Proton Magnetic Resonance Studies of Compounds with Bridgehead Nitrogen. Part XXIX.[1] Configurational and Conformational Studies with Derivatives of Perhydro-oxazolo[4,3-*c*][1,4]thiazine

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Configurational and conformational assignments have been made to a range of substituted perhydro-oxazolo-[4,3-*c*][1,4]thiazines on the basis of n.m.r. and i.r. spectroscopic data. In contrast to perhydro-oxazolo[4,3-*c*][1,4]-oxazine which exists in solution at room temperature as *ca.* 86% *cis*-fused conformation in equilibrium with 14% *trans*-fused conformation, perhydro-oxazolo[4,3-*c*][1,4]thiazine is shown to exist as *ca.* 84% of the *trans*-fused conformation. This difference in conformational preference is discussed in terms of ring fusion strain. *cis*-(6-H-8a-H)-6-Methyl-, 6-ethyl-, and 6-phenyl-perhydro-oxazolo[4,3-*c*][1,4]thiazine exist in solution at room temperature as *cis*-fused ⇌ *trans*-fused conformational equilibria containing *ca.* 44, 34, and 63% *cis*-fused conformers respectively.

WHEREAS perhydro-oxazolo[3,4-*a*]pyridine exists in solution at room temperature as an equilibrium mixture (1) ⇌ (2) containing from *ca.* 68% (CCl_4)[2] to *ca.* 76% ($CDCl_3$)[3] of the *trans*-fused conformer (1), perhydro-oxazolo[4,3-c][1,4]oxazine exists, under the same conditions, as *ca.* 86% *cis*-fused conformation (4) in equilibrium

[1] Part XXVIII, T. A. Crabb and G. C. Jackson, *Org. Magnetic Resonance*, in the press.

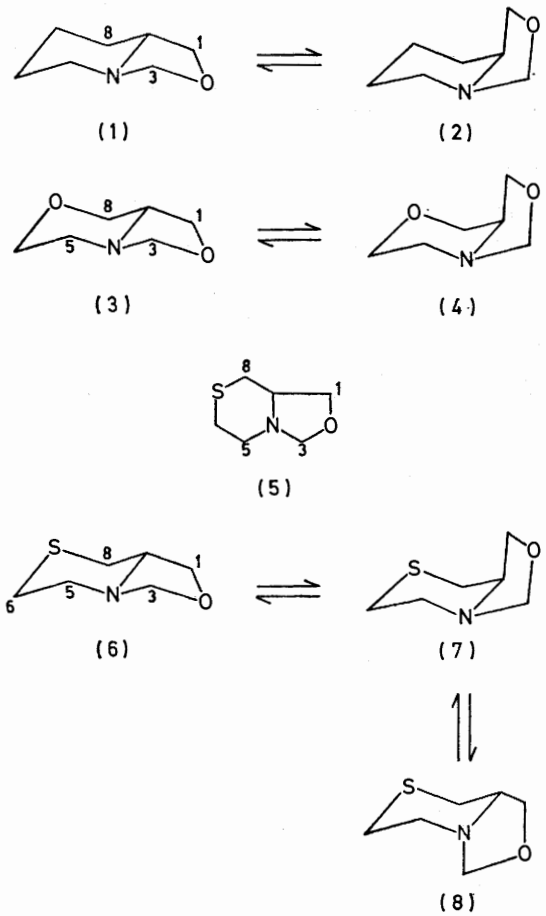
[2] T. A. Crabb and M. J. Hall, *J.C.S. Perkin II*, 1974, 1419.

[3] Y. Takeuchi, P. J. Chivers, and T. A. Crabb, *J.C.S. Perkin II*, 1974, 51.

with *ca.* 14% of (3). The alternative *cis*-fused conformations in both systems are not present in detectable amounts.*

This difference in conformational preference was interpreted in terms of an increase in the strain involved in ring-fusion in (3) consequent upon the smaller morpholine ring in (3) compared with the piperidine ring in (1) and the replacement of a *gauche* butane interaction in (2) by an energetically far more favoured [4] *gauche* propanol type interaction in (4).

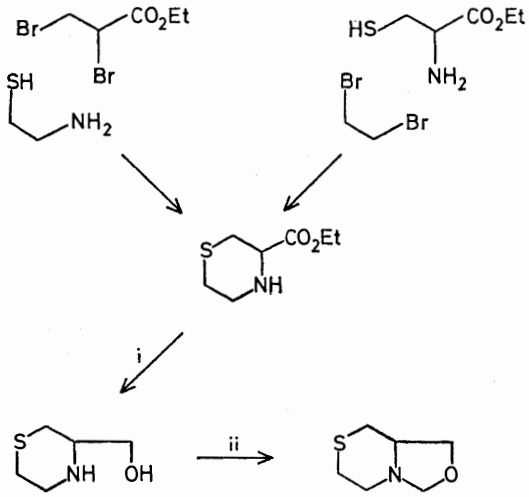
In order to investigate these effects further perhydro-oxazolo[4,3-*c*][1,4]thiazine (5) and its derivatives were selected for study since here the ring fusion strain in (6)



should be much less than in (1) and (3) as a result of the presence in (6) of the long C–S bonds (1.82 Å, *cf.* C–O, 1.43 Å; C–C, 1.54 Å) which gives the tetrahydro-1,4-thiazine ring considerable flexibility. Examination of published work [4] concerned with non-bonded interactions involving heteroatoms suggests a negligible energy difference between the *gauche* propanol type interaction in (4) and the *gauche* propanethiol type interaction in (7), so that this factor should not be responsible for a marked difference between the positions of conformational equilibria in the two systems [(3) ⇌ (4) and (6) ⇌ (7)].

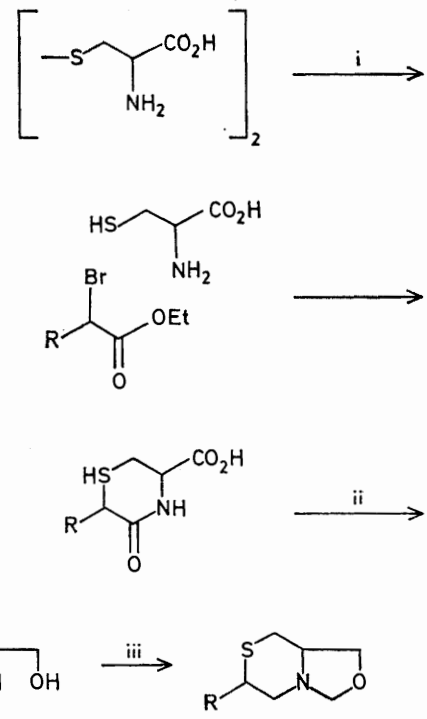
* The compounds described in this paper exist as racemates and in the conformational equilibria the structures are drawn for ease of representation and do not necessarily correspond to the same enantiomer.

