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Unprecedented Conversion of Triethylamine and Disulfur Dichloride into a Thienopentathiepin and a Heptathiocane

Lidia S. Konstantinova,[†] Oleg A. Rakitin,*[,†] Charles W. Rees,*[,‡] Ljudmila I. Souvorova,[†] Denis G. Golovanov,[§] and Konstantin A. Lyssenko[§]

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninsky Prospect, 47, 119991 Moscow, Russia, Department of Chemistry, Imperial College of Science, Technology and Medicine, London, UK SW7 2AY, and A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, Vavilov Str., 28, 119991 Moscow, Russia

orakitin@ioc.ac.ru

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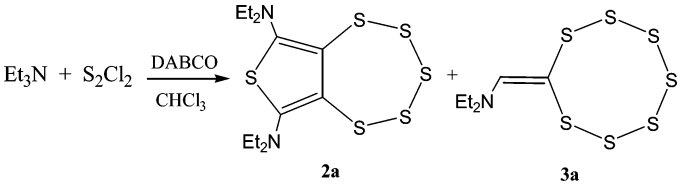
ABSTRACT



In a remarkable cascade reaction, triethylamine is converted into the thienopentathiepin 2a and the heptathiocane 3a by a preequilibrated solution of disulfur dichloride and DABCO in chloroform.

We have shown that when tertiary aliphatic amines are treated with disulfur dichloride and DABCO in chloroform, *N*-isopropyl groups react faster than ethyl groups to give a variety of monocyclic,[1] bicyclic,[2] and fused tricyclic 1,2-dithioles[3] in one-pot reactions. However, at lower temperatures (0 °C), followed by quenching with formic acid, *N*-ethyl groups react faster than isopropyl to give di- and tri-chloroacetyl derivatives.[4] We assumed that in these reactions, a complex between S_2Cl_2 and DABCO such as **1** was probably a key intermediate, and we then hoped to increase reaction yields by preforming this complex.

Thus, equimolar amounts of S_2Cl_2 and DABCO were stirred in chloroform at 0 °C for 48 h since this reaction is much slower than that of S_2Cl_2 with triethylamine. The S_2Cl_2−DABCO solution thus formed retained its activity for a few days at 0 °C. Addition of triethylamine after 48 h at 0 °C, followed by refluxing for 2 h, gave two entirely new and unexpected products, **2a** and **3a** (Scheme 1), different from all those produced when the reagents were not premixed.

Compound **2a** (up to 30% yield) is a yellow oil, $C_{12}H_{20}N_2S_6$, showing an *N*-ethyl group and two different sp^2 carbons in

[†] N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences.

[‡] Imperial College of Science, Technology and Medicine.

[§] Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences.

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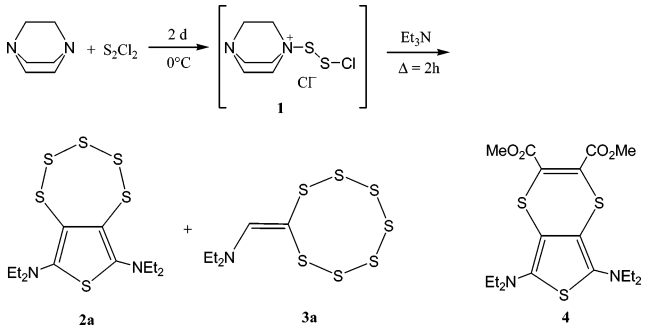
Scheme 1



the ^{1}H and ^{13}C NMR spectra. Thus, two triethylamines had combined with all the hydrogens of two ethyl groups being replaced by six sulfur atoms, leaving four identical ethyl groups. High symmetry and the striking stability of the polysulfur array suggested a thienopentathiepin structure **2a**; this was supported by the major loss of S_2 in the mass spectrum characteristic of pentathiepins[5] and by the mild reaction of **2a** with DMAD and triphenylphosphine in DCM at room temperature to give the 1,4-dithiin **4** (78%), mp 96−98 °C, characteristic of pentathiepins.[6] Structure **2a** was proved by an X-ray structure determination of a closely related analogue **2f** (Figure 2).

Compound **3a**, yellow crystals, mp 72−73 °C, $C_6H_{11}NS_7$, showed in its ^{1}H and ^{13}C NMR spectra an *N*-ethyl group, a vinylic hydrogen, and two sp^2 carbons. Thus, four hydrogens of one ethyl group of triethylamine had been replaced by seven sulfur atoms. The rare heptathiocane ring structure **3a** was proved by X-ray crystallography (Figure 1).

