

# A Facile Synthesis and Structure Determination from $^{13}\text{C}$ -NMR Spectroscopy of a Novel Heterocycle 1,1'-Ethylenebis[2,3,8,8a-tetrahydro-5,8a-dimethyl-1*H*-imidazo[2,1-*c*][1,4]thiazine], a Case of Transannular Stabilization

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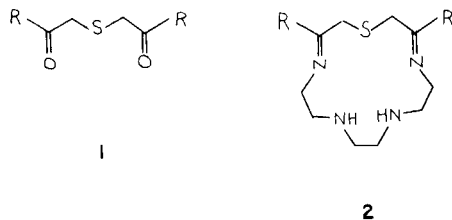
The condensation of 4-thiaheptane-2,6-dione with triethylenetetramine does not produce the macrocycle 1-thia-3,14-dimethyl-4,7,10-13-tetraazacyclopentadeca-3,13-diene; instead two molecules of the dione condense with one of the amine to give the title compound.

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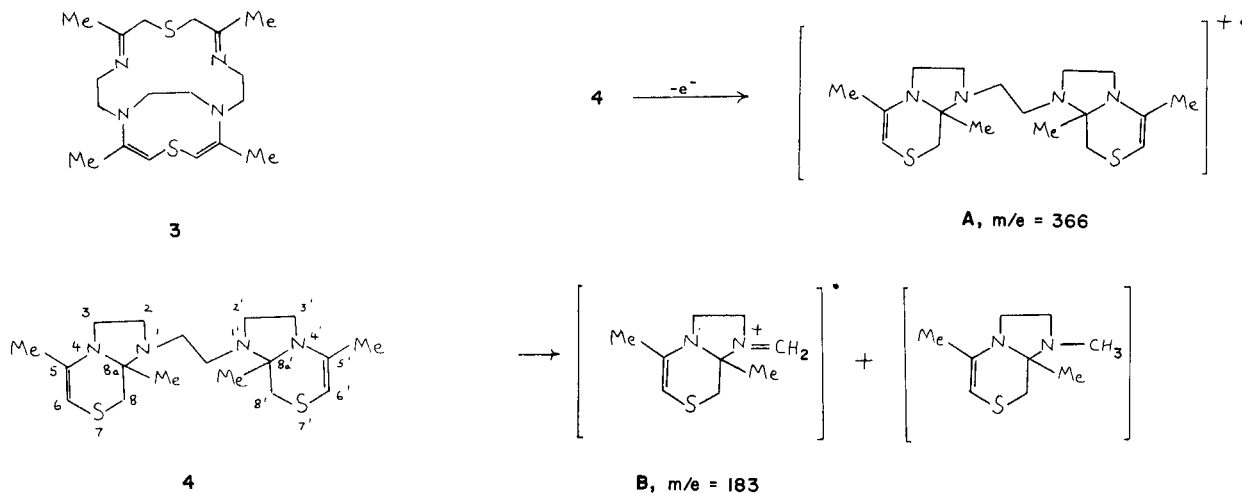
Earlier we reported [3-6] that the condensations of diphenacyl sulphide (**1**, R = Ph) with hydrazine hydrate, 1,2-diaminoethane, 1,2-diaminopropane and 1,3-diaminopropane result in the formation of 1,4,5-thiadiazepine, 2,3,8,8a-tetrahydro-5,8a-diaryl-1*H*-imidazo[2,1-*c*][1,4]thiazine, 2,3,8,8a-tetrahydro-5,8a-diphenyl-2-methyl-1*H*-imidazo[2,1-*c*][1,4]thiazine (two isomeric products) and 1,2,3,4,9,9a-hexahydro-6,9a-diarylpyrimido[2,1-*c*][1,4]thiazine respectively. However, an attempt to prepare the macrocyclic compound, 1-thia-3,14-diphenyl-4,7,10,13-tetraazacyclopentadeca-3,13-diene (**2**, R = Ph) by the reaction of the diphenacyl sulphide with triethylenetetramine under the same conditions was not successful. Subse-

quently, the reaction of more reactive 4-thiaheptane-2,6-dione (**1**, R = Me) and triethylenetetramine resulted in the formation in good yield of fine needles of a product with a parent ion peak at  $m/e$  366 in its mass spectrum which could be due to a compound formed from the cyclodehydrative condensation of one molecule of triethylenetetramine with two molecules of the thiodiketone (**1**, R = Me), but could not be due to the methyl analogue of the macrocycle **2**. The ir spectrum of the product contained no bands due to carbonyl and NH stretching vibrations, and from the mass spectrum two structures **3** and **4** can be proposed.