Conformation (8) should contribute only to a very small extent to the room temperature equilibrium.



SCHEME 1 Reagents: i, $LiAlH_4$; ii, 40% aqueous CH_2O

Synthesis of Compounds.—Perhydro-oxazolo[4,3-*c*]-[1,4]thiazine (5) was prepared as shown in Scheme 1. Cysteamine was condensed [5] with ethyl 2,3-dibromopropionate in the presence of triethylamine to give ethyl



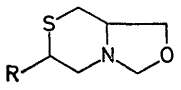
SCHEME 2 Reagents: i, Na–NH_3; ii, $LiAlH_4$; iii, 40% aqueous CH_2O

perhydro-1,4-thiazine-3-carboxylate. This was reduced [6] with lithium aluminium hydride to perhydro-1,4-thiazin-3-ylmethanol in rather poor yield, a large amount of gummy material being also produced. Condensation

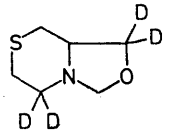
[4] E. L. Eliel, *Accounts Chem. Res.*, 1970, **3**, 1.
[5] B. Belleau, *J. Medicin. Pharm. Chem.*, 1960, **2**, 553.
[6] J. R. Piper and T. P. Johnson, *J. Org. Chem.*, 1963, **28**, 981.

of this amino-alcohol with formaldehyde gave the required perhydro-oxazolo[4,3-*c*][1,4]thiazine (5).

The remaining perhydro-oxazolo[4,3-*c*][1,4]thiazines (9)—(11) were synthesised [7] according to the route outlined in Scheme 2. Cystine was reduced with sodium in



(9) R = Me
(10) R = Et
(11) R = Ph



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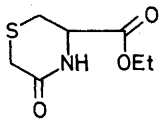


(13)

liquid ammonia to cysteine which was reacted *in situ* with an ethyl α-bromo-ester to give the 6-substituted 5-oxoperhydro-1,4-thiazine-3-carboxylic acid. Reduction with lithium aluminium hydride gave the 6-substituted perhydro-1,4-thiazin-3-ylmethanol which was condensed with formaldehyde to give the 6-substituted perhydro-oxazolo[4,3-*c*][1,4]thiazine. In each case, n.m.r. spectroscopy showed the product to be a mixture of two isomers, and one isomer of each pair, designated isomer A [shown below to be the *trans*(6-H,8a-H)-6-substituted isomer] was readily separated by fractional recrystallisation. Isomer B of (9) and of (10) was not obtained pure, but column chromatography followed by careful recrystallisation provided isomer B of (11) in a pure state.

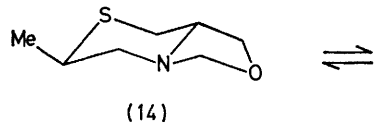
To assist in the interpretation of the n.m.r. spectra of these compounds 1,1,5,5-tetradeuterioperhydro-oxazolo-[4,3-*c*][1,4]thiazine (12) was synthesised from ethyl 5-oxoperhydro-1,4-thiazine-3-carboxylate (13), itself prepared by reaction of cysteine ethyl ester with ethyl chloroacetate. Reduction of (13) with lithium aluminium deuteride gave dideuterio-(5,5-dideuterioperhydro-1,4-thiazin-3-yl)methanol in poor yield, along with a considerable amount of gummy material. Condensation of this compound with formaldehyde afforded perhydro-1,1,5,5-tetradeuterio-oxazolo[4,3-*c*][1,4]thiazine (12).

Assignment of Stereochemistry.— (a) *I.r. spectra.* It may readily be seen from the 2 800—2 500 cm^{-1} region of the i.r. spectra of the perhydro-oxazolo[4,3-*c*][1,4]thiazines (tabulated in Table 1) that the compounds fall into two distinct groups, those with very strong Bohlmann bands [8] and those with weaker bands. The former group, which includes the parent compound (5) must therefore exist predominantly in the *trans*-fused conformation, and the latter predominantly in one of the *cis*-fused conformations.

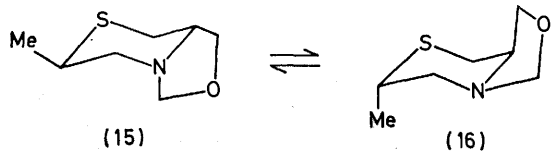
[7] M. Nakanishi and T. Muro, *Yakugaku Zasshi*, 1970, **90**, 570.
[8] F. Bohlmann, *Angew. Chem.*, 1957, **69**, 641.

From a consideration of these results and of Dreiding models it is possible to make preliminary configurational and conformational assignments. In the case of the *trans*(6-H,8a-H)-6-methyl isomer (Figure), both (14) and (15) suffer from an unfavourable generalised anomeric effect.[9] An approximate assessment of non-bonded interactions shows the anomeric effect to be relieved in (16) at the expense of introducing two *gauche* butane interactions, a methyl–nitrogen atom interaction, a methylene–sulphur atom interaction, and a methylene–oxygen atom interaction. Similarly, *cis*-fusion in (15) involves two *gauche* butane interactions in addition to the unfavourable anomeric effect. Hence it would appear probable that the *trans*(6-H,8a-H)-6-methyl isomer exists predominantly in conformation (14).

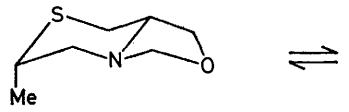
Similar argument applied to the *cis*(6-H,8a-H)-6-methyl isomer. Structures (17)—(19) (Figure) suggest



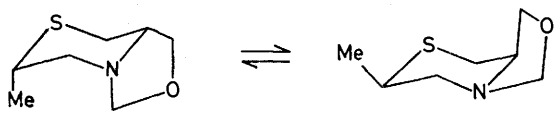
(14)



(15) (16)



(17)



(18) (19)

FIGURE Conformational equilibria for *trans*- and *cis*-(6-H,-8a-H)-6-methylperhydro-oxazolo[4,3-*c*][1,4]thiazine

that the compound might be expected to exist predominantly as an equilibrium mixture between (17) and (19). In the former there exists an unfavourable anomeric effect and a *gauche* butane and *gauche* propylamine interaction associated with the axial methyl group, while in the latter the dipolar interaction is relieved but *gauche* butane and methylene–heteroatom interactions, due to the *cis*-ring-fusion, are present. Conformation (18) however can be discounted since, not only is the dipolar geometry still unfavourable, but also there are non-bonded interactions

[9] S. Wolfe, A. Rauk, L. M. Tel, and I. G. Csizmadia, *J. Chem. Soc.* (*B*), 1971, 136; H. Booth and R. U. Lemieux, *Canad. J. Chem.*, 1971, **49**, 777.

present due to the axial methyl group and the *cis*-fusion. Similar arguments apply to the other diastereoisomeric pairs, (10) and (11).