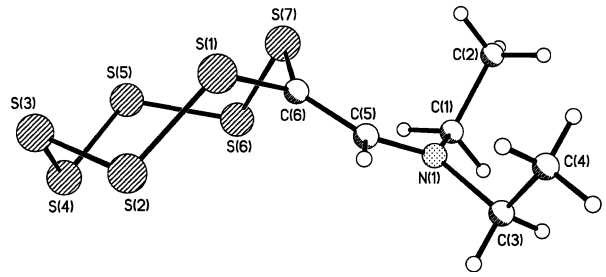


Figure 1. X-ray structure of molecule **3a**. Selected bond lengths (Å) and bond angles (°): S(1)−C(6) 1.756(5), S(1)−S(2) 2.062(1), S(2)−S(3) 2.040(2), S(3)−S(4) 2.031(2), S(4)−S(5) 2.043(2), S(5)−S(6) 2.042(2), S(6)−S(7) 2.068(2), S(7)−C(6) 1.734(4), C(5)−N(1) 1.327(1), C(5)−C(6) 1.372(1), C(6)−S(1)−S(2) 109.75(1), S(3)−S(2)−S(1) 108.50(7), S(4)−S(3)−S(2) 107.98(8), S(3)−S(4)−S(5) 107.70(8), S(4)−S(5)−S(6) 108.35-(9), S(5)−S(6)−S(7) 108.45(10), C(6)−S(7)−S(6) 107.71(15), N(1)−C(5)−C(6) 134.3(5), C(5)−C(6)−S(7) 127.7(4), C(5)C(6)−S(1) 115.0(3), S(7)−C(6)−S(1) 116.7(3).

This unprecedented conversion (Scheme 1) of triethylamine into pentathiepin **2a**, in which a thiophene ring is created from two *N*-ethyl groups with the formation of a carbon−carbon bond between unactivated methyl groups, and into the heptathiocane **3a** was investigated further. The two products were not interconverted under the reaction conditions and were presumably formed in simultaneous, competing reactions. An equimolar ratio of S_2Cl_2, DABCO, and Et_3N gave **2a** (23%) and **3a** (10%); a 2-fold excess of Et_3N gave more **2a** (30%) and less **3a** (4%), and a higher concentration of Et_3N suppressed the yields of **3a** still further, as might be expected.

Given that these are reactions of the ethyl group, Et_3N should be a favored substrate; the same reactions were observed with other tertiary *N*-ethylamines but in lower yields. Diethyl *n*-propylamine **5b**, ethyldiisopropylamine **5c**, benzyldiethylamine **5d**, dibenzylethylamine **5e**, and *N*-ethylpiperidine **5f** all gave corresponding thienopentathiepins **2b**−**f** (1−28%) analogous to **2a**; three of the amines, **5b**−**d**, gave corresponding heptathiocanes **3b**−**d** (3−10%) analogous to **3a**. The former products were closely related spectroscopically to **2a** and the latter to **3a**. The structure of the bispiperidinothienopentathiepin **2f** was confirmed by X-ray diffraction (Figure 2). While the yields of products **2** and **3** were mostly low, they are readily prepared in one pot from cheap starting materials.[7]

