Bridged thiazolium salts as models for thiamin: NMR, crystallographic and molecular mechanics studies

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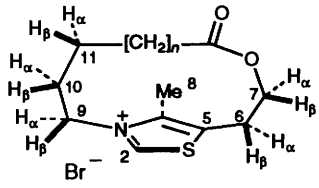
NMR data for the bridged thiazolium salts **1b** and **c** and thiazole-2(3*H*)-thiones **2b** and **c** are described which allow their conformations in solution to be deduced. These are in full agreement with the X-ray crystal structures for **2b** and **c**. The structures and conformations of the two atropisomers of the substituted thiazole-2(3*H*)-thiones **6** and **7** have also been deduced. Molecular mechanics calculations agree with the deduced conformations and have been used to predict the strain involved in the bridged thiazolium salts and the degree to which this strain is relieved in some of their reactions.

In a recent paper,[1] syntheses of bridged thiazolium salts **1b** and **c** and their precursors thiazole-2(3*H*)-thiones **2b** and **c** were described. The aim of these syntheses was to study the effect of the strain caused by a short bridge on the catalytic reactions of thiazolium salts. It was found that the longer bridge of **1c** had little effect on the rates of the reactions studied but that the shorter bridge of **1b** prevented catalysis of the benzoin condensation and instead allowed the isolation of a by-product **5**.

Derivatives of the longer bridged thiazole-2(3*H*)-thione **2c** were also prepared in which dimethylamino **6** and acetamido **7** substituents are positioned adjacent to the carbonyl. In both cases the introduction of this chiral centre led to the isolation of two non-interconverting atropisomers, **6a** and **b** and **7a** and **b**. We present here a detailed study of the structure of the bridged compounds by NMR spectroscopy, backed up by molecular mechanics calculations and X-ray crystallography.

In order to substantiate the suggestion that the inability of thiazolium salt **1b** to catalyse the benzoin condensation is caused by the additional strain of the bridge, we have extended the molecular mechanics calculations to obtain a numerical value for the relevant strain in each of the compounds as well as for the even shorter bridged compounds **1a** and **2a**, which could not be synthesised. The results of these studies are also presented.



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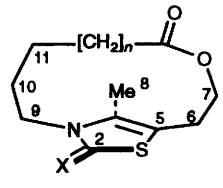
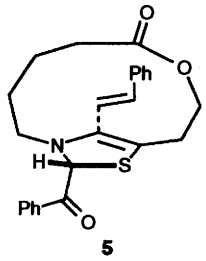


2 X = S
3 X = O
4 X = H,H

a *n* = 0, **b** *n* = 1, **c** *n* = 2



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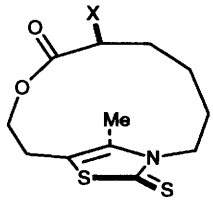
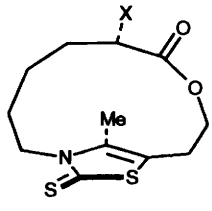


6a X = NMe_2
7a X = NHAc



6b X = NMe_2
7b X = NHAc

Results and discussion

NMR spectroscopy

The 400 MHz ^1H NMR spectra of the unsubstituted bridged compounds, **1** and **2**, are shown in Fig. 1(*a*)–(*d*) and the full ^1H NMR data for all the bridged compounds are given in Tables 1 and 2.† The assignments of the protons of the thiazole-2(3*H*)-thiones, **2b** and **c**, and thiazolium salt **1c** were performed with the help of either a full set of decoupling experiments or a 2D-COSY experiment. For thiazolium salt **1b** the assignment was made by comparison with the corresponding thione **2b**. Stereochemical assignments are based on NOE measurements (shown by the arrows on the structures in Fig. 2) and on coupling constants where these are large enough ($\geq$9.8 Hz) to suggest a predominantly antiperiplanar orientation of two hydrogen atoms.

For all the bridged thiazole-2(3*H*)-thiones there is a large difference between the chemical shifts of the two hydrogens on C-9. The NOE studies showed that the more upfield of the two protons is close to the methyl group and hence is the α-proton (at the back as viewed in structures **1**–**7**). The β-proton in these compounds lies close to the side of the C=S double bond and therefore experiences a strong downfield shift. This conclusion is confirmed by the chemical shifts in the thiazolium salts **1b** and **c**, which, lacking the thione, show much less difference between the 9α- and 9β-protons. In all the unsubstituted bridged compounds, **1b** and **c** and **2b** and **c**, the 9β-proton has two rather different vicinal coupling constants. The larger of these (9.8–13.8 Hz) suggests that there is a largely antiperiplanar relationship between 9β-H and 10α-H.

In a similar way to the protons on C-9, the α-proton on C-6 can be identified by NOEs to and from the methyl group. In all compounds, except the minor atropisomers **6b** and **7b**, 6α-H has a large vicinal coupling (9.9–13.1 Hz) indicative of an antiperiplanar relationship with 7β-H. In all these compounds

† For the numbering scheme used in this paper see structures **1** and **2**.