(b) *N.m.r. spectra.* (i) *Perhydro-oxazolo*[4,3-*c*][1,4]-thiazine (5). Clearly discernible in the n.m.r. spectrum

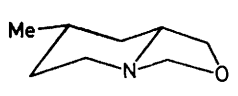
TABLE 1

I.r. spectra (CCl_4) of perhydro-oxazolo[4,3-*c*][1,4]thiazines

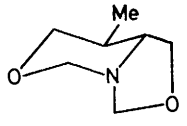
Perhydro-oxazolo [4,3-*c*][1,4]thiazine	Wavenumber (cm^{-1})	ε_{max} (apparent)
(5)	2 773	103
	2 744	56
	2 710	33
	2 699	36
(9A)	2 776	105
trans(6-H,8a-H)-6-Methyl	2 745	40
	2 710	26
	2 697	26
(10A)	2 772	111
trans(6-H,8a-H)-6-Ethyl	2 745	44
	2 713	30
	2 698	31
	2 660	16
(11A)	2 775	93
trans(6-H,8a-H)-6-Phenyl	2 740	35
	2 713	26
	2 700	23
(9B)	2 766	66
cis(6-H,8a-H)-6-Methyl *	2 740	36
	2 700	13
(11B)	2 777	44
cis(6-H,8a-H)-6-Phenyl	2 752	15

* The values for this compound were obtained from a 0.2M solution of a mixture of (9B) (*ca.* 75%) and (9A) (*ca.* 25%) from which the peak-heights obtained from a 0.05M solution of (9A) were subtracted before ε_{max}(apparent) was calculated for a 0.15M solution of (9B). The percentage composition of the mixture was gained from the integration of its n.m.r. spectrum. In all cases the path length was 0.1 mm.

of (5) is the low field AB quartet for 3-H_2 with δ 4.40 and 3.66. The J_{gem} value of −1.6 Hz implies [10,11] that either (6) or (8) predominates in the conformational equilibrium which exists among (6)—(8). The higher field half of the quartet partially obscures a multiplet corresponding to one of 1-H_2 but the sum of $|J_{1'ax',1'eq'}|$ and the vicinal coupling with 8a-H was readily measured as 12.7 Hz. The signal for the other proton on C(1) appears as a quartet centred at δ 3.27 and analysis gave coupling



(20)



(21)

constants of 6.6 and 9.1 Hz. These values correspond closely with the coupling constants between the higher field 1-H and 8a-H in the *trans*-fused derivatives of perhydro-oxazolo[3,4-*a*]pyridine [*e.g.* (20), $J_{1'ax',1'eq'}$ −6.4 $J_{1'ax',8a}$ 9.2 Hz [10]], while bearing no relation to the values for the corresponding protons in the *cis*-fused perhydro-oxazolo[3,4-*c*][1,3]oxazines [*e.g.* (21), $J_{1\alpha,1\beta}$ −7.6, $J_{1\beta,8a}$ 1.4 Hz [11]]. Thus the quartet centred at δ 3.27 may be assigned to 1'ax'-H and the couplings to $J_{1'ax',1'eq'}$ (−6.6 Hz) and $J_{1'ax',8a}$ (9.1 Hz) in conformation (6).

[10] T. A. Crabb and R. F. Newton, *Tetrahedron*, 1968, **24**, 1997.
[11] T. A. Crabb and M. J. Hall, *J.C.S. Perkin II*, 1973, 1379.

Since $|J_{1'ax',1'eq'}| + J_{1'eq',8a}$ has been determined as 12.7 Hz, $J_{1'eq',8a}$ is seen to be 6.1 Hz which corresponds with the value of $J_{1'eq',8a}$ in (20) (6.0 Hz).

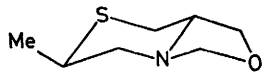
In the n.m.r. spectrum of 1,1,5,5-tetradeuterioperhydro-oxazolo[4,3-*c*][1,4]thiazine (12), the 1-H_2 signals are, as expected, absent. Further simplification can be seen in the region of δ 2.75, for the two-proton multiplet observed in the n.m.r. of (5) has been replaced by a one-proton broadened doublet (*J* 13.2 Hz). This multiplet must be due to one of 6-H_2, a conclusion derived from its chemical shift and its simplification by deuteriation at C(5). In the n.m.r. spectra of many saturated heterocyclic systems [12,13] containing a sulphur atom axial protons absorb at lower field than the geminal equatorial protons and this has been attributed to the difference in anisotropy of the C–S bonds compared with the C–C bonds in the carbocyclic analogues. Thus in (6), 6ax-H is expected to absorb at lower field than 6eq-H and accordingly the broadened doublet at δ 2.65 was assigned to the former proton. In support of this is the J_{gem} of −13.2 Hz, typical of S-CH_2 protons in a six-membered ring.[13]

In conclusion, therefore, the i.r. and n.m.r. data are completely in accord with the existence of perhydro-oxazolo[4,3-*c*][1,4]thiazine (5) predominantly in the *trans*-fused conformation (6), and if $J_{3ax,3eq}$ −0.8 and $J_{3ax,3eq}$ −6.0 Hz are taken as values typical of 100% *trans*-fused and 100% *cis*-fused conformations respectively [2] then $J_{3ax,3eq}$ −1.6 Hz observed for (12) indicates an equilibrium containing *ca.* 84% (6).

(ii) *6-Methyl-, 6-ethyl-, and 6-phenylperhydro-oxazolo-*[4,3-*c*][1,4]*thiazines* (9A)—(11A). Of the two isomers which were obtained in each case by the route shown in Scheme 2, one, designated A, was separated easily by fraction recrystallisation (the methyl compound), or column chromatography (the ethyl compound), and in each case was assigned (see below) the *trans*(6-H,8a-H)-6-substituted configuration and a *trans*-fused conformation.

