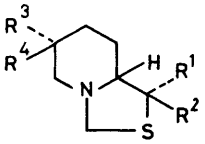
Compounds with Bridgehead Nitrogen. Part 54.[1] The Stereochemistry of some Derivatives of Perhydrothiazolo[3,4-*a*]pyridine and the Synthesis of 9-Methylperhydro-3,8-methano-1,3-thiazocines

Trevor A. Crabb * and Andrew N. Trethewey
Department of Chemistry, Portsmouth Polytechnic, Portsmouth, Hampshire, PO1 2DT
Yoshito Takeuchi
Department of Chemistry, College of General Education, University of Tokyo, Komaba, Meguro-ku, Tokyo, Japan

The position of conformational equilibria ($CDCl_3$ solution; 298 K) of perhydrothiazolo[3,4-*a*]pyridine and the corresponding 6-ethyl-substituted derivatives have been determined by ^1H and ^{13}C n.m.r. spectroscopy. The reported synthesis of the 1-methylperhydrothiazolo[3,4-*a*]pyridines *via* 1-bromo-1-(2-piperidyl)ethane hydrobromide gave in addition the isomeric 9-methylperhydro-3,8-methano-1,3-thiazocines. Contrary to an earlier report *trans*-(1H,8aH)-1-methylperhydrothiazolo[3,4-*a*]pyridine was found to adopt an 87% *trans*-fused ⇌ 13% *cis*-fused conformational equilibrium ($CDCl_3$; 193 K).

The conformational equilibrium (**1a**) ⇌ (**1b**) for perhydrothiazolo[3,4-*a*]pyridine (**1**) has been studied by ^1H n.m.r. spectroscopy[2,3] and values in the range 58—64% for the *trans*-fused conformer (**1a**) in the equilibrium ($CDCl_3$; 298 K) have been obtained. ^1H N.m.r. spectral measurements also indicated[3] an equilibrium (**2a**) ⇌ (**2b**) ⇌ (**2c**) for *cis*-(1H,8aH)-1-methylperhydrothiazolo[3,4-*a*]pyridine (**2**) containing >99% *trans*-fused conformer (**2a**) and an almost complete bias towards the *O*-inside *cis*-fused conformer (**3b**)

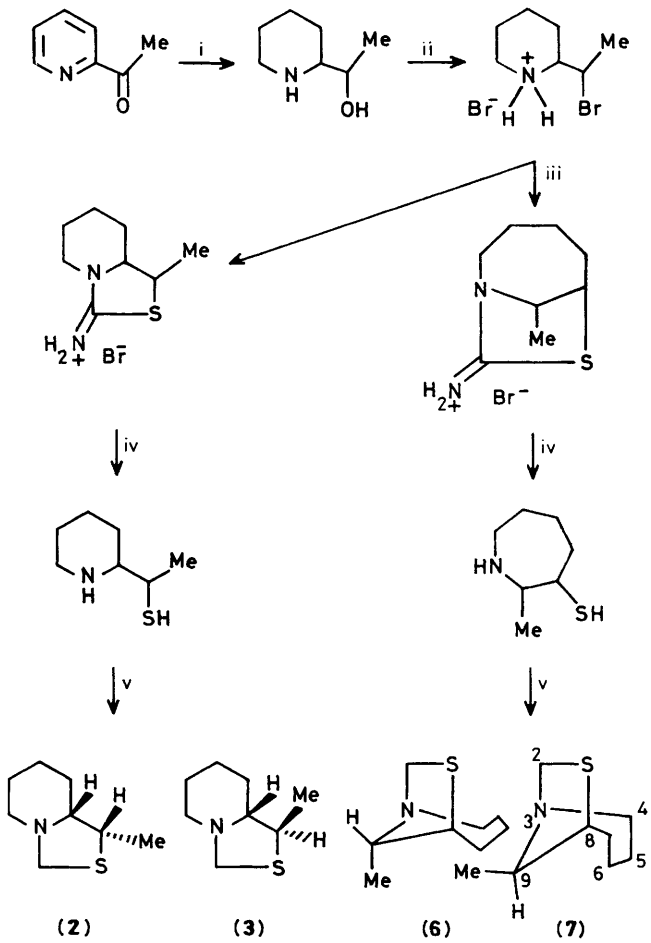


(**1**) $R^1 = R^2 = R^3 = R^4 = H$
(**2**) $R^2 = R^3 = R^4 = H, R^1 = Me$
(**3**) $R^2 = R^3 = R^4 = H, R^2 = Me$
(**4**) $R^1 = R^2 = R^3 = H, R^4 = Et$
(**5**) $R^1 = R^2 = R^4 = H, R^3 = Et$

for *trans*-(1H,8aH)-1-methylperhydrothiazolo[3,4-*a*]pyridine (**3**). The marked difference reported between the (**3a**) ⇌ (**3b**) equilibrium position and that for the corresponding oxa-analogue *trans*(1H,8aH)-1-methylperhydrooxazolo[3,4-*a*]pyridine (73% *trans*-fused conformer ⇌ 27% *O*-inside *cis*-fused conformer)[3,4] prompted a reinvestigation of the conformational equilibria for the perhydrothiazolo[3,4-*a*]pyridines. The 6-ethylperhydrothiazolo[3,4-*a*]pyridines (**4**) and (**5**) were synthesized as model compounds since these are expected to exist in conformational equilibria biased towards the *trans*-fused (**4a**) and *O*-inside *cis*-fused (**5b**) conformations.