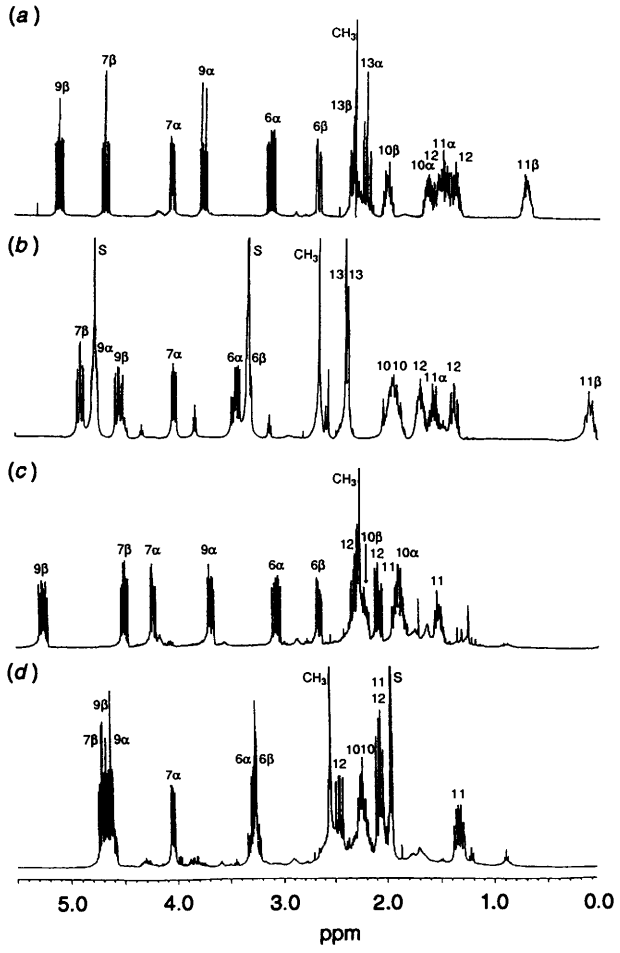


Fig. 1 400 MHz ^{1}H NMR spectra of (*a*) **2c** in $CDCl_3$, (*b*) **1c** in CD_3OD, (*c*) **2b** in $CDCl_3$, (*d*) **1b** in CD_3CN. Assignments are given above each multiplet. Solvent peaks are marked S.

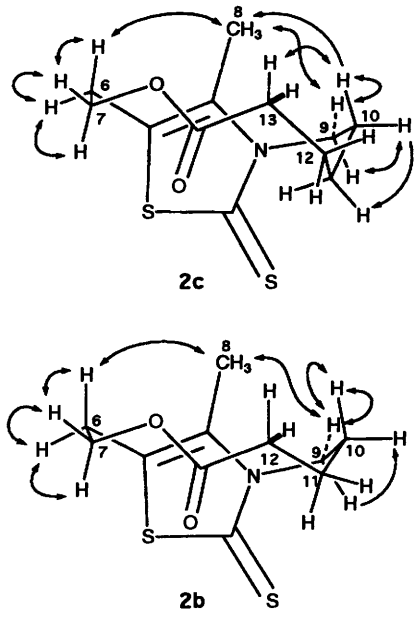


Fig. 2 Solution structures of the thiazole-2(3*H*)-thiones, **2c** and **2b**, deduced from ^{1}H NMR spectroscopy. The arrows indicate NOEs observed. NOEs which could not be unambiguously attributed and NOEs between geminal hydrogens have been omitted for the sake of clarity.

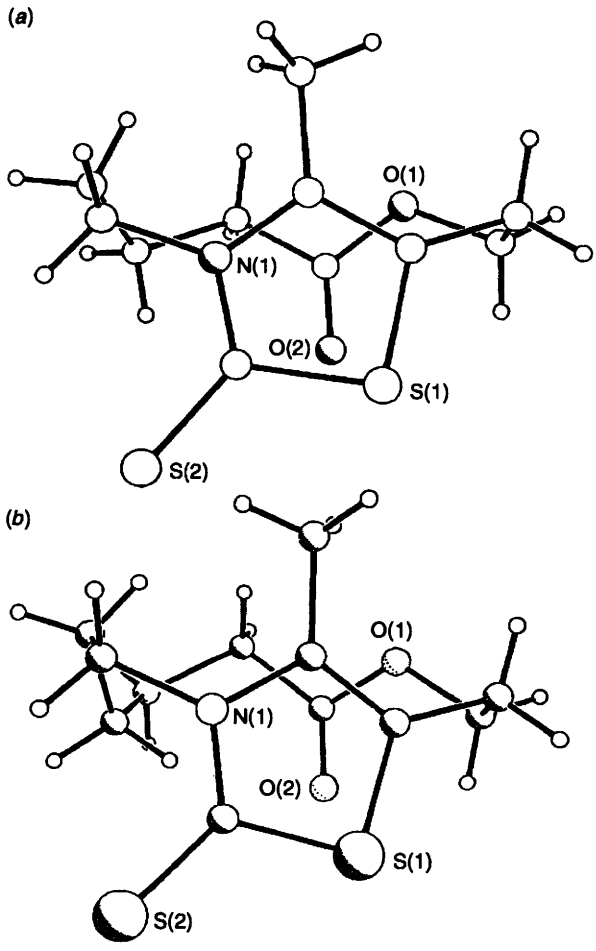


Fig. 3 The molecular structures of the thiazole-2(3*H*)-thiones, (*a*) **2b**, (*b*) **2c** as determined by single crystal X-ray diffraction

7β-H is considerably more downfield than 7α-H, indicating that it is in the deshielding region alongside the ester carbonyl group.

These considerations, along with the reasonable assumption that the ester adopts the more stable *trans* configuration, define the conformations of the majority of the bridge atoms of compounds **1b** and **c** and **2b** and **c** to be similar to those shown in Fig. 2. The only atoms whose position could still vary are C-11, 12 and (for the longer bridge) 13.

For the longer thiazole-2(3*H*)-thione **2c**, two important observations allow the conformation of the remaining atoms to be deduced. The first is an NOE between one of the protons on C-13 and 10α-H. This proton, which must be 13α-H, showed a large, presumably antiperiplanar, coupling with a proton on C-12 (12β-H). The other observation is that one of the protons on C-11 is at abnormally high field (δ 0.68). This suggests that it lies above (or below) the face of either the thione or the ester carbonyl or both. Using molecular models, the only conformation for compound **2c** that can account for these observations is that shown in Fig. 2. In this conformation 11β-H does indeed point inwards and lies almost above the thione and not too far from the face of the ester carbonyl. Though deduced first from the NMR data, the conformation for compound **2c** in Fig. 2 was subsequently fully confirmed by X-ray crystallography as shown in Fig. 3(*a*).

