UNEXPECTED 'ONE-POT' FORMATION OF THE NOVEL MACROCYCLE 1,8,15-TRITHIA[2.2.2](3,5)-1,3,4-THIADIAZOLINOPHANE-4,11,18-TRITHIONE

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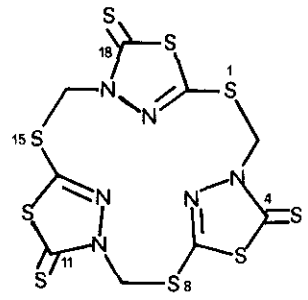
Abstract— The title compound (1) is obtained in 15% yield from the reaction of equimolar amounts of 2,5-dimercapto-1,3,4-thiadiazole (2), dibromomethane and potassium hydroxide in ethanol. A possible mechanism, involving the self-condensation of the extremely reactive intermediate 3-bromomethyl-5-mercapto-1,3,4-thiadiazoline-2-thione (12a) to macrocycle (1), is proposed.

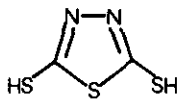
Following our research work on the inclusion of 1,3,4-thiadiazole moieties in a macrocyclic framework[1], we report herein the 'one-pot' formation and a possible genesis of 1,8,15-trithia-[2.2.2](3,5)-1,3,4-thiazolinophane-4,11,18-trithione (1)[2], isolated in the course of our studies on the base-catalysed reaction of 2,5-dimercapto-1,3,4-thiadiazole (2) with aliphatic dihalides. This is the first, to the best of our knowledge, example of enforcement of 1,3,4-thiadiazoline-2-thione moieties in a macrocyclic array.

Theoretically, the starting dithiol (2) can exist in any of three tautomeric forms (2a), (2b), and (2c). Despite the demonstrated preponderance of the 2-mercapto-5-thione structure (2b) both in the solid state[3] and solution[4-6], direct alkylation of (2) with alkyl halides in alkaline medium has been reported to give only S-alkylation[7].

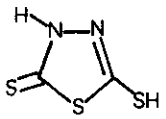
In order to produce thiadiazolophanes with bridging methylenes, dithiol (2) was treated



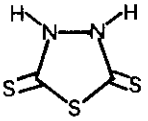
(1)



(2a)

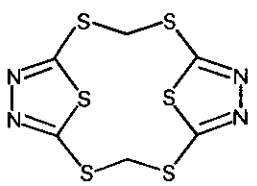


(2b)

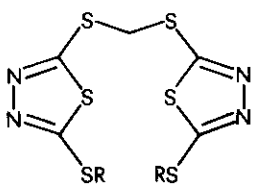


(2c)

with one equivalent of CH_2Br_2 in boiling ethanol in the presence of two equivalents of KOH, under high-dilution conditions. From the reaction, a crystalline compound of molecular formula $C_6H_4N_4S_6$, mp 265–267 °C (DMF) [MS, m/e 324 (M^+, 100%; ^1H nmr ([$^2H_6$]DMSO, 120 °C) δ 5.27], was isolated in 25% yield. To this compound the 1,3,9,11-tetrathia[3.3](2,5)-1,3,4-thiadiazolophane structure (3) was tentatively assigned on the basis of a comparison of the chemical shift of its methylene protons (δ 5.27) with those of models di-(5-methylthio-1,3,4-thiadiazol-2-ylthio)methane (4)[8] and 1,3,9,11,17,19-hexathia[3.3.3](2,5)-1,3,4-thiadiazolophane (5)[9], which were found at δ 5.20 and 5.22, respectively. On the other hand, the methylene protons between the endocyclic nitrogen and the bridged sulphur atom as in model compound (6)[10] resonate at δ 5.85. Nevertheless, the mass spectrum of the new macrocycle shows ions at m/e 248 ([M – CS_2]$^+$, 2%) and 172 ([M – $2CS_2$]$^+$, 69%), indicating the possibility of the alternative structures (7) and (8). ^{13}C nmr spectroscopy has been shown to provide a powerful tool for distinguishing between substitution on nitrogen and/or sulphur in heteroaromatic thiols capable of thiol-thione tautomerism[11]; unfortunately, no ^{13}C nmr spectra could be obtained for the new macrocycle, because of its sparing solubility in most organic solvents. Thus, to confirm the assignment made, a stepwise synthesis of (3) was attempted via the known intermediate di-(5-mercapto-1,3,4-thiadiazol-2-ylthio)methane (9)[12]. Surprisingly, treatment of the mono-potassium salt of (2) (generated by addition of one equivalent of KOH to 2) with one equivalent of CH_2Br_2 in aqueous ethanol did not produce the expected dithiol (9), but gave (15%) the new macrocycle 1,8,15-trithia[2.2.2](3,5)-1,3,4-thiadiazolinophane-4,11,18-trithione (1), mp 176–179 °C (H_2O) [MS, m/e 486 (M^+, 2.7%); ^1H nmr ([$^2H_6$]DMSO)