The 220 MHz n.m.r. spectrum (Tables 2 and 3) of the methyl isomer which melted at 74—75° (9A), was completely analysable and defined the stereochemistry (22) exactly.

trans-Fusion is confirmed by the value of −0.7 Hz for $J_{3'ax',3'eq'}$ and the coupling constants associated with the protons on C(8), C(8a), and C(1). $J_{8ax,8eq}$ (−12.2 Hz), $J_{8ax,8a}$ (10.2 Hz), and $J_{8eq,8a}$ (1.9 Hz) are typical of a chair conformation of the six-membered ring and the latter two



(22)

constants, being typical of ax,ax- and ax,eq-geometries, show 8a-H to be axial with respect to the six-membered

[12] E. Campaigne, N. F. Chamberlain, and B. E. Edwards, *J. Org. Chem.*, 1962, **27**, 135; T. A. Crabb and R. F. Newton, *Tetrahedron*, 1970, **26**, 3941.
[13] Y. Allingham, R. C. Cookson, and T. A. Crabb, *Tetrahedron*, 1968, **24**, 1989.

ring. By comparison with the spectra of *trans*-fused perhydro-oxazolo[3,4-*a*]pyridines [10] the values of $J_{8a,1\alpha}$ (6.0 Hz) and $J_{8a,1\beta}$ (9.4 Hz) prove the predominance of (22) in the conformational equilibrium.

The conformation about C(6) is revealed by the magnitude of the couplings between the protons on C(5) and of an equatorial 6-methyl group. Additional evidence is given by the large chemical shift difference (0.89 p.p.m.) between the C(5) protons. This is due to the shielding effect that an equatorial methyl group imposes upon a vicinal axial proton,[15] superimposed upon the preferential shielding of 5ax-H by the lone pair on the nitrogen atom [16]

TABLE 2

N.m.r. spectra (chemical shifts) of the predominantly *trans*-fused perhydro-oxazolo[4,3-*c*][1,4]thiazines in benzene

Perhydro-oxazolo-[4,3-*c*][1,4]-thiazine	Spectrometer operating frequency	Chemical shifts (δ)										
		3'eq'-H	3 'ax'-H	1'eq'-H	1'ax'-H	6ax-H	5eq-H	8ax-H	8a-H	8eq-H	5ax-H	Others
(5)	220	4.40	3.66	3.65	3.27	*ca.* 2.7 (m)	2.62	2.42—2.25 (m)		2.22 (m)		1.98 including 6eq-H
(9A)	220	4.46	3.66	3.67	3.24	2.90	2.58	2.41	2.22	2.02	1.69	0.91 (6eq-Me)
(10A)	60	4.50	3.73	3.76	3.31	*ca.* 2.72	2.82	2.6	—	2.0 (m)	1.80	1.34 and 0.88 (6eq-Et)
(11A)	220	4.44	3.70	3.71	3.29	4.03	2.81	2.50	2.32	2.07	2.25	

TABLE 3

N.m.r. spectra (coupling constants) of perhydro-oxazolo[4,3-*c*][1,4]thiazines in C_6H_6

Perhydro-oxazolo-[4,3-*c*][1,4]-thiazine	Spectrometer operating frequency	Coupling constants (Hz)										
		$J_{3ax,3eq}$	$J_{1ax,1eq}$	$J_{5ax,5eq}$	$J_{8ax,8eq}$	$J_{5ax,6ax}$	$J_{5eq,6ax}$	$J_{8ax,8a}$	$J_{8eq,8a}$	$J_{8a,1eq}$	$J_{8a,1eq}$	Others
(5)	220	−1.6	−6.6							6.1	9.1	$J_{6ex,6eq}$ −13.2
(9A)	220	−0.7	−7.0	−10.9	−12.2	10.3	3.2	10.2	1.9	6.0	9.4	$J_{6ax,Me}$ 6.8
(10A)	60	−1.0	−6.5	−11.3		10.8	2.8			5.5	9.0	$J_{6ax-methylene}$ 6.7
(11A)	220	−1.2	−6.9	−11.2	−12.3	10.6	3.0	10.4	1.9	6.2	9.2	

C(6). While the magnitude of $J_{5ax,5eq}$ (−10.9 Hz) confirms the chair conformation of the six-membered ring with an axially orientated nitrogen lone pair, the other couplings,

TABLE 4

N.m.r. spectra (chemical shifts) of the *cis*(6-H,8a-H)-6-substituted perhydro-oxazolo[4,3-*c*][1,4]thiazines in benzene

(23)	(24)	Chemical shifts (δ) R = Me *	R = Et †	R = Ph
3 ' eq '-H	3 ' eq '-H	4.32	4.40	4.27
3 ' ax '-H	3 ' ax '-H	3.82	3.87	3.95
6eq-H	6ax-H	2.54		3.70
1 'eq '-H	1 ' eq '-H	3.51		3.46
1 ' ax '-H	1 ' ax '-H	3.41		3.60
5 ' eq '-H	5 ' ax '-H	*ca.* 2.33		3.06
8a-H	8a-H	2.56		2.71
5ax-H	5eq-H	*ca.* 2.33		2.63
8eq-H	8ax-H	2.32		2.60
8ax-H	8eq-H	2.44		2.25
6ax-Me	6eq-Me	1.23		
Spectrometer operating frequency (MHz)		220	60	220

* N.m.r. data for this compound were obtained from an isomeric mixture containing *ca.* 20% of the *trans*-(6H,8a-H)-6-methyl isomer. † N.m.r. data for this compound were obtained from an isomeric mixture containing *ca.* 80% of the *trans*(6-H,8a-H)-6-ethyl isomer.

10.3 and 3.2 Hz, being typical [14] ax,ax- and ax,eq-couplings, are indicative of an axial proton on C(6) and therefore and by the 3-methylene group.[17] [An axial methyl group at C(6) would be expected [15] to shield the vicinal equatorial proton and to deshield the vicinal axial proton, resulting in a small chemical shift difference between the C(5) protons.] As in the parent compound, axial protons adjacent to the sulphur atom absorb at lower field than their equatorial counterparts.

The MHz n.m.r. spectrum of the 6-ethyl (10A) and of the 6-phenyl analogue (11A) showed marked similarities to that of the 6-methyl compound, from which it was concluded that the preferred conformation of both is *trans*-fused.