The ^{1}H NMR spectrum of the corresponding thiazolium salt **1c** shows considerable similarity to that of the thione **2c**, especially in the coupling constants. These indicate that the conformation remains substantially the same. The chemical shifts of hydrogen atoms adjacent to the heterocyclic ring

Table 1 ^{1}H Chemical shifts for the bridged compounds **1**, **2** and **5–7**

	Chemical shift (δ)															
Compound[a]	2-H	6-H$_\alpha$	6-H$_\beta$	7-H$_\alpha$	7-H$_\beta$	8-H$_3$	9-H$_\alpha$	9-H$_\beta$	10-H$_\alpha$	10-H$_\beta$	11-H$_\alpha$	11-H$_\beta$	12-H$_\alpha$	12-H$_\beta$	13-H$_\alpha$	13-H$_\beta$	Other
1b	9.60	3.27	3.23	4.03	4.70	2.53	4.59	4.65	2.20[b]	2.26[b]	2.05[b]	1.32[b]	2.05[b]	2.44[b]	—	—	—
2b	—	3.07	2.66	4.24	4.51	2.26	3.69	5.26	1.88	2.2	1.92[b]	1.52[b]	2.08[b]	2.31[b]	—	—	—
5	5.93	3.25	2.48	3.85	5.00	—	3.59	3.15	1.65	2.04	1.95	1.65	2.15	2.45	—	—	7.07/6.76 (CH=CH) 7.2–7.9 (Ph)
1c	9.93	3.42	3.30	4.00	4.89	2.62	4.75	4.53	1.87[b]	1.92[b]	1.54	0.07	1.35[b]	1.66[b]	2.35	2.35	—
2c	—	3.10	2.64	4.02	4.65	2.27	3.72	5.08	1.6	1.97	1.45	0.68	1.35[b]	1.50[b]	2.17	2.30	—
6a	—	3.13	2.66	4.07	4.64	2.28	3.74	5.09	1.70	2.00	1.4	0.68	1.4	1.4	3.02	—	2.28 (NMe_2)
6b	—	3.14	2.77	4.83	4.12	2.23	3.77	4.70	1.6[b]	2.5[b]	1.25	1.25	1.7	0.86	—	2.72	2.21 (NMe_2)
7a	—	3.20	2.70	4.10	4.53	2.30	3.82	4.88	1.61	2.42	1.42	0.87	1.27[b]	1.48[b]	4.44	—	1.97 (MeCO), 5.91 (NH)
7b	—	3.21	2.82	4.92	3.99	2.17	3.71	4.73	1.65	2.41	1.53	0.93	1.91	0.65	—	4.50	1.98 (MeCO), 5.91 (NH)

[a] All samples dissolved in $CDCl_3$ except **1b** in CD_3CN and **1c** in CD_3OD. [b] Assignments of α and β stereochemistry are uncertain.

Table 2 ^{1}H–^{1}H Coupling constants for the bridged compounds **1**, **2** and **5–7**[a]

	Coupling constant (J/Hz)															
Compound	6$_\alpha$–6$_\beta$	6$_\alpha$–7$_\alpha$	6$_\alpha$–7$_\beta$	6$_\beta$–7$_\alpha$	6$_\beta$–7$_\beta$	7$_\alpha$–7$_\beta$	9$_\alpha$–9$_\beta$	9$_\alpha$–10	9$_\beta$–10	11–12$_\alpha$	11–12$_\beta$	12$_\alpha$–12$_\beta$	12–13$_\alpha$	12–13$_\beta$	13$_\alpha$–13$_\beta$	Other
1b	14.8	6.0	10.7	1.4	5.0	11.0	14.4	6.4, 2.4	11.7, 6.5	9.4, 1.0	10.9, 1.4	16.0				
2b	14.7	7.3	9.9	2.1	5.8	10.9	14.4	5.7, 3.6	10.6, 5.9	9.8, 2.1	9.5, 2.3	15.5				
5	14.5	5.6	13.1	0.9	3.1	11.2	15.3	8.5, 0	6.7, 0	13.3, 2.7	m	13.3				15.8 (CH=CH)
1c	15.0	6.0	12.0	1.0	3.9	11.3	13.8	5.0, 2.6	12.4, 4.8	m	m	m	m	4.6, 4.6	—	
2c	15.1	6.0	11.2	2.4	4.2	11.1	14.0	5.0, 5.0	9.8, 5.0	m	m	m	11.9, 3.2	5.0, 4.0	15.1	
6a	15.2	5.8	11.5	2.3	3.9	11.0	14.0	5.1, 5.1	9.2, 4.8	m	m	m	7.2, 6.6	—	—	
6b	15.4	6.6	6.0	7.3	6.7	11.3	13.8	11.4, 5.1	6.2, 2.1	m	m	m	—	7.0, br	—	
7a	15.2	5.8	11.8	2.0	4.0	11.0	14.1	8.6, 5.5	5.9, 5.2	m	m	m	6.2, 4.3	—	—	7.3 (CH–NH)
7b	15.4	6.9	5.4	7.5	7.4	11.4	13.8	12.8, 4.0	5.5, 1.4	m	m	m	—	7.1, 1.9	—	6.8 (CH–NH)

[a] Signals for protons on C-10, C-11 and (for longer bridged compounds) C-12 were mostly complex multiplets from which coupling constants could not be obtained.

mostly show the expected downfield shifts compared with **2c** with the exception of 9β-H which moves upfield due to the removal of the thiocarbonyl. The 11β-H moves even further upfield, to δ 0.07, as it is now located over an aromatic ring. This is further proof that the preferred conformation is essentially the same as that shown for the thione **2c** in Fig. 2.

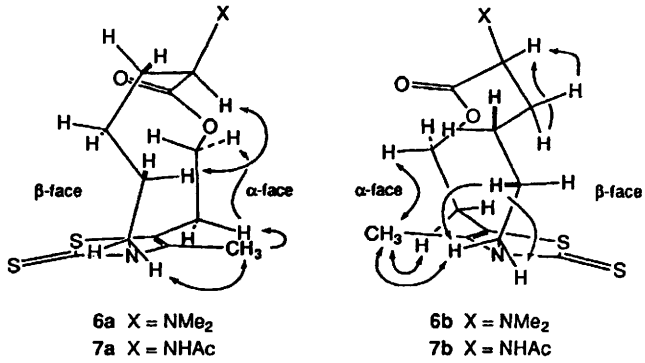
For the shorter bridged thiazole-2(3*H*)-thione **2b**, the overlap of critical signals in the ^{1}H NMR spectrum meant that NOE enhancements which might have helped to define the conformation of C-11 and C-12 could not be unambiguously assigned. The conformation illustrated in Fig. 2, based on the X-ray crystal structure shown in Fig. 3(*b*), fits all the NMR data available and is almost certainly the major contributor to the structure in solution. Although one of the protons on C-11 does appear upfield of the others at δ 1.52, it is not shifted nearly as much as 11β-H of the higher homologue **2c**. This is consistent with the fact that, in the conformation for **2b** shown in Fig. 2, 11β-H is much less tucked in over the heterocyclic ring than in compound **2c**.