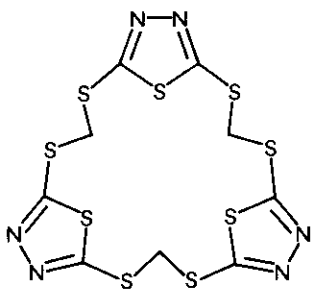


(3)

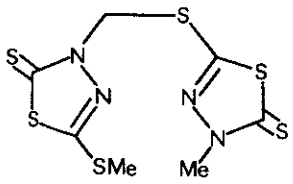


(4) R = Me

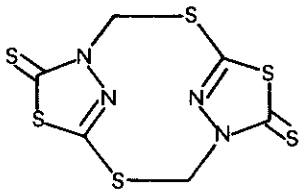
(9) R = H



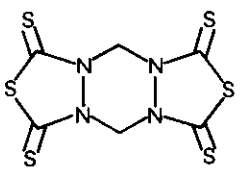
(5)



(6)



(7)

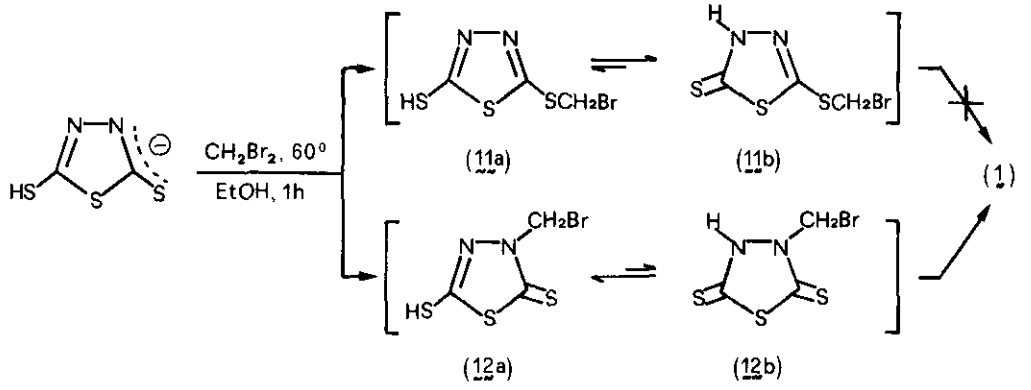


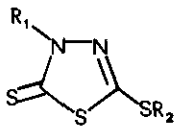
(8)

δ 5.09; ^{13}C nmr ([$^{2}H_6$]DMSO), ppm from TMS: 188.5 (C=S), 155.6 (C-S), and 39.5 (NCH_2S); ^{13}C nmr ([$^{2}H_6$]Me_2CO): 190.9 (C=S), 156.1 (C-S), and 38.3 ppm (NCH_2S)|, along with a considerable amount of uncharacterized gummy material.

Convincing evidence for structure (1) was provided by comparison of the ^{13}C chemical-shift values of the two magnetically non-equivalent endocyclic carbon atoms in the heterocyclic subunits of (1) with those in models 2-methylthio-4-methyl-1,3,4-thiadiazoline-5-thione (10)[13] [^{13}C nmr ([$^{2}H_6$]Me_2CO) 186.7 (C=S), 157.6 (C-S), 39.0 (NMe), and 15.8 ppm (SMe)] and (6)[10]. Conversely, the macrocyclic isomer (5) exhibited the expected single peak for the endocyclic carbons at 164.7 ppm[9]. It is worth noting that the bridged methylenes in (1) experience a remarkable shielding relative to the methylene in acyclic model (6), with proton and carbon upfield shifts of 0.76 and 13.2 ppm, respectively, probably due to the anisotropic effect of the juxtaposed heterocyclic moieties.