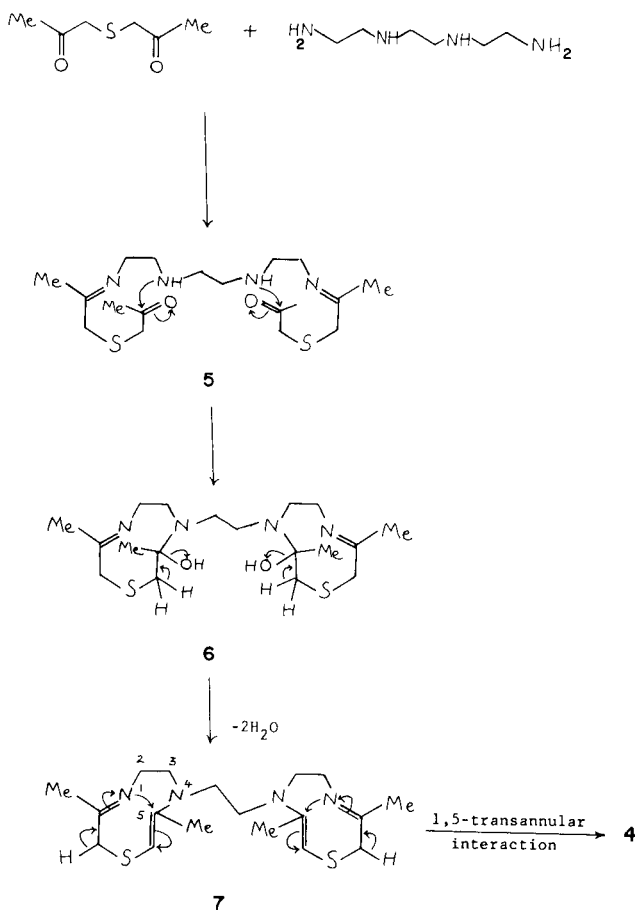
All signals in the  $^1\text{H}$  nmr spectrum (Table) could be explained equally well by the two structural possibilities **3** and **4**, except those at  $\delta$  1.04 and 1.05. The four singlets each of three hydrogens at  $\delta$  1.04, 1.05, 1.92 and 1.93 are due to four methyl groups. This indicates that two pairs of methyl groups are present in different environments but the two methyl groups of each pair are equivalent appearing approximately at the same chemical shifts. The appea-



Scheme 1



Scheme 2



rance of two methyl groups in the upfield region ( $\delta$  1.04 and 1.05) could not be explained by the structure **3** which contains four equivalent methyl groups linked to  $sp^2$  hybridized carbon atoms expected to resonate downfield at about  $\delta$  2.00. The non equivalent pairs of methyl groups can only be explained by structure **4** which has two methyl groups attached to  $sp^3$  hybridized bridgehead carbon atoms (C-8a and C-8a'). The two singlets each of three hydrogens at  $\delta$  1.92 and 1.93 are thus due to two methyl groups linked to olefinic carbon atoms (C-5 and C-5'). A complex multiplet of sixteen hydrogens at  $\delta$  1.96-3.60 is due to the eight methylene groups, and the singlet of two hydrogens at  $\delta$  4.89 which exchange slowly [4,5] with deuterium is due to the olefinic hydrogens.

In confirmation, the  $^{13}\text{C}$  nmr spectrum (Figure and Table) was successfully assigned in accordance with structure **4**. The signals at 18.30 ppm and 18.48 ppm which split into quartets in the off-resonance proton decoupled spectrum are due to the carbon atoms of the two methyl groups linked to the  $sp^3$  hybridized bridgehead carbon atoms (C-8a and C-8a') in structure **4**. The appearance of these two signals in the upfield region (18.30-18.48 ppm) clearly

supports structure **4** and rules out the possibility of structure **3** which has all methyl groups attached to  $sp^2$  hybridized carbon atoms so that the methyl resonance would be expected at 22.00 ppm [8]. The signal at 22.11 ppm which splits into an overlapping quartet [9] has been assigned to the methyl groups attached to the carbon atoms C-5 and C-5'. The appearance of signals at the same position is indicative of their source in identical methyl groups as required by structure **4**. The signals at 32.71 and 32.89 ppm which split into triplets [9] are due to carbon atoms C-8 and C-8' of the methylene groups adjacent to sulphur. Those at 46.75, 47.46, 47.58, 48.39 and 48.79 ppm, which split into triplets [9] forming a complex unresolved multiplet have been assigned to the carbon atoms C-2, C-3, C-2' and C-3' of the methylene groups adjacent to the nitrogen