In the shorter bridged thiazolium salt **1b** the coupling constants around C-6, C-7 and C-9 indicate that the conformation of C-6–C-7 and C-9–C-10 remains essentially the same as for the corresponding thiazole-2(3*H*)-thione **2b**. A further small upfield shift of the signal tentatively assigned to 11β-H to δ 1.32 is seen but again this is much smaller than in the longer bridged series.

In the cases of the thiazole-2(3*H*)-thiones with dimethylamino and acetamido substituents on the bridges, **6** and **7**, two atropisomers of each were observed. Comparisons of the chemical shifts and coupling constants show that it is the major isomer in each case (**6a** and **7a**) which has a similar conformation to that of the equivalent unsubstituted compound **2c**. In particular they show that (*i*) it is 6α-H that has the large antiperiplanar coupling to 7β-H, (*ii*) 7β-H is further downfield than 7α-H, (*iii*) one of the protons on C-11 is shifted abnormally upfield (accordingly assigned as 11β-H) and (*iv*) NOEs are seen between 10α-H and the proton on C-13 (hence assigned as 13α-H). The deduced conformation for these isomers (viewed from a different angle from that in Fig. 2) is reproduced in Fig. 4 along with selected NOE data. The assignment of the proton on C-13 as being in the α-position indicates that the substituent on C-13 occupies the β-position in both the major isomers as shown in structures **6a** and **7a**. This was the expected result because inspection of the predominant conformation of compound **2c** clearly shows that there is room for a bulky substituent in the β-position but no room in the α-position.

There are indications, however, that the structure for compounds **6a** and **7a** given in Fig. 4 is not the only significant conformation. Irradiation of the upfield 11β-H gives small NOEs to 13α-H and to *both* 10α- and 10β-H. Furthermore the difference between the two vicinal coupling constants for 9β-H is smaller for compound **6a** than **2c** and almost disappears for **7a**. Both these observations indicate the existence of alternative conformation(s) for C-9 to C-11, which are minor for compound **6a** but more significant for **7a**. However, the conformation of C-6 and C-7 (and probably the ester group also) appears to be relatively fixed.

The ^{1}H NMR spectra of the minor isomers, **6b** and **7b**, show that they have quite different conformations from the major isomers. Significant observations for these compounds are: (*i*) it is 9α- rather than 9β-H that has the large antiperiplanar coupling constant (to 10β-H), hence C-10 bends towards the β- rather than the α-face; (*ii*) it is 7α-H which is more downfield than 7β-H by a considerable margin, suggesting that the ester carbonyl group is α in these isomers; (*iii*) there is still one abnormally upfield signal for each minor isomer but the COSY spectra showed that these are due to protons attached to C-12 rather than C-11; (*iv*) the vicinal coupling constants between



6a X = NMe_2 **6b** X = NMe_2
7a X = NHAc **7b** X = NHAc

Fig. 4 Preferred conformations of the two atropisomers of the substituted thiazole-2(3*H*)-thiones, **6** and **7**, deduced from ^{1}H NMR spectroscopy. The arrows indicate NOEs.

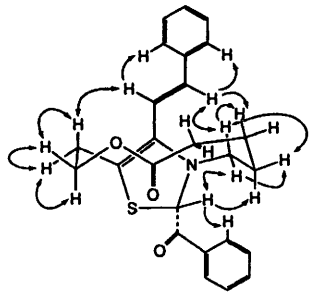


Fig. 5 Preferred conformation of the 2-benzoyl-2,3-dihydrothiazole **5** deduced from ^{1}H NMR spectroscopy. The arrows indicate NOEs.

protons on C-6 and C-7 are all approximately equal (5.4–7.5 Hz), probably indicating flexibility in this part of the bridge.

Molecular mechanics calculations were used to indicate possible conformations for these minor isomers, **6b** and **7b** (see later). The lowest energy conformation in both cases was that shown in Fig. 4. This conformation accounts very well for the observations (*i*)–(*iii*) above; the ester is α, C-10 points towards the β-face, and 12β-H is tucked in close above the thiocarbonyl and would be expected to experience an upfield shift. There were some other predicted conformations not much higher in energy one of which is very similar in the position of all the atoms except that C-7 points to the β- rather than α-face and the others have the ester carbonyl β. Rapid interconversion of such conformations would account for observation (*iv*) above. It seems very likely that the conformation shown in Fig. 4 is indeed the major conformation adopted by both minor isomers, **6b** and **7b**.

Finally we consider the conformation of the 2-benzoyl-2,3-dihydrothiazole **5**, produced by reaction of thiazolium salt **2b** with benzaldehyde in the presence of a base. NOE data and coupling constants for this compound gave a good indication that the conformation is as shown in Fig. 5. Particularly informative were NOEs observed from the olefinic protons and from 2-H. The downfield olefinic proton (assumed to be the one closer to the phenyl ring) gave NOEs to protons on C-9 and C-11 (hence assigned as 9α-H and 11α-H) whereas the upfield olefinic proton gave an NOE to a proton on C-6 (6α-H). The proton on C-2, on the other hand, showed NOEs to the other hydrogen atom attached to C-9 (9β-H) and one on C-10 (10β-H). These data and the other NOEs indicated by the arrows in Fig. 5 indicate that the conformation shown there is distinctly preferred. It will be noticed that this conformation differs from that deduced for the shorter bridged thiazole-2(3*H*)-thione and thiazolium salt in the orientation of C-10 and C-11. This change may be to avoid a steric interaction between 10α-H and the bulkier styryl side-chain and is probably facilitated by the fact that the dihydrothiazole ring no longer needs to be planar.

Molecular mechanics calculations

All calculations were performed using the MacroModel program[2] (version 2.5) and MM2 parameters. Starting conformations were generated using the MULTIC procedure which generates a set number of dihedral angles about rotatable bonds and minimizes those conformations which bring two specified atoms within a fixed distance to form the bridge (see Experimental section).

After minimization, it was found that all the conformations close in energy to the lowest one for each of the bridged compounds could be classified in one of a relatively small number of different ways, based on whether each atom of the bridge, from C-10 through the ester linkage to C-7, points towards the α or β side of the molecule or is intermediate between these two (denoted by -). Using this system, the conformation for the thione **2c** in Fig. 2 is described as αβ–αβαβ. Details of the other conformations found by the calculations on the compounds described in this paper are given in the Experimental section and their relative energies are shown in Fig. 6.

