—d**, **5**, and **7** agreed with the literature data.[6]

6-Ethyl-6*H*-[1,2,3,4,5]pentathiepino[6,7-*b*]pyrrole (3b), a yellow oil. Found (%): C, 28.25; H, 2.64; N, 5.14. $C_6H_7NS_5$. Calculated (%): C, 28.44; H, 2.78; N, 5.53. ^{1}H NMR ($CDCl_3$), δ: 1.42 (t, 3 H, CH_3, $J = 6.8$ Hz); 4.11 (q, 2 H, CH_2, $J = 6.8$ Hz); 6.45, 6.58 (both d, 1 H each, CH, $J = 3.0$ Hz). ^{13}C NMR ($CDCl_3$), δ: 17.31 (CH_3); 43.87 (CH_2); 115.47, 122.22 (2 CH); 128.22, 131.72 (sp^2 of the quaternary C atoms). MS (EI, 70 eV), m/z (I_{rel} (%)): 253 $[M]^+$ (13), 221 (2), 189 $[M - S_2]$ (100), 156 (26), 128 (26). Found: m/z 252.9181 $[M]^+$. $C_6H_7NS_5$. Calculated: 252.9182.

6-Isopropyl-6*H*-[1,2,3,4,5]pentathiepino[6,7-*b*]pyrrole (3c), a yellow oil. Found (%): C, 31.68; H, 3.53; N, 4.94. $C_7H_9NS_5$. Calculated (%): C, 31.44; H, 3.39; N, 5.24. ^{1}H NMR ($CDCl_3$), δ: 1.40 (d, 3 H, 2 CH_3, $J = 6.8$ Hz); 4.80 (septet, 1 H, CH, $J = 6.8$ Hz); 6.48, 6.65 (both d, 1 H each, CH, $J = 2.8$ Hz). ^{13}C NMR ($CDCl_3$), δ: 23.85, 24.00 (2 CH_3); 49.74 (CH); 115.67, 118.80 (2 CH); 127.74, 131.80 (sp^2 of the quaternary C atoms). MS (EI, 70 eV), m/z (I_{rel} (%)): 267 $[M]^+$ (15), 235 (2), 203 $[M - S_2]$ (75), 161 (95), 138 (24), 128 (74). Found: m/z 266.9331 $[M]^+$. $C_7H_9NS_5$. Calculated: 266.9338.

6-*tert*-Butyl-6*H*-[1,2,3,4,5]pentathiepino[6,7-*b*]pyrrole (3d), a yellow oil. Found (%): C, 34.37; H, 3.86; N, 5.26. $C_8H_{11}NS_5$. Calculated (%): C, 34.14; H, 3.94; N, 4.98. ^{1}H NMR ($CDCl_3$), δ: 1.71 (s, 9 H, 3 CH_3); 6.39, 6.71 (both d, 1 H each, CH, $J = 2.9$ Hz). ^{13}C NMR ($CDCl_3$), δ: 31.31 (CH_3); 59.43 ($\underline{C}$—$(CH_3)_3$); 114.18, 121.03 (2 CH); 130.88, 131.84 (sp^2 of the quaternary C atoms). MS (EI, 70 eV), m/z (I_{rel} (%)): 281 $[M]^+$ (21), 253 (7), 217 $[M - S_2]$ (93), 161 (100). Found: m/z 280.9490 $[M]^+$. $C_8H_{11}NS_5$. Calculated: 280.9495.

6-Methyl-6*H*-[1,2,3,4,5]pentathiepino[6,7-*b*]indole (6a), yellow crystals, m.p. 123—125 °C. Found (%): C, 37.55; H, 2.34; N, 4.91. $C_9H_7NS_5$. Calculated (%): C, 37.32; H, 2.44; N, 4.87. ^{1}H NMR ($CDCl_3$), δ: 3.91 (s, 3 H, CH_3); 7.30 (m, 3 H, PhH); 7.70 (m, 1 H, PhH). ^{13}C NMR, δ: 32.10 (CH_3); 111.06, 119.61, 122.70, 125.22 (4 CH); 126.01, 129.47, 137.08, 141.84 (sp^2 of the quaternary C atoms). MS (EI, 70 eV), m/z (I_{rel} (%)): 289 $[M]^+$ (22), 225 $[M - S_2]$ (100), 192 (42).

6-Ethyl-6*H*-[1,2,3,4,5]pentathiepino[6,7-*b*]indole (6b), yellow crystals, m.p. 95—97 °C. Found (%): C, 39.32; H, 3.04; N, 4.85. $C_{10}H_9NS_5$. Calculated (%): C, 39.61; H, 3.10; N, 4.62. ^{1}H NMR ($CDCl_3$), δ: 1.42 (t, 3 H, CH_3, $J = 7.5$ Hz); 4.40 (q, 2 H, CH_2, $J = 7.5$ Hz); 7.29 (m, 3 H, PhH); 7.73 (m, 1 H, PhH). ^{13}C NMR ($CDCl_3$), δ: 16.10 (CH_3); 39.94 (CH_2); 110.31, 120.60, 121.92, 124.47 (4 CH); 119.05, 129.07, 135.29, 140.37 (sp^2 of the quaternary C atoms). MS (EI, 70 eV), m/z (I_{rel} (%)): 303 $[M]^+$ (28), 239 $[M - S_2]$ (100), 206 (42), 64 (46). Found: m/z 302.9352 $[M]^+$. $C_{10}H_9NS_5$. Calculated: 302.9339.

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