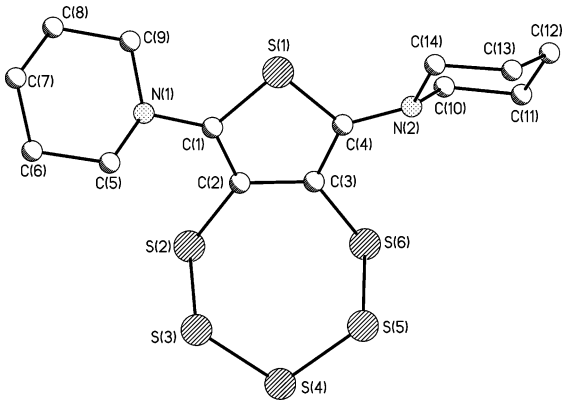


Figure 2. X-ray structure of molecule **2f**. Selected bond lengths (Å) and bond angles (°): S(1)−C(1) 1.746(2), S(1)−C(4) 1.750(2), S(2)−C(2) 1.748(2), S(2)−S(3) 2.065(1), S(3)−S(4) 2.046(1), S(4)−S(5) 2.049(1), S(5)−S(6) 2.049(1), S(6)−C(3) 1.754(2), N(1)−C(1) 1.390(2), N(2)−C(4) 1.383(2), C(1)−C(2) 1.374(2), C(2)−C(3) 1.444(2), C(3)−C(4) 1.365(2), C(1)−S(1)−C(4) 92.75(7), C(2)−S(2)−S(3) 104.03(5), S(4)−S(3)−S(2) 104.67(3), S(3)−S(4)−S(5) 104.19(3), S(4)−S(5)−S(6) 104.55(3), C(3)−S(6)−S(5) 103.69(5), C(2)−C(1)−S(1) 110.3(1), C(1)−C(2)−C(3) 113.0(1), C(1)−C(2)−S(2) 123.3(1), C(3)−C(2)−S(2) 123.6(1), C(4)−C(3)−C(2) 113.7(1), C(4)−C(3)−S(6) 121.6(1), C(2)−C(3)−S(6) 124.7(1), C(3)−C(4)−S(1) 110.2(1).

The heptathiocane and pentathiepin rings have the expected crown and chair-type conformations, respectively. The S−S bond lengths vary in the narrow range of 2.046(1)−

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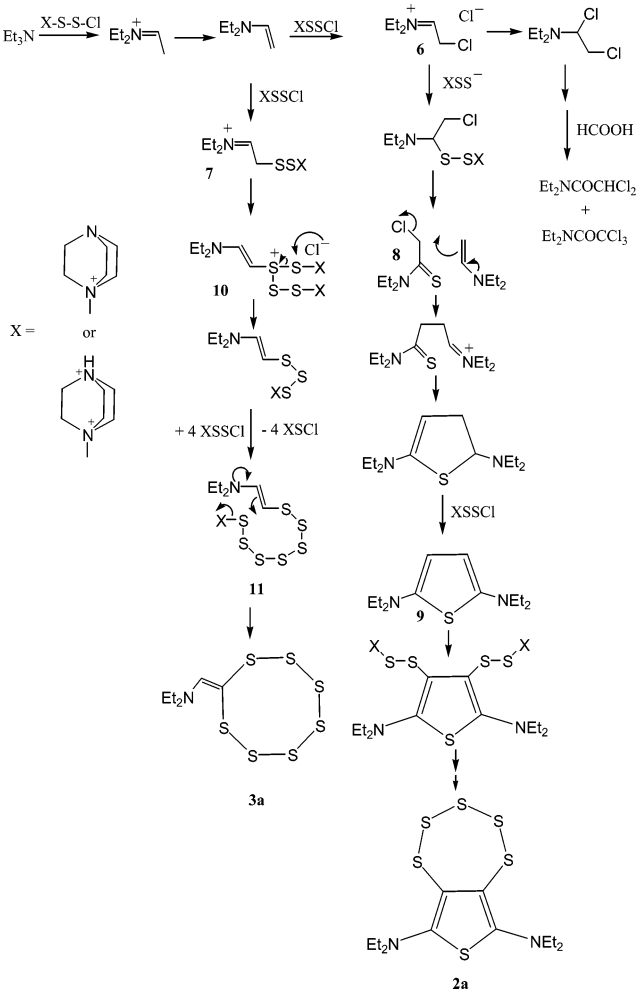
2.065(1) and 2.031(2)−2.068(2) Å in the crystal structures of **2f** and **3a**, respectively. Despite some lengthening of S−S bonds in the case of **2f**, the above lengths are within the range of known values for pentathiepins.[6]

In general, the geometry of **2f** is quite close to other pentathiepins with only some elongation of the thiophen C−S bonds presumably resulting from the presence of piperidyl substituents. The enamine nitrogen in **3a** is planar, the significant elongation of the C(5)−C(6) bond (1.372(7) Å) and shortening of the C(5)−N(1) bond (1.327(7) Å) giving further support to the enamine delocalization.