Using this knowledge of the types of conformation to be expected, the conformations found by the computer's conformation-searching program were checked to see if any expected ones had been missed for any particular compound. Where this had occurred, the relevant conformation of that compound was generated manually and minimized. In this way, we have ensured that no low energy conformations have been overlooked.

Initial molecular mechanics calculations on the thiazolium salt **1c** were performed using the default relative permittivity value of 1, *i.e.* in the gas phase. These calculations indicated that the preferred conformation is essentially the same as that determined for the thione **2c** by NMR spectroscopy and X-ray crystallography (Fig. 2). This conformation of the bridge was the most favourable one by a margin of 6.6 kJ mol^{-1}. It is notable that the four lowest predicted conformations all had the same conformation of C-6, C-7, and the ester (with the carbonyl oxygen atom β) and the lowest energy conformation to differ substantially in this part of the bridge (with the carbonyl oxygen atom α) was the fifth one, 12.85 kJ mol^{-1} above the lowest.

Calculations at a relative permittivity of 1, however, are clearly not appropriate for charged molecules such as the thiazolium ion **1c**, which is only soluble in polar solvents. Furthermore it became apparent that the relative permittivity used in the calculations was having a marked effect on the relative energies of different conformations. Thus at low relative permittivity conformations of **1c** having the ester carbonyl β were favoured compared with ones having the ester carbonyl α. To our surprise the opposite effect was observed when calculations were performed on the thiazol-2(3*H*)-one‡ **3c**. In this compound conformations having the ester carbonyl α were favoured by using a low relative permittivity in the calculations. A likely explanation for this effect is that in the thiazolium ion there is attraction between the negatively charged oxygen of the ester carbonyl group and the positively charged ring whereas in the thiazol-2(3*H*)-one there is repulsion between the two carbonyl groups. At higher relative permittivity these charge–charge interactions would be less significant. Therefore for all further calculations a relative permittivity of 20 was chosen, this value being a compromise between the values for the various solvents used for NMR spectroscopy, chloroform (4.8), methanol (33) and acetonitrile (39).

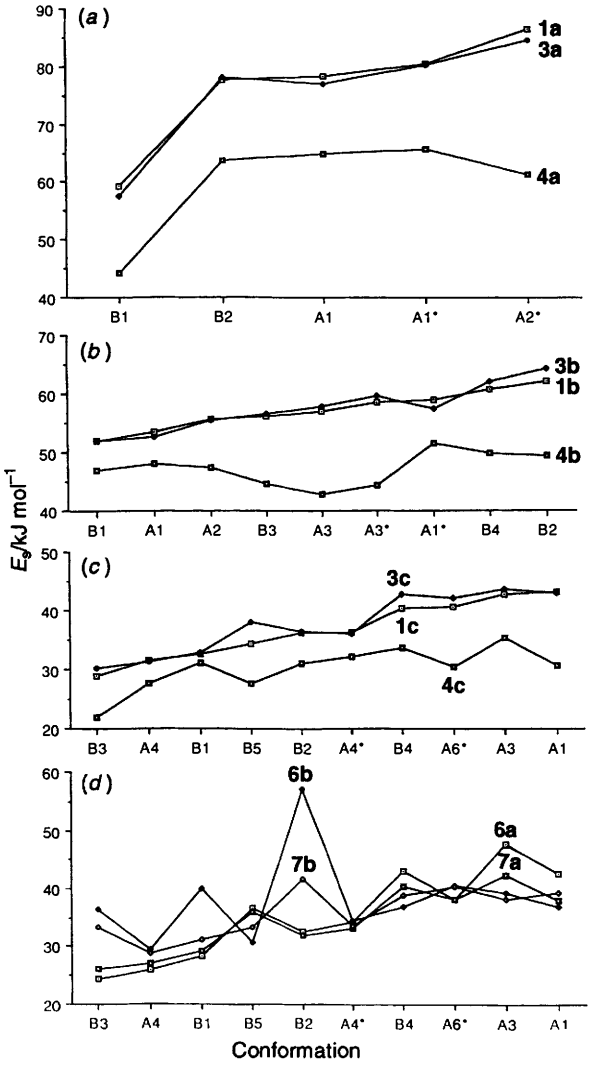


Fig. 6 Strain energies of the different conformations of the bridged compounds calculated by molecular mechanics: (*a*) shorter-bridged compounds: **1a**, **3a**, **4a**; (*b*) medium-bridged compounds: **1b**, **3b**, **4b**; (*c*) unsubstituted longer-bridged compounds: **1c**, **3c**, **4c**; (*d*) substituted longer-bridged compounds: **6a**, **6b**, **7a**, **7b**. The conformations, which are described in the Experimental section, are listed in the order of increasing strain energy for the thiazolium salts **1a–c**. The lines simply connect the points belonging to the same compound and are not intended to indicate a pathway for interconverting the different conformations.

The calculations at a relative permittivity of 20 still predict that the lowest energy conformation of the thiazolium salt **1c** is as shown in Fig. 2. This was also the most stable conformation of the corresponding thiazol-2(3*H*)-one **3c**§ and dihydrothiazole **4c**. However, the second conformation for all three of these compounds was now predicted to be one having the carbonyl oxygen atom α (βαβ–αβα). For **3c** this conformation was only *ca.* 1 kJ mol^{-1} above the lowest one. It should be noted, however, that MM2 calculations do not deal very well with delocalized systems, especially cyclic ones. Furthermore the MM2 parameters used contained the charge distribution for a normal thiazolium cation but not for a thiazol-2(3*H*)-one.

‡ Unfortunately the MM2 parameters were not available for the thione functionality of thiazole-2(3*H*)-thiones **2a–c**. The predicted conformations for **3c** are very similar in structure and relative energy to those predicted for the thiazole-2(3*H*)-thione **2c** using some estimated parameters (based on bond lengths from the crystal structures and otherwise keeping the same parameters as for the equivalent C=O).

§ On comparing the calculated lowest energy conformation for thiazol-2(3*H*)-one **3c** with the crystal structure of the corresponding thione **2c**, the RMS deviation of the positions of the atoms of the bridge (including N-3 and C-5) was 0.06 Å.