Synthesis of Compounds.—Perhydrothiazolo[3,4-*a*]pyridine (**1**) was synthesised as described previously.[2] The 6-ethylperhydrothiazolo[3,4-*a*]pyridines (**4**) and (**5**) were prepared by a similar route and the isomers were separated by column chromatography over neutral alumina. The first isomer eluted from the column was assigned as *cis*-(6H,8aH)-6-ethylperhydrothiazolo[3,4-*a*]pyridine (**5**).

The mixture of isomeric 1-methylperhydrothiazolo[3,4-*a*]pyridines (**2**) and (**3**) was prepared as described previously[3] as shown in the Scheme. On ring closure of the mixture of thiols the product was found by chromatography to be a four-component mixture consisting of the 1-methylper-



Scheme. Synthesis of the 1-methylperhydrothiazolo[3,4-*a*]pyridines and 9-methylperhydro-3,8-methano-1,3-thiazocines. *Reagents:* i, H_2–PtO_2; ii, HBr–PBr_3; iii, thiourea; iv, tetraethylenepentamine; v, aqueous CH_2O

hydrothiazolo[3,4-*a*]pyridines (**2**) and (**3**) and the 9-methylperhydro-3,8-methano-1,3-thiazocines (**6**) and (**7**). All four components were separated by column chromatography over neutral alumina; the order of elution being (**7**), (**2**), (**6**), and (**3**). In the previously reported[3] synthesis of the 1-methylperhydrothiazolo[3,4-*a*]pyridines (**2**) and (**3**) following the same route as that depicted in the Scheme, the first isomer eluted in the chromatographic separation of the reaction product was incorrectly assigned as *trans*-(1H,8aH)-1-methylperhydrothiazolo[3,4-*a*]pyridine (**3**) rather than (**7**). The structures of these compounds were assigned on the basis of the ^{1}H and ^{13}C n.m.r. spectra described below. Since 1-azabicyclo[4.1.0]heptane had been prepared[5] by treatment of 2-piperidylmethyl hydrogen sulphate with base it would seem reasonable for the formation of (**6**) and (**7**) to proceed *via* a similar aziridine intermediate produced by intramolecular displacement of the bromide ion in 2-(1-bromoethyl)piperidine by the nitrogen lone pair.

Configurational and Conformational Studies of the 6-Ethylperhydrothiazolo[3,4-*a*]*pyridines.*—The ^{1}H n.m.r. spectra (Table 1) of the two isomers show very different values for $J_{3ax',3eq'}$, $\Delta_{3ax',3eq'}$, and $\Delta_{5ax',5eq'}$. Large chemical shift differences between the protons adjacent to nitrogen and the larger J_{gem} value indicate the *trans*-fused conformation[2,6] and so that isomer exhibiting these was assigned the *trans*-(6H,8aH)-configuration and the *trans*-fused conformation (**4a**). The high-field shift of 5-H$_{ax}$ in this isomer shows shielding resulting from its antiperiplanar relationship to the nitrogen lone pair[7] together with the expected shielding of an axial proton by vicinal equatorial alkyl group.[8] In addition the $J_{5ax,6ax}$ value of 10.6 Hz supports the stereochemistry (**4a**) with the equatorial ethyl group.[9]

The ^{13}C n.m.r. spectrum (Table 2) of *trans*-(6H,8aH)-6-ethylperhydrothiazolo[3,4-*a*]pyridine (**4**) also supports the *trans*-conformation (**4a**). This is shown partially by comparison of the shifts of (**4a**) and of *trans*-(6H,8aH)-6-ethylindolizidine.[10] The ^{13}C n.m.r. spectra of (**4**) were run over a range of temperatures (183, 220, 260, and 301 K) but no signals were observed in the low temperature spectrum corresponding to the *cis*-fused conformer.

cis-(6H,8aH)-6-Ethylperhydrothiazolo[3,4-*a*]pyridine (**5**) is expected to exist as an equilibrium between (**5a**) and (**5b**) with considerable bias towards (**5b**). The ^{1}H n.m.r. spectrum showed a triplet at δ 2.19 ($J_{5ax,5eq}$ −10.6 Hz, $J_{5ax,5ax}$ of 10.6 Hz) for 5-H$_{ax}$ indicating an equatorial ethyl group and hence the *S*-inside *cis*-fused conformer (**5b**). This conformation is confirmed by the $J_{3'ax',3'eq'}$ of −9.1 Hz, $\Delta_{3'ax',3'eq'}$ of −0.29 p.p.m. and $\Delta_{5ax,5eq}$ of 0.36 p.p.m. The γ-axial shieldings [relative to (**4a**)] of 4.3, 4.7, and 4.6 p.p.m. for C-1, C-5, and C-7 respectively in the ^{13}C n.m.r. spectrum of (**5**) also indicates the *S*-inside *cis*-fused conformation. The ^{13}C n.m.r. spectrum in $CDCl_3$–$CFCl_3$ at 183 K showed only one set of signals.