(iii) *6-Methyl-, 6-ethyl-, and 6-phenyl-perhydro-oxazolo-*[4,3-*c*][1,4]*thiazines* (9B)—(11B). These compounds, which by elimination are the *cis*(6-H,8a-H)-6-substituted compounds, may exist as conformational equilibria among (23)—(25) with very little expected contribution from (25).

While the values of $J_{3'ax',3'eq'}$ (*ca.* −1.0 Hz) for the *trans*-(6-H,8a-H)-6-substituted isomers A of these compounds were indicative and characteristic of predominant *trans*-fusion, *a priori* consideration of the probable magnitude of $J_{3'ax',3'eq'}$ for the *cis*-fused conformation (24) suggests a value of *ca.* −6.0 Hz.[2]

Thus, on the basis of the values of $J_{3'ax',3'eq'}$, the

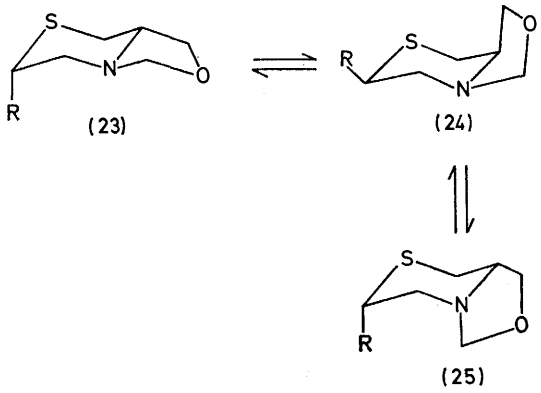
[14] H. Booth in ' Progress in Nuclear Magnetic Resonance Spectroscopy,' eds. J. W. Emsley, J. Feeney, and L. H. Sutcliffe, Pergamon Press, London, 1969, vol. 5.

[15] H. Booth, *Tetrahedron*, 1966, **22**, 615.

[16] H. P. Hamlow, S. Okuda, and N. Nakagawa, *Tetrahedron Letters*, 1964, 2553.

[17] M. J. T. Robinson, *Tetrahedron Letters*, 1968, 1153; H. Booth and J. H. Little, *Tetrahedron*, 1967, **23**, 291.

observed values (Table 5) for the *cis*(6-H,8a-H)-6-substituted isomers indicate conformational mixtures



containing considerable proportions of both (23) and (24) as shown in Table 6.

TABLE 5

N.m.r. spectra (coupling constants) of the *cis*(6-H,8a-H)-6-substituted-perhydro-oxazolo[4,3-*c*][1,4]thiazines in benzene

		Coupling constants (Hz)		
(23)	(24)	R = Me *	R = Et *	R = Ph
$J_{3'ax',3'eq'}$ ⇌	$J_{3'ax',3eq'}$	−3.1	−2.6	−4.1
$J_{1'ax',1'eq'}$ ⇌	$J_{1'ax',1eq'}$	−7.0		−7.0
$J_{5ax,5eq}$ ⇌	$J_{5eq,5ax}$			−11.5
$J_{8ax,8eq}$ ⇌	$J_{8eq,8ax}$	−10.9		−13.6
$J_{5eq,6eq}$ ⇌	$J_{5ax,6ax}$	7.1		7.5
$J_{5ax,6eq}$ ⇌	$J_{5eq,6ax}$	2.7		3.1
$J_{8eq,8a}$ ⇌	$J_{8ax,8a}$	3.1		3.5
$J_{8ax,8a}$ ⇌	$J_{8eq,8a}$	5.4		5.7
$J_{8a,1'eq'}$ ⇌	$J_{8a,1'eq'}$	9.7		9.9
$J_{8a,1'ax'}$ ⇌	$J_{8a,1'ax'}$	6.9		7.0
$J_{6eq,Me}$ ⇌	$J_{6ax,Me}$	6.3		
Spectrometer operating frequency (MHz)		220	60	220

* See footnotes of Table 4.

The 220 MHz n.m.r. spectrum of the *cis*(6-H,8a-H)-6-methyl isomer yields further conformational information. In the n.m.r. spectrum of a conformational mixture [*e.g.* (23) ⇌ (24)] any vicinal $J_{ax,eq}$ in (23) which in (24) becomes a $J_{eq,ax}$ will display a value little different, regardless of the position of equilibrium, from the value expected for either single conformation since these couplings are of approximately the same magnitude. However when a $J_{eq,eq}$ (*ca.* 1 Hz) becomes a $J_{ax,ax}$ (*ca.* 11 Hz) then the n.m.r. being a weighted average of the spectra of (23) and (24) will record a value between the two extremes, the exact magnitude depending on the position of equilibrium. This occurs in the $J_{5eq,6eq}$ ⇌ $J_{5ax,6ax}$ and the $J_{8ax,8a}$ ⇌ $J_{8eq,8a}$ cases, where values of 7.1 and 5.4 Hz respectively are observed.

DISCUSSION

The results described in this paper now permit a comparison of the conformation preferences of the closely related systems (3) ⇌ (4) and (6) ⇌ (7). Dramatically perhydro-oxazolo[4,3-*c*][1,4]thiazine prefers the *trans*-fused conformation (6) [$\Delta G°_{25°}$(*trans* ⇌ *cis*) +1.0 kcal mol^{-1}], whereas perhydro-oxazolo[4,3-*c*][1,4]oxazine preferentially adopts the *cis*-fused conformation (4) [$\Delta G°_{25°}$(*trans* ⇌ *cis*) −1.1 kcal mol^{-1}]. In attempting to rationalise this conformational difference three factors must be considered.

(a) *Dipolar Type Interactions.*—The difference in energy associated with dipolar interactions between the *cis*- and *trans*-fused conformations of each system is expected to be almost identical, since a study of Dreiding models shows that the geometries of the oxazolidine ring in the different types of conformation do not differ to any appreciable extent. Accordingly this factor cannot be responsible for the different positions of conformational equilibrium between the two systems.

(b) *Non-bonded Interactions.*—The *gauche* propanol interaction in (4), which was considered [2] to be partly responsible for the stabilisation of this conformation (relative to the *cis*-fused conformation of perhydro-oxazolo[3,4-*a*]-pyridine, in which a *gauche* butane interaction exists), is replaced in the corresponding *cis*-fused conformation (7) of the 7-thia analogue, by a *gauche* propanethiol interaction. These *gauche* propanol and *gauche* propanethiol interactions are considered [4] to be of comparable energy and so this interaction also cannot be responsible for the difference between the two systems (3) ⇌ (4) and (6) ⇌ (7).