Therefore the calculations on the latter type of compounds should be regarded as less reliable.

For the dimethylamino- and acetamido-substituted compounds, **6** and **7**, the predictions from the molecular mechanics calculations on the corresponding thiazol-2(3*H*)-ones are entirely in accord with the NMR data. The lowest energy conformation calculated for both major isomers, **6a** and **7a**, is the same as for the unsubstituted thiazolinone **3c** (αβ–αβαβ, see Fig. 2). For both minor isomers **4b** and **5b**, however, this conformation is considerably raised in energy due to steric interactions of the acetamido or dimethylamino substituent, mainly with the methyl group on the ring. As a result the conformation that was the second lowest for **3c** (βαβ–αβα) becomes the lowest for these compounds. This again is fully in accord with the NMR data (see Fig. 4).

Calculations on the shorter bridged thiazolium salt **1b** and its corresponding thiazol-2(3*H*)-one **3b** showed the lowest energy conformation to be as illustrated in Fig. 2 (αβαβαβ), fully consistent with the NMR data and virtually identical to the conformation of the corresponding thiazolinethione **2b** in the crystal structure.¶ For **3b** this lowest energy conformation was closely followed by a second one (βαβαβα) only 0.5 kJ mol^{-1} higher in energy. There is some evidence from the NMR spectrum that this might be a minor contributing conformation: the coupling constant between 6α-H and 7β-H (9.9 Hz) is lower than expected for the antiperiplanar relationship shown in Fig. 2. However, the contribution of this second conformation cannot be as high as indicated by the small difference in calculated energies. It seems that the predicted energies for conformations of thiazol-2(3*H*)-ones having the ester carbonyl α are still too low compared with ones with the ester carbonyl β despite the change in relative permittivity. For the thiazolium salt **1b** the equivalent conformation is 1.5 kJ mol^{-1} above the lowest one.

The conformations of the dihydrothiazole **4b** were also investigated. Surprisingly the most stable conformation (αβ–αβα) was quite different from that of **1b** or **3b**. A further new conformation (βα–βαβ), only 1.7 kJ mol^{-1} higher in energy, corresponds to the conformation deduced from NMR data for the bridge in the 2-benzoyldihydrothiazole **5** (see Fig. 5). It was speculated above that this conformation is observed because other conformations would be destabilized by steric interactions with the styryl group on C-4. This was confirmed by molecular mechanics calculations on the 4-styryl derivative of **4b** (*i.e.* compound **5** without the benzoyl group) in which the conformation shown in Fig. 4 becomes the most stable by 4.0 kJ mol^{-1}. In every predicted conformation the styryl group is twisted out of the plane of the atoms N–C-4=C-5, apparently due to steric repulsion between the benzylidene hydrogen atom and 9α-H, but the conformation shown in Fig. 4 is the one in which the least twisting of the styryl group is required.

Calculation of ring-strain

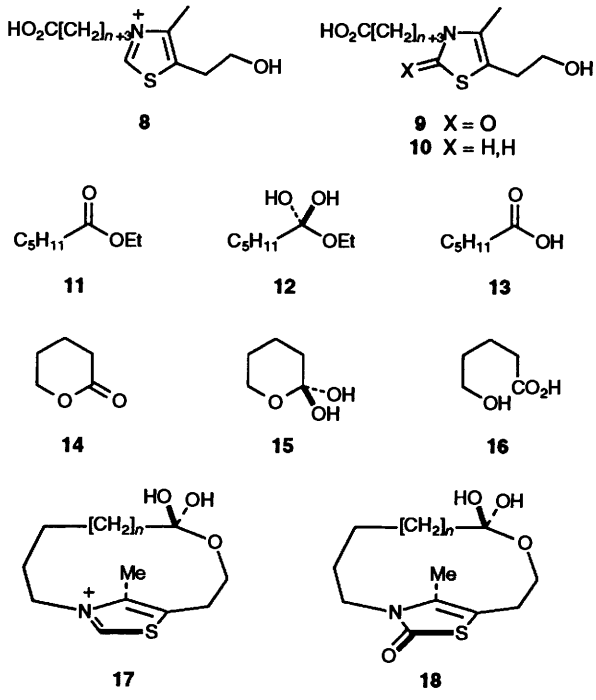
The success of the molecular mechanics calculations in predicting the observed conformations of the various bridged compounds gave us confidence to extend the calculations to provide a measure of the strain caused by the bridge. Because the energies calculated by molecular mechanics can only be taken as relative and not absolute, it is important to compare the energy of the strained molecules with analogues which are as close as possible but lack the strain. Therefore, the energies calculated for the most stable conformation of each of the bridged compounds **1a–c** were compared with the corresponding energies of the corresponding open-chain hydroxy acids **8a–c**, in their most extended conformations. The results are shown in Table 3. The difference in energy between the ester and its hydrolysis product (ΔE) should be compared with the corresponding value (ΔE_0) calculated for an unstrained acyclic compound (14.01 kJ mol^{-1} for ethyl hexanoate **11** ⟶ hexanoic acid **13** + ethanol). The value of $\Delta E - \Delta E_0$ provides a measure

¶ On comparing the calculated lowest energy conformation for thiazol-2(3*H*)-one **3b** with the crystal structure of the corresponding thione **2b**, the RMS deviation of the positions of the atoms of the bridge (including N-3 and C-5) was 0.07 Å.

Table 3 Steric energies (kJ mol^{-1}) calculated by molecular mechanics (MM2) and the calculation of strain energies for the bridged compounds

Steric energy (E)						Strain energy ($\Delta E - \Delta E_0$)[a]	
Ester		Hydrate		Hydroxyacid		Ester	Hydrate
Acyclic standard							
11	21.69	**12**	51.00	**13** + EtOH	7.68	0	0
Shortest bridged compounds							
1a	86.52	**17a**	147.97	**8a**	13.34	59.17	91.31
3a	92.48	**18a**	152.67	**9a**	20.92	57.55	88.43
4a	72.41			**10a**	14.16	44.24	
Medium bridged compounds							
1b	82.09	**17b**	123.29	**8b**	16.07	52.01	63.90
3b	89.70	**18b**	132.47	**9b**	23.63	52.06	65.62
4b	73.64			**10b**	16.87	42.76	
Longer bridged compounds							
1c	61.69	**17c**	100.20	**8c**	18.73	28.95	38.15
3c	70.62	**18c**	108.51	**9c**	26.34	30.27	38.85
4c	55.57			**10c**	19.57	21.99	
Six-membered ring							
14	22.45	**15**	52.62	**16**	1.38	7.06	7.92