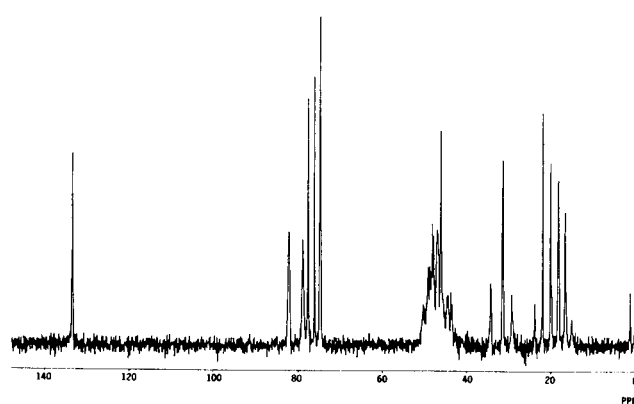
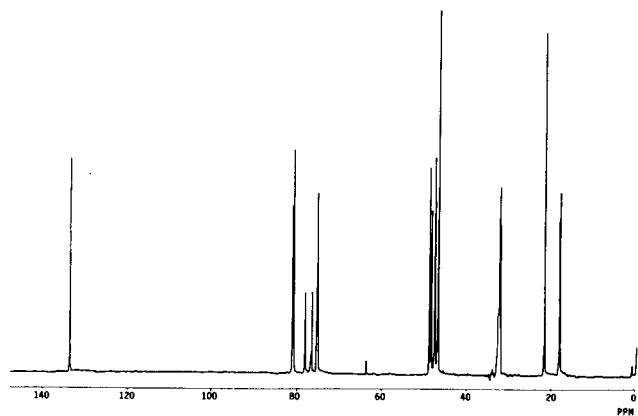


Figure. The  $^{13}\text{C}$  nmr spectrum of 1,1'-ethylenebis[2,3,8,8a-tetrahydro-5,8a-dimethyl-1H-imidazo[2,1-c][1,4]thiazine] in deuteriochloroform (a) proton-decoupled, and (b) off-resonance proton de-coupled.

atoms [4,8]. The resonances at 75.44 ppm and 75.53 ppm which remain unsplit [9] are due to the  $sp^3$  hybridized bridgehead carbon atoms (C-8a and C-8a') in structure **4**. Their appearance very clearly rules out structure **3** which has no bridgehead carbon atoms [4,10]. The resonances at

Table

<sup>13</sup>C-, <sup>1</sup>H-NMR, and IR Data of 1,1'-Ethylenebis[2,3,8,8a-tetrahydro-5,8a-dimethyl-1*H*-imidazo[2,1-*c*][1,4]thiazine

<sup>13</sup> C-NMR (deuteriochloroform) Peak Position (ppm)	Assignment	<sup>1</sup> H-NMR (deuteriochloroform) (ppm)
18.30 (q)	Methyl groups linked to C-8a and C-8a'	1.04 (s, 3H, CH <sub>3</sub> ), 1.05 (s, 3H, CH <sub>3</sub> ),
18.48 (q)		1.92 (s, 3H, CH <sub>3</sub> ), 1.93 (s, 3H, CH <sub>3</sub> ),
22.11 (q)		1.96-3.73 (m, 16H, CH <sub>2</sub> ), 4.48 (s, 2H=CH-)
32.71 (t)	C-8 and C-8'	
32.89 (t)		
46.75	C-2, C-3, C-2', C-3' and methylene groups of 1,2-diaminoethane moiety	
47.46		
47.58 (Complex multiplets)		
48.39		IR (nujol): (cm <sup>-1</sup> ) 1602 vs, 1345 m, 1330 m, 1242 s, 1215 m, 1200 m, 1160 s, 1145 m, 1028 m, 975 m, 875 m, 820 m, 700 m
75.44 (s)	C-8a and C-8a'	
75.54 (s)		
81.29 (d)	C-6 and C-6'	
81.52 (d)		
134.92 (s)	C-5 and C-5'	

81.29 and 81.52 ppm which split into doublets [9] are due to the olefinic carbon atoms C-6 and C-6'. In imidazo[2,1-*c*][1,4]thiazine and pyrimido[2,1-*c*][1,4]thiazine, where the olefinic group is conjugated with the aryl group, the carbon atoms of the olefinic groups appear at 92.18-95.70 ppm, but in the present case the upfield shift in the position of the olefinic carbons (81.29-81.52) is attributed to the electron-donating effect of the methyl groups linked to C-5 and C-5'. The signal at 134.92 which remains unsplit [9] is due to sp<sup>2</sup> hybridized carbon atoms devoid of hydrogen (C-5 and C-5') [4].