Estimations of the energies [18] of all the H–H non-

TABLE 6

Conformational equilibria in perhydro-oxazolo[4,3-*c*][1,4]thiazines and related systems †

Equilibrium	$-J_{3ax,3eq}$/Hz	% *trans*-fused conformation	% *cis*-fused conformation	$\Delta G°_{25}$/kcal mol^{-1}
(1) ⇌ (2)	2.5	68	32	+0.4
(26; R = Me) ⇌ (27; R = Me)	5.0	20	80	−0.8
(3) ⇌ (4)	5.3	14	86	−1.1
(6) ⇌ (7)	1.6	84	16	+1.0
(23; R = Me) ⇌ (24; R = Me)	3.1	56	44	+0.1
(23; R = Et) ⇌ (24; R = Et)	2.6	66	34	+0.4
(23; R = Ph) ⇌ (24; R = Ph)	4.1	37	63	−0.3

† The errors in the equilibrium constants are difficult to assess since these are not so much dependent upon the error in the measurement of J as in the assumed values for the individual conformers. The percentage compositions of the equilibria are based on an assumed value of −0.8 Hz for the *trans*-fused conformer and of −6.0 Hz for the *cis*-fused conformer.[2] The former value is taken from both locked (T. A. Crabb and R. F. Newton, *Chem. Comm.*, 1970, 1123) and anancomeric model systems and utilisation of this value in the estimation of the positions of conformational equilibria seems reasonable. Some justification for the use of the latter value has been given [2] but this could be in error by up to ±0.2 Hz corresponding to errors in $\Delta G°$ of up to ±0.1 kcal mol^{-1}.

[18] L. F. Fieser and M. Fieser, ' Steroids,' Reinhold, New York, 1959.

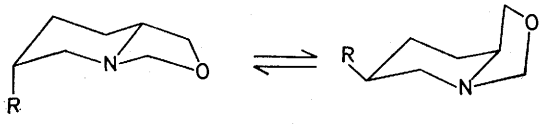
bonded interactions in (3) and (4) shows that, on these grounds alone, the *cis*-fused conformation (4) is strongly disfavoured with respect to the *trans*-fused (3). However since in fact the compound exists predominantly in the *cis*-fused conformation (4) [2] then the dipole relief and ring-fusion strain release associated with this conformation relative to (3) must be very important factors in influencing the position of the conformational equilibrium.

A similar estimation of the energies of H–H non-bonded interactions in (6) and (7) shows, again solely on these grounds, that these conformations are of comparable enthalpy and hence, in the absence of drastic changes in dipolar and strain effects, perhydro-oxazolo[4,3-*c*][1,4]-thiazine should exist as an equilibrium mixture (6) ⇌ (7) containing an even higher proportion of *cis*-fused conformation (7) than exists in the (6) ⇌ (7) equilibrium mixture. That the opposite situation in reality exists [*i.e.* (6) is highly preferred] means that an as yet unconsidered factor is operative.

(c) *Ring-fusion-Strain in* trans-*Fused Conformations.*—The ring-fusion strain present in (3) (*cf.* *trans*-hydrindane) [19] is much reduced in (6) by the presence of the large perhydrothiazine ring. Accordingly if this was the only factor to be considered then perhydro-oxazolo-[4,3-*c*][1,4]thiazine should exist as an equilibrium mixture containing a much higher percentage of the *trans*-fused conformation than would perhydro-oxazolo[4,3-*c*][1,4]-oxazine.

Thus a consideration of all three factors outlined above indicates that the major influence which gives rise to the differing positions of conformational equilibrium in the two systems is the strain associated with ring-fusion in the *trans*-fused conformations.

The predominant existence of the *trans*(6-H,8a-H)-6-substituted isomers in their *trans*-fused conformations follows naturally from the application of conformational principles, since here the substituents are equatorially orientated [(22)]. However, unlike the *cis*(6-H,8a-H)-6-substituted perhydro-oxazolo[3,4-*a*]pyridines, (26) ⇌ (27), which prefer the *cis*-fused conformation [10] [ΔG°_{25} for (26; R = Me) ⇌ (27; R = Me) −0.8 kcal mol^{-1}, *i.e.* 80% (27)], the *cis*(6-H,8a-H)-6-methyl-, -6-ethyl-, and



(26) (27)

-6-phenyl-perhydro-oxazolo[4,3-*c*][1,4]thiazines adopt equilibria (23) ⇌ (24) containing *ca.* 56, 66, and 37% of the *trans*-fused conformation (23) respectively. This reflects the relative stability of the *trans*-fused conformation (6) of the parent compound compared with the *cis*-fused (7). Examination of Dreiding models, however, provides evidence of an additional effect. Thus in (26; R = Me) the distance of closest approach between the hydrogens on the axial methyl group and the *syn*-axial hydrogen on C(8) is only 2.0 Å whereas the corresponding distance in (23; R = Me) is 2.5 Å. On this basis, *cis*(6-H,8a-H)-6-methylperhydro-oxazolo[4,3-*c*]-[1,4]thiazine should exhibit more (23; R = Me) in its conformational equilibrium mixture (23; R = Me) ⇌ (24; R = Me) than does (26; R = Me) ⇌ (27; R = Me).

The variation in the position of the equilibrium (23) ⇌ (24) with R is in accord with the relative conformational free energies of the substituents. It has been shown [20] that while the values of the methyl and ethyl groups are of the same order (*ca.* 1.7 kcal mol^{-1} for methyl- and ethyl-cyclohexane) the phenyl group has a considerably larger value (*ca.* 2.5 kcal mol^{-1} for phenylcyclohexane) indicating that an axial phenyl group in the present series (23; R = Ph) is more unfavourable than an axial methyl or ethyl group so that, as observed, the *cis*(6-H,8a-H)-6-phenylperhydro-oxazolo[4,3-*c*][1,4]-thiazine exists as an equilibrium mixture containing less of the conformation in which the substituent group is axial (23; R = Ph) than do the 6-methyl and 6-ethyl analogues.

EXPERIMENTAL

Elemental analyses were carried out by the Analytical Section, Department of Chemistry, Portsmouth Polytechnic. I.r. spectra were recorded on a Perkin-Elmer 457 instrument as 0.2M solutions. N.m.r. spectra were determined on Varian T66 and HR220 spectrometers as 10% solutions with tetramethylsilane as internal reference.