[a] The strain energy given is $\Delta E - \Delta E_0$ where ΔE is (energy of the ester or tetrahedral intermediate) − (energy of the open-chain compound) and ΔE_0 is the ΔE value for ethyl hexanoate (14.01 kJ mol^{-1}) or its tetrahedral intermediate (43.32 kJ mol^{-1}) as appropriate.



of the strain in each bridged compound.‖ As expected this value decreases with increasing bridge length from 59.17 kJ mol^{-1} for **1a** to 52.01 kJ mol^{-1} for **1b** and 28.95 kJ mol^{-1} for **1c**. For comparison, the strain energy for the six-membered ring lactone **14**, calculated in the same way, came to 7.06 kJ mol^{-1}.

The steric energy calculated by molecular mechanics is an enthalpy value and takes no account of the contribution of entropy to the total free energy. Compounds in which there is greater flexibility will have higher entropy and thus lower free energy. Some idea of the flexibility of a compound can come from the number of conformations close in energy to the lowest one. For thiazolium salt **1c** there were nine further conformations predicted within 14.3 kJ mol^{-1} of the lowest one and for **1b** there were eight within 10.1 kJ mol^{-1}, but for **1c** there were no other conformations within 18 kJ mol^{-1} of the lowest one. Hence considerations of entropy would increase the difference in strain energy between thiazolium salts **1b** and **1a**.

In our previous paper it was argued that it was relief of strain that led to the formation of the 2-benzoyl-2,3-dihydrothiazole **5** from the thiazolium salt **1b**. In order to test this proposal it was necessary to assess the degree of strain in bridged 2,3-dihydrothiazoles **4a–c**, again comparing the energies with those of the corresponding hydrolysed compounds **10a–c**. These results are also shown in Table 3. In all cases, it can be seen that the predicted strain is reduced in going from the thiazolium salt to the dihydrothiazole. Furthermore, the magnitude of the strain released increases as the bridge gets shorter from 6.96 kJ mol^{-1} for **1c** to 9.25 kJ mol^{-1} for **1b** and 14.93 kJ mol^{-1} for **1a**. The additional 2.29 kJ mol^{-1} of strain released for thiazolium salt **1b** compared with **1c** may be enough to account for the isolation of a 2-benzoyl-2,3-dihydrothiazole from the former but not the latter.

In order to understand why it was relatively easy to synthesize thiazole-2(3*H*)-thione **2c** by a macrolactonization procedure, more difficult for **2b** and impossible for **2a**, the strain energies of the three thiazol-2(3*H*)-ones **3a–c** and the three corresponding tetrahedral intermediates **18a–c** were calculated (see Table 3). For the longer bridged intermediate **18c** the strain is 8.58 kJ mol^{-1} higher than for the ester **3c**, but for **18b** it is 13.56 kJ mol^{-1} higher than in **3b**, and for **18a** it is 30.88 kJ mol^{-1} higher than in **3a**. Thus the strain in the ester is magnified in the tetrahedral intermediate. It is reasonable to assume that the strains involved in the transition states for the macrolactonization reactions would follow a similar trend and this provides a satisfactory rationale for the yields obtained. Similar increases in strain were observed in going from thiazolium esters **1a–c** to their tetrahedral intermediates **17a–c** (see Table 3). In contrast the strain of the simple six-membered ring lactone **14** scarcely increased at all on going to its tetrahedral intermediate **15**. This implies that it should be more difficult to hydrolyse esters **1a–c** than normal esters. This is exactly what was observed: hydrolysis of the ester groups of the open-chain thiazolium salt **8** occurred much more readily than for the corresponding bridged compounds **1a** and **b**.[1] A more sophisticated approach to the calculation of the rates of lactonization reactions by Dorigo and Houk[4] uses a modified MM2 force-field to predict the relative energies of the transition states for the lactonization of various rigid hydroxy acids. However the simple approach used here appears to explain the observed differences in rates quite adequately and so more sophisticated methods were not attempted.

‖ A similar definition of strain has been adopted in a recent paper on simple lactones[3] but there the ring was broken by replacing a sp^{3}C–sp^{3}C bond by two C–H bonds and the standard 'unstrained' ring-opening reaction was cyclohexane ⟶ hexane. Using this definition the measured strain for valerolactone **14** was 11.2 kcal mol^{-1} (1 cal = 4.184 J).

Table 4 Crystal data and solution and refinement parameters for compounds **2b** and **2c**

	2b	**2c**
Empirical formula	$C_{11}H_{15}NO_2S_2$	$C_{12}H_{17}NO_2S_2$
Formula weight	257.36	271.39
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/n$	$P2_1/c$
Unit cell dimensions		
a/Å	10.888(3)	10.151(1)
b/Å	10.153(3)	10.447(1)
c/Å	11.456(4)	12.484(2)
β/°	92.78(2)	90.51(1)
V/Å^3	1264.9(7)	1323.8(3)
Z	4	4
D_c/g cm^{-3}	1.351	1.362
F(000)	544	576
X-Ray wavelength/Å	1.5418	1.5418
μ(Cu-Kα)/cm^{-1}	37.06	35.69
Crystal dimensions/mm	0.29 × 0.35 × 0.41	0.14 × 0.48 × 0.48
Reflections collected	1889	3711
θ range for data collection/°	5.0–116.0	7.0–116.0
Independent reflections	1723	1805
Number of parameters refined	149	208
Goodness-of-fit on F^2	1.043	0.894
R indices [$I > 2\sigma(I)$]	$R_1 = 0.1218$	$R_1 = 0.0325$
	$wR_2 = 0.3228$	$wR_2 = 0.0876$
R indices (all data)	$R_1 = 0.1255$	$R_1 = 0.0342$
	$wR_2 = 0.3301$	$wR_2 = 0.0893$
Largest diff. peak and hole (e Å^{-3})	1.136, −1.303	0.258, −0.194

In summary, the values for the strain energy predicted by these calculations appear to conform qualitatively both with what would be expected and what has been observed in the synthesis and reactions of these compounds. It would seem that molecular mechanics calculations, if applied carefully, can give useful estimates for the degree of strain to be expected in bridged compounds. The strain energies of tetrahedral intermediates such as **18a–c** can give guidelines as to which compounds will be difficult to make by macrolactonization. From the values in Table 3, it would be reasonable to conclude that strain energies up to 40 kJ mol^{-1} should present no special difficulties, reduced yields may be seen for energies up to 70 kJ mol^{-1}, and it would be extremely difficult to obtain useful yields if the strain energy is even higher.