The fragmentation pattern of the molecule in its mass spectrum (Scheme 1) is in agreement with structure **4**. The parent ion A (*m/e* 366) undergoes homolytic fission of the C-C bond of the central ethylenediamine moiety to form the base ion B (*m/e* 183), a type of fission possible only in structure **4**.

A possible mechanism for the formation of compound **4** is given in Scheme 2. In the first step, condensation of the terminal amino groups of triethylenetetramine with carbonyl groups of two molecules of thiodiketone occurs resulting in the formation of the intermediate **5** which undergoes self-condensation with the secondary amine nitrogen to form intermediate **6** which may rearrange to give the intermediate 5,9,14,18-tetramethyl-7,16-dithia-1,4,10,13-tetraazabicyclo[11.5.2]jicosa-4,9,14-17-tetraene (**7**). The intermediate **7** may be unstable and undergo preferred 1,5-transannular interaction

see formula

to form the stabilized system **4** which is a novel hetero-

cycle [11]. Such transannular stabilization of imidazo[2,1-*c*][1,4]thiazines and pyrimido[2,1-*c*][1,4]thiazines has already been reported [4]. The compound **4** hydrolyses on tlc plates and on a column (silica gel, chloroform) resulting in the formation of many products. The major component separated by column chromatography was the starting material (**1**, R = Me) (mp and mass spectrum). The residue contained products with carbonyl and NH absorptions. This may be due to the presence of the intermediate **5** as one product.

As shown above, the macrocycle **2** (R = Me) was not obtained by direct reaction of **1**, R = Me and triethylenetetramine, but it has been prepared [12] as its nickel(II) complex by template synthesis.

## EXPERIMENTAL

The chemicals used were of AnalaR or BDH grade. Melting points were determined by the capillary method and are uncorrected. The IR spectra of nujol mulls were recorded on a Perkin Elmer 577 instrument. The <sup>1</sup>H- and <sup>13</sup>C nmr spectra were recorded on a Bruker WH-90 Pulse Fourier Transform nmr spectrometer (22.636 MHz for <sup>13</sup>C). Microanalyses were carried out at the University of Surrey.

Preparation of **1**, 4-Thiaheptane-2,6-dione (I, R = Me).

A solution of sodium sulphide (12 g) in water (40 ml) was added in small portions with constant stirring over about two hours to chloroacetone (25 ml) in a 250 ml round-bottomed flask, and the reaction mixture stirred for two hours more. It was extracted with chloroform (4 × 50 ml), and after the extract had been dried over anhydrous sodium sulphate the chloroform was removed under reduced pressure at room temperature. The semi-solid thiodiketone thus obtained solidified overnight. It was recrystallized from ether, yield, 40%, mp 44°; ms: *m/e* 146.

*Anal.* Calcd. for C<sub>6</sub>H<sub>10</sub>O<sub>2</sub>S: C, 49.29; H, 6.89. Found: C, 49.08; H, 7.29.

Preparation of 4,1,1'-Ethylenebis[2,3,8,8a-tetrahydro-5,8a-dimethyl-1*H*-imidazo[2,1-*c*][1,4]thiazine].

The thiodiketone (1 g) was dissolved in a 3:2 mixture of ethyleneglycol and ethanol (50 ml). To this solution, triethylenetetramine (1 ml) was added dropwise with constant shaking. After about half an hour fine white crystals separated; they were filtered off, washed (5 × 5 ml) with ethanol and dried in a vacuum desiccator. The compound was also prepared by refluxing the reactants in ethanol on a water bath for about 15 minutes, yield, 95% mp 165-167° (darkened at 145-150°); ms: m/e, 366.

*Anal.* Calcd. for C<sub>18</sub>H<sub>30</sub>N<sub>4</sub>S<sub>2</sub>: C, 58.97; H, 8.25; N, 15.29. Found: C, 58.49; H, 8.16; N, 15.12.

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[2] To whom correspondence should be directed.

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[9] The multiplicities of signals in the <sup>13</sup>C nmr spectrum refer to the off-resonance proton-decoupled spectrum throughout the manuscript.

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[11] We thank Dr. Kurt L. Loening, Nomenclature Director, Chemical Abstracts Service, Columbus, Ohio (USA) for naming the compound.

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