Ethyl Perhydro-1,4-thiazine-3-carboxylate.—This was prepared (i) by treating a solution of 2-mercaptoethylamine (cysteamine) hydrochloride (0.2M) and triethylamine (0.6M) in chloroform (200 ml) with a solution of ethyl 2,3-dibromopropionate (0.2M) in chloroform–benzene (3.5; 175 ml) at such a rate as to sustain gentle reflux. The mixture was allowed to stir at room temperature for 16 h when the resulting white suspension was filtered from the solution. The solute was concentrated and refiltered repeatedly until only a little solvent remained, whereupon the mixture was transferred to a Claisen flask and distilled. The product was collected as a pale yellow mobile liquid (18.2 g, 52%), b.p. 118—121° at 8.5 mmHg (lit.,[5] 114—118° at 8 mmHg) (Found: C, 48.2; H, 7.55; N, 7.9. Calc. for $C_7H_{13}NO_2S$: C, 48.0; H, 7.5; N, 8.0%). Method (ii) involved mixing in one portion a solution of cysteine ethyl ester hydrochloride (0.133M) and triethylamine (0.4M) in chloroform (200 ml) with a solution of ethylene dibromide (0.133M) in chloroform–benzene (3 : 5; 120 ml). The mixture was refluxed for 1 h and then stirred at room temperature for 16 h, when the suspended white solid was filtered and the solvents evaporated. Following a final filtration the crude product was distilled to give a noxious yellow oil (5.9 g, 25%) at 120—134° at 8 mmHg. Redistillation gave a noxious pale yellow oil (5.5 g), b.p. 117—120° at 8 mmHg (Found: C, 48.2; H, 7.3; N, 7.8%).

Ethyl 5-oxoperhydro-1,4-thiazine-3-carboxylate.—This was obtained by dropwise addition of a freshly prepared sample of the free base of cysteine ethyl ester (0.1M) to a cooled, stirred sample of ethyl chloroacetate (0.1M). The brown solution was warmed on a water-bath for 0.5 h, cooled, and

[19] E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, 'Conformational Analysis,' Interscience, New York, 1965, p. 228.
[20] Ref. 19, p. 440.

potassium carbonate solution added carefully. When addition of further carbonate produced no more effervescence the organic layer was extracted three times with chloroform (50 ml). The combined extracts were dried (Na_2SO_4), concentrated, and distilled. The fraction collected at 158—166° at 0.65 mmHg (10.2 g), on standing gave a yellow oily solid which was recrystallised from benzene–cyclohexane to colourless *prisms* (3.8 g, 20%), m.p. 84—84.5° (Found: C, 44.6; H, 5.9; N, 7.3. $C_7H_{11}NO_3S$ requires C, 44.4; H, 5.9; N, 7.4%).

6-*Substituted* 5-*Oxoperhydro*-1,4-*thiazine*-3-*carboxylic Acids. General Procedure.*—L-Cystine (0.1M) and sodium metal (0.44M) were added in small portions alternately to stirred liquid ammonia (600 ml) in a flask fitted with a Bunsen valve. When addition was complete the blue colour was just destroyed by addition of solid ammonium chloride. To this mixture was added a solution of the appropriate ethyl α-bromo-ester (0.22M) in di-isopropyl ether (100 ml) over 2 h. After stirring for another 3 h, the mixture was left without external cooling for the ammonia to evaporate. The last traces of ammonia were removed by warming the flask to 50° and the resulting solid brown mass was dissolved in water (*ca.* 150 ml) and the ether layer removed. The pH of the aqueous layer was then adjusted to pH 2 with concentrated hydrochloric acid and the flocculent white solid which separated filtered. The solid was recrystallised from methanol–water. The 6-*methyl compound* was obtained from ethyl 2-bromopropionate as a crystalline powder (12.6 g, 36%), m.p. 179—180° (lit.,[7] 180—182°) (Found: C, 40.95; H, 5.3; N, 8.1. Calc. for $C_6H_9NO_3S$: C, 41.1; H, 5.2; N, 8.0%). The 6-*ethyl compound* was prepared from ethyl 2-bromo-n-butyrate as a powdery solid (35.0 g, 85%), m.p. 173—174.5° (lit.,[7] 174—175°) (Found: C, 44.1; H, 5.7; N, 7.5. Calc. for $C_7H_{11}NO_3S$: C, 44.4; H, 5.9; N, 7.4%).

The 6-phenyl compound was obtained from ethyl 2-bromophenylacetate as a white crystalline powder (37.4 g, 79%), m.p. 173—175° (decomp.) [lit.,[7] 175—178° (decomp.)] (Found: C, 55.5; H, 4.65; N, 5.7. Calc. for $C_{11}H_{11}NO_3S$: C, 55.7; H, 4.7; N, 5.9%).

Perhydro-1,4-*thiazin*-3-*ylmethanol* was synthesised by reacting a solution of ethyl perhydro-1,4-thiazin-3-carboxylate (0.172M) in dry ether (200 ml) with a slurry of lithium aluminium hydride (0.18M) in dry ether (500 ml) over 0.75 h. The mixture was stirred for 1 h, refluxed for 0.5 h, and while the flask was cooled in ice–water, water (7.5 ml), 15% sodium hydroxide solution (17.2 ml), and more water (17.2 ml) were added carefully. The mixture was stirred 0.5 h more and then filtered. The solids were washed twice with ether and twice with chloroform. The combined extracts were dried ($MgSO_4$) and concentrated under high vacuum to give an oil which crystallised readily. Recrystallisations from ethyl acetate gave yellow powdery crystals (13.5 g, 59%), m.p. 88—89° (lit.,[6] 90—91°) (Found: C, 44.9; H, 8.5; N, 10.65. Calc. for $C_5H_{11}NOS$: C, 45.1; H, 8.3; N, 10.5%).

Dideuterio-(5,5-*dideuterioperhydro*-1,4-*thiazin*-3-*yl*)*methanol.*—This was obtained by dropping a solution of ethyl 5-oxoperhydro-1,4-thiazine-3-carboxylate (0.02M) in dry ether (50 ml) into a stirred slurry of lithium aluminium deuteride (0.03M) in dry ether (50 ml). After refluxing the mixture for 1 h the excess of deuteride was destroyed by adding water carefully. The white solids were filtered off and washed well with dry ether. The combined filtrate and washings were dried (Na_2SO_4) and concentrated to give a yellow oil which eventually crystallised. Recrystallisations from ethyl acetate afforded pale yellow needles (1.1 g, 45%), m.p. 88—89°.