Owing to the ambifunctional[14] nature of the monoanion of (2), it is likely that its reaction with CH_2Br_2 gives first a mixture of 2-bromomethylthio-5-mercapto-1,3,4-thiadiazole (11a) and 3-bromomethyl-5-mercapto-1,3,4-thiadiazoline-2-thione (12a). Subsequently, both intermediates might undergo (in their thiol-thione tautomeric forms 11b and 12a) self-condensation to macrocycle (1) in the absence of base, the latter having been consumed to promote the first step. To make a choise between the two alternative pathways shown below, two N- and S-chloromethyl model isomers (13)[15] and (14)[16], in which substitution of methyl groups for





	R_1	R_2
(10)	Me	Me
(13)	CH_2Cl	Me
(14)	Me	CH_2Cl
(15)	H	Me
(16)	Me	H

NH or SH hydrogens forces each molecule in the thiol-thione form, were synthesized and subjected to a reactivity test with isomeric thiols (15)[1a] and (16)[13], chosen on purpose because of their different nature and reactivity[17]. The results obtained have shown that (13) and (14) undergo a ready and regioselective nucleophilic displacement by thiol sulphur (as in 16) even in the absence of base with no evidence for N-alkylation, while their reactions with thione sulphur (as in 15) require extended time with only partial conversion to the corresponding S-alkyl derivative[18]. Moreover, the N-chloromethyl derivative (13) is found to be by

far more reactive than the S-chloromethyl isomer (14)[19].

These data clearly indicate that macrocycle (1) is produced by the extremely reactive intermediate N-bromomethyl derivative (12a), the global mechanism being quite consistent with that observed for the Mannich reaction of (2)[20].

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8. (4): mp 77-78 °C (MeOH); MS, m/e 340 (M^+, 5%); ^{1}H nmr ($CDCl_3$) δ 5.20 (s, SCH_2S, 2H) and 2.85 (s, SMe, 6H); ^{13}C nmr ($CDCl_3$) 167.8 (C-S), 162.6 (C-S), 37.7 (SCH_2S) and 16.5 ppm (SMe).
9. (5): isolated in 3% yield from the high-dilution reaction of (2) and CH_2Br_2 in the presence of triethylamine, mp 215-218 °C (DMF); MS, m/e 486 (M^+, 34%); ^{1}H nmr ([$^2H_6$]DMSO) δ 5.22 (s, SCH_2S); ^{13}C nmr ([$^2H_6$]DMSO) 164.7 (C-S) and 39.7 ppm (SCH_2S).
10. (6): mp 114-115 °C (AcOEt); MS, m/e 340 (M^+, 17%); ^{1}H nmr ([$^2H_6$]DMSO) δ 5.85 (s, NCH_2S, 2H), 3.80 (s, NMe, 3H), and 2.62 (s, SMe, 3H); ^{13}C nmr ([$^2H_6$]DMSO) 186.8 (C=S), 185.7 (C=S), 158.0 (C-S), 151.1 (C-S), 52.7 (NCH_2S), 38.5 (NMe), and 15.1 ppm (SMe).
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15. (13): mp 66.5-68 °C (Et_2O); MS, m/e 212 (M^+, 100%); ^{13}C nmr ($CDCl_3$) 187.4 (C=S), 157.6 (C-S), 55.3 (NCH_2Cl), and 15.2 ppm (SMe).
16. (14): mp 81-82.5 °C (C_6H_{12}); MS, m/e 212 (M^+, 100%); ^{13}C nmr ([$^2H_6$]Me_2CO) 182.1 (C=S), 147.9 (C-S), 48.2 (SCH_2Cl), and 39.2 ppm (NMe).
17. ^{13}C nmr spectra show that (15) (very stable in the air) exists predominantly in the thione form, while (16) exists in the thiol form, as shown also by its spontaneous oxidation in the air to the corresponding disulphide.
18. Details on the characterization of these new compounds will be reported in a full paper.
19. For the interesting and unexpected reactivity of related N-chloromethyl derivatives see: T. Rhada Vakula and W. R. Srinivasan, Indian J. Chem., 1969, 7, 583; H. Kristinsson, Abstracts of the 8th International Congress of Heterocyclic Chemistry, Graz/Austria August 23-28, 1981, p.257.
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