The conversions of Et_3N into pentathiepin **2a** and heptathiocane **3a** both involve an oxidative reaction of one ethyl group together with several other transformations. For the earlier reactions,[1−4] we proposed that the *N*-alkyl group was oxidized by S_2Cl_2 or by S_2Cl_2 activated by complexation with DABCO (as for example in **1**) to give an iminium ion that equilibrated with an enamine that was chlorinated (see first steps of Scheme 2). This sequence could be repeated to give, after hydrolysis, the di- and trichloroacetyl derivatives.[4] In the present reactions, these intermediates were partly diverted to form the sulfur-rich products **2** and **3**, though the chloroacetyl derivatives could still be isolated if the reaction mixture was heated with formic acid as before.[4] Presumably a new reactive species is formed from S_2Cl_2 and DABCO during the premixing stage; if this is the 1:1 complex **1**, then S_2Cl_2 itself may have been dominant in the earlier reactions. Alternatively, the long premixing period may have led to more extensive complexation of S_2Cl_2 and DABCO to form 1:2 or oligomeric complexes or to the decomposition of **1**, possibly to SCl_2 and the *N*-sulfide of DABCO. The latter could decompose to DABCO and S_2 or other highly reactive S_n species that could become incorporated into the polysulfur products observed. For the present, we suggest one possible mechanistic scheme, shown for triethylamine (Scheme 2), but other similar sequences can be envisaged.

The enamine could react with the complex X−S−S−Cl at chlorine to give **6** or at sulfur to give **7**. Further chlorination of **6** would lead to the chloroacetyl derivatives mentioned above;[4] however, **6** could also yield the thioamide **8**, and the reaction of this with the enamine followed by cyclization and oxidation would give the diaminothiophene **9**. Conversion of **9** into the pentathiepin **2a** follows reasonably from earlier work.[8] The enamine intermediate derived from **7** could react again with the complex at sulfur via its β-carbon (not shown) or to give **10** and hence extend the polysulfur chain, which when it contains seven sulfur atoms can cyclize to the heptathiocane **3a**. Incorporation of only one carbon into the heterocyclic ring from the ethyl group

Scheme 2



rather than both (to give a stable pentathiepin, for example) is presumably controlled by the enamine reactivity **11**. The two products isolated, **2a** and **3a**, are probably the most stable members of polysulfur rings containing two and one sp^2 carbons, respectively.

The stoichiometries of these reactions are not yet known; yields are based on S_2Cl_2 since triethylamine is in excess. On the basis of above mechanism, 4 and 7 mol of S_2Cl_2 and DABCO, respectively, are required for the conversion of 1 mol of Et_3N into **2a** and **3a**.

Thus, a range of rare thienopentathiepins **2** and dialkylaminomethylene heptathiocanes **3** are readily prepared, though in low yield, in an unprecedented one-pot reaction from simple starting materials. These products are particularly interesting since benzopentathiepins with aminoalkyl side chains, including the natural products varacin and the lissoclinotoxins, are cytotoxic, antibacterial, and antifungal and have thiol-dependent DNA cleaving ability.[9]

Acknowledgment. We gratefully acknowledge financial support from the Royal Society, MDL Information Systems

(7) **Typical Experimental Procedure.** Disulfur dichloride (100 mmol) was added dropwise at −15 to −20 °C to a stirred solution of DABCO (100 mmol) in chloroform. The mixture was stirred at 0 °C for 48 h. The corresponding amine (200 mmol) was added; the mixture was refluxed for 2 h and filtered, and solvents were evaporated. The residue was separated by column chromatography (Silica gel Merck 60, light petroleum and then light petroleum−CH_2Cl_2 mixtures). Thienopentathiepins **2** and heptathiocanes **3** were isolated with the yields indicated: **2a** (30%), **2b** (2%), **2c** (1%), **2d** (28%), **2e** (21%), **2f** (8%), **3a** (4%), **3b** (3%), **3c** (10%), and **3d** (3%).

(8) Konstantinova, L. S.; Rakitin, O. A.; Rees C. W. *Chem. Commun*. **2002**, 1204.

(9) Greer A. *J. Am. Chem. Soc*. **2001**, *113*, 10379 and references therein.

(UK), Ltd., and we thank the Wolfson Foundation for establishing the Wolfson Centre for Organic Chemistry in Medical Science at Imperial College.

Supporting Information Available: Experimental procedure and full characterization for compounds **2**−**4** and X-ray data for **3a** and **2f** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org. X-ray data for **3a** and **2f** have been also deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 206853 and 206854 and can be obtained upon request (phone, +44 1223 336408; fax, +44 1223 336033).

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