It is hoped that the analysis of the predicted strain energies presented here will prove useful in evaluating other macrolactonization reactions and that the techniques can be extended to other types of cyclization.

Experimental

X-Ray crystal structure determinations

The structures of compounds **2b** and **2c** were determined by single-crystal X-ray diffraction. Details of data collection parameters and of the structure solutions and refinement are presented in Table 4. Data was collected at room temperature on a Nicolet R3mμ diffractometer using graphite-monochromated Cu-Kα radiation. Semi-empirical absorption corrections based on psi-scan data were applied. The structures were solved by direct methods and refined, with non-hydrogen atoms assigned anisotropic displacement parameters, by full-matrix least-squares based on F^2. For compound **2b** the H-atoms were placed in idealized positions and allowed to ride on the relevant C-atom. For compound **2c** the H-atoms were located in the electron-density difference map and refined freely. During the final cycles of refinement a weighting scheme of the general form $wr^{-1} = [\sigma^2(F^2) + (xP)^2 + yP]$ where $P = (F_o^2 + 2F_c^2)/3$ was

applied and the structures refined to convergence. Calculations were performed on a Viglen 486 DX33 computer using SHELXTL-PLUS[5] and SHELXL-93.[6] Atomic coordinates, bond lengths and angles and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre. See Instructions for Authors, *J. Chem. Soc., Perkin Trans. 2*, 1995, Issue 1.

Molecular mechanics calculations

All calculations were performed with the MacroModel program,[2] version 2.5, using the MM2 parameters contained in that program and running on a MicroVax 3 computer with an Evans and Sutherland PS390 display. Energy minimization was carried out using the BDNR method. To find the global minimum energy conformation a large number of starting conformations were generated by varying dihedral angles about the bonds in the bridge in order to bring two specified atoms of the bridge within a reasonable closure distance. For **1c**, **3c** and **4c** the dihedral angles about C-5/6, C-6/7, C-7/O, N-3/C-9, C-9/10 and C-10/11 were set at six 60° intervals (from 180 to −120°), the angle about the ester C–O bond was set at 0 and 180°. C-12 and C-13 were chosen as the ring-closure atoms. Acceptable ring-closure distances were between 0.5 and 3 Å and the minimum non-bonded distance allowed was 1 Å (except that for **4c** values of 1–2 Å and 1.5 Å were used). For the shorter bridged compounds the same parameters were used (except that less dihedral angles were needed); the ring-closure atoms were always the ones α and β to the ester. For **6a** and **b** and **7a** and **b** the angles about N-3/C-9 and C-5/6 were set at 60 and 120° only so as to avoid obtaining the other atropisomer (*i.e.* bridge under the thiazolium ring instead of over) and six dihedral angles were also set for the C-13/N bond. The number of acceptable conformations which were then minimized was 120–140 for the longer bridged compounds and 70–100 for the shorter ones. When comparison of the conformations found for different compounds revealed a conformation missing for one of the compounds, it was generated by modification of the corresponding conformation of the other compound. In this way a complete set of conformations was constructed for all the compounds studied.

It was found convenient to classify the various conformations in terms of the direction in which each atom of the bridge is pointed (starting with C-10 and finishing with C-7): 'α' indicates pointing towards the side of C-4 and the methyl group, 'β' indicates pointing towards the side of S-1 and C-2, '–' indicates an intermediate position. Thus the conformation of thiazole-3(2*H*)-thione **2c** shown in Fig. 2 would be classified as αβ–αβαβ. The various possible conformations have been given labels in which the first letter, A or B, indicates whether the ester carbonyl group is α or β respectively. For the longer bridges the conformations are then numbered as follows: A1, αβαβαβα; A2, β–αβαβα; A3, βα–βαβα; A4, βαβ–αβα; A5, ααββαβα; A6, ββααβα. The B conformations are exactly the reverse of the A ones, *viz.*: B1, βαβαβαβ; B2, α–βαβαβ; B3, αβ–αβαβ; B4, αβα–βαβ; B5, ββααβαβ. An asterisk following one of these conformation numbers indicates that C-7 adopts the opposite orientation but all the other atoms have the same orientation. In the unsubstituted bridged compounds, **1c**, **3c** and **4c**, there was only one of each type of conformation found (except there was one minor variant of B1 at relatively high energy), whereas for the substituted analogues, **6** and **7**, up to three conformations of each type were found due to rotamers about the C-13–N bond [only the lowest energy of each set of three is shown in Fig. 6(*d*)]. No other conformations other than those classified above were found within 16 kJ mol^{-1} of the lowest energy one for any of the compounds.

In the medium bridged compounds, **1b**, **3b** and **4b**, a similar labelling system for the predicted conformations is used: A1, βαβαβα; A2, α–βαβα; A3, αβ–αβα; B1, αβαβαβ; B2, β–αβαβ; B3, βα–βαβ; B4, ββαβαβ. For the shortest bridged compounds, **1a**, **3a** and **4a**, the labels used are: A1, αβαβα; A2, β–αβα; B1, βαβαβ; B2, α–βαβ.

The strain energies of all the major conformations are collected in Fig. 6.

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References

1 F. J. Leeper and D. H. C. Smith, *J. Chem. Soc., Perkin Trans. 1*, 1995, 861.
2 F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson and W. C. Still, *J. Comput. Chem.*, 1990, **11**, 440.
3 K. B. Wiberg and R. F. Waldron, *J. Am. Chem. Soc.*, 1991, **113**, 7697.
4 A. E. Dorigo and K. N. Houk, *J. Am. Chem. Soc.*, 1987, **109**, 3698.
5 SHELXTL-PLUS, Version 4.0, Siemens Analytical X-Ray Instruments Inc., Madison, WI, 1990.
6 G. M. Sheldrick, SHELXL 93, Package for crystal structure refinement, Göttingen, 1993.

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