6-*Substituted Perhydro*-1,4-*thiazin*-3-*ylmethanols. General Procedure.*—The appropriate 6-substituted 5-oxoperhydro-1,4-thiazine-3-carboxylic acid (0.1M) in a porous thimble was placed in a Soxhlet device over a flask containing a stirred slurry of lithium aluminium hydride (0.3M) in dry ether (250 ml). After refluxing for 7 days *ca.* 90% of the solids in the thimble had been dissolved and the excess of hydride was then destroyed by careful addition of water. Stirring for 24 h was necessary to produce the expected degradation products. These solids were filtered and washed well with ether and hot chloroform. The combined filtrate and washings were dried (Na_2SO_4) and concentrated. On standing, the resulting yellow oils solidified. The 6-*methyl compound* was obtained from the 6-methyl-substituted acid, following recrystallisation from light petroleum (b.p. 40—60°)–ether, as pale yellow crystals (9.9 g, 67%), m.p. 90—91° (Found: C, 49.25; H, 9.1; N, 9.5. $C_6H_{13}NOS$ requires C, 49.0; H, 8.9; N, 9.5%). The 6-*ethyl compound* was synthesised from the 6-ethyl-substituted acid. Recrystallisation from ethyl acetate afforded plates (8.9 g, 55%), m.p. 99—101° (Found: C, 52.1; H, 9.6; N, 8.7. $C_7H_{15}NOS$ requires C, 52.15; H, 9.4; N, 8.7%). The 6-*phenyl compound* was obtained from the 6-phenyl-substituted acid, following recrystallisation from ethyl acetate, as needles (16.9 g, 81%), m.p. 137—138° (Found: C, 63.1; H, 7.4; N, 6.6. $C_{11}H_{15}NO_2$ requires C, 63.1; H, 7.2; N, 6.7%).

Perhydro-oxazolo[4,3-c][1,4]*thiazines. Central Procedure.*—These compounds were prepared by treating the appropriate perhydro-1,4-thiazin-3-yl methanol dropwise with an excess of 40% formaldehyde solution while cooling the flask under the tap. After shaking at room temperature for 0.5 h the solution was basified with saturated sodium hydroxide solution and immediately extracted three times with ether (50 ml). The combined extracts were dried (Na_2SO_4) and concentrated.

Perhydro-oxazolo[4,3-c][1,4]*thiazine* was prepared from perhydro-1,4-thiazin-3-ylmethanol (0.05M). On distillation, the fraction of b.p. 99° at 9 mmHg solidified on standing and was recrystallised from light petroleum (b.p. 40—60°) to give large plates (5.7 g, 79%), m.p. 40—41° (Found: C, 49.5; H, 7.6; N, 9.5; S, 22.0. $C_6H_{11}NOS$ requires C, 49.6; H, 7.6; N, 9.65; S, 22.05%).

1,1,5,5-Tetradeuterioperhydro-oxazolo[4,3-*c*][1,4]thiazine was obtained from dideuterio-(5,5-dideuterioperhydro-1,4-thiazin-3-yl)methanol (0.005M) after distillation as an oil, b.p. 64° at 0.8 mmHg, which solidified on standing. Recrystallisation from light petroleum (b.p. 40—60°) gave plates (0.54 g, 75%), m.p. 39—40°.

cis and *trans*(6-H,8a-H)-6-Methylperhydro-oxazolo[4,3-*c*][1,4]thiazine were obtained from the appropriate methanol (0.05M), after distillation, as an oil (7.0 g, 88%), b.p. 97—98° at 6 mmHg (Found: C, 52.9; H, 8.2; N, 8.75. $C_7H_{13}NOS$ requires C, 52.8; H, 8.2; N, 8.8%). Fractional recrystallisation from light petroleum (b.p. 40—60°)–ether gave the *trans*(6-H,8a-H)-6-methyl isomer in a pure state as plates, m.p. 74—75° (Found: C, 53.0; H, 8.0; N, 8.9. $C_7H_{13}NOS$ requires C, 52.8; H, 8.2; N, 8.8%). Repeated fractional recrystallisations left an oil (0.5 g) which was shown by n.m.r. to comprise *ca.* 20% of the *trans*(6-H,8a-H)-6-methyl isomer and 80% of the *cis*(6-H,8a-H)-6-methyl isomer, b.p. 106—108° at 9.0 mmHg. This sample was used for the spectral work.

cis and *trans*(6-H,8a-H)-6-Ethylperhydro-oxazolo[4,3-*c*]-[1,4]thiazine were obtained from the appropriate methanol (0.05M), following distillation, as a mobile oil (8.2 g, 95%),

b.p. 115—116° at 8.5 mmHg (Found: C, 55.4; H, 9.0; N, 8.0. Calc. for $C_8H_{15}NOS$: C, 55.5; H, 8.7; N, 8.1%). N.m.r. spectroscopy showed the sample to consist of the two isomers in the ratio *ca.* 4 : 1. Fractional recrystallisation from light petroleum (b.p. 40—60°)–ether, followed by very rapid separation of the solid formed gave, at room temperature, a pure sample of the major trans(6-H,8a-H)-6-*ethyl isomer* (Found: C, 55.4; H, 8.8; N, 7.8%), but the other isomer could not be obtained in even reasonable purity. Column chromatography using 40 g Grade III Woelm alumina per 1 g of mixture also gave a pure sample of the major isomer, but ensuing fractions all contained a mixture.

cis and *trans*(6-H,8a-H)-6-Phenyloxazolo[4,3-*c*][1,4]thiazine were prepared from the appropriate methanol (0.05M). Distillation gave a pale yellow oil (11.3 g, 93%), b.p 132—134° at 0.02 mmHg (Found: C, 62.25; H, 6.9; N, 6.3. $C_{12}H_{15}NOS$ requires C, 65.1; H, 6.8; N, 6.3%). N.m.r. spectroscopy indicated that the sample was an isomeric mixture containing approximately equal proportions of both isomers. Fractional recrystallisation from light petroleum (b.p. 40—60°)–ether gave a pure sample of the trans(6-H,8a-H)-6-*phenyl isomer*, m.p. 62—63° (Found: C, 65.2; H, 6.65; N, 6.4%), as needles. Column chromatography, using 40 g Grade III Woelm alumina per 1 g of mixture and light petroleum (b.p. 60—80°) as eluant provided a nearly pure sample of the *cis*(6-H,8a-H)-6-phenyl isomer which on recrystallisation from light petroleum (b.p. 30—40°) gave white flowers, m.p. 62—63°.

We thank the S.R.C. for the 220 MHz spectra.

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