Conformational Equilibrium for Perhydrothiazolo[3,4-a]*pyridine* (**1**).—Previous estimates[2] of the position of conformational equilibria in (**1**) were based on comparison of 60 MHz ^{1}H n.m.r. data obtained on (**1**) and on conformationally biased systems. In order to remove the uncertainties in such an approach, the ^{1}H n.m.r. spectrum of (**1**) was obtained at 173 K when signals were observed from both (**1a**) and (**1b**). Signal assignments were aided by comparison with those from the 6-ethylperhydrothiazolo[3,4-*a*]pyridines (**4**) and (**5**) which also permitted identification of the conformers. Integration of various sets of signals gave a (**1a**) ⇌ (**1b**) equilibrium containing *ca.* 60% *trans*-fused conformer (**1a**).

A further estimate of the position of the equilibrium was obtained from the ^{13}C n.m.r. spectrum of perhydrothiazolo[3,4-*a*]pyridine (**1**) recorded in $CDCl_3$–$CFCl_3$ at 193 K which showed the presence of two conformers (Table 2). Comparison of the chemical shifts shows γ-axial shieldings for the *cis*-fused conformer with respect to the *trans*-fused conformer for C-5 and C-7 of 6.6 and 5.5 p.p.m., respectively. These shieldings, together with the negligible shift difference for C-6 identify the *S*-inside *cis*-fused conformation (**1b**).

Estimates based on the low temperature data were obtained from integration and chemical shift difference. The integration of the low temperature spectrum gives values at 193 K from C-3, C-5, and C-8a signals of 60, 59, and 57% *trans*-conformer, respectively which compare well with the estimate based on the low temperature ^{1}H n.m.r. spectrum.

Configurational and Conformational Studies of 1-*Methylperhydrothiazolo*[3,4-a]*pyridines.*—For *cis*-(1H,8aH)-1-methylperhydrothiazolo[3,4-*a*]pyridine (**2**) the equilibrium (**2a**) ⇌ (**2b**) ⇌ (**2c**) is expected to favour exclusively the *trans*-fused conformer (**2a**) and this is supported by the $J_{3'ax',3'eq'}$ of −6.3 Hz, the $\Delta_{3'ax',3'eq'}$ of 0.73, and $\Delta_{5ax,5eq}$ of 1.17 p.p.m. and the similarity of the C-3, C-5, C-6, and C-7 ^{13}C n.m.r. shifts to the *trans*-fused conformer (**1a**) of perhydrothiazolo[3,4-*a*]pyridine (**1**). Thus the n.m.r. spectral evidence supports the original assignment of stereochemistry.[3]

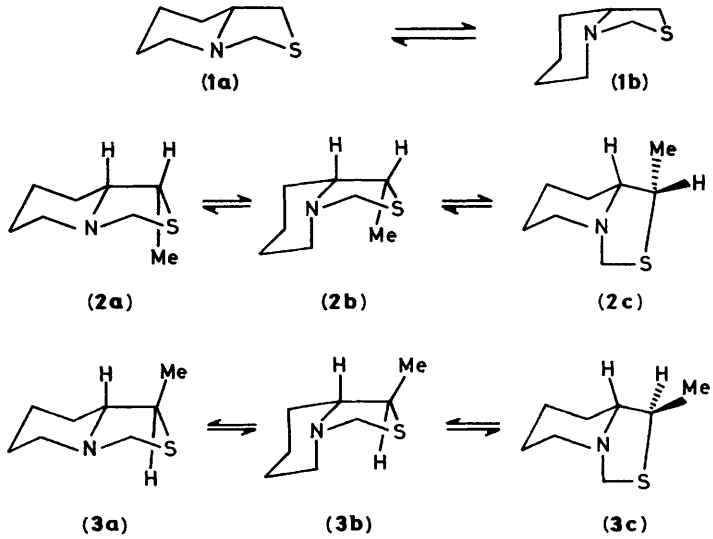


Table 1. ^{1}H N.m.r. spectra of perhydrothiazolo[3,4-*a*]pyridines

			δ_H														J (Hz)			
Compd.	Solvent	Temp. (K)	1-H_{eq}	1-H_{ax}	3-H_{eq}	3-H_{ax}	5-H_{eq}	5-H_{ax}	6-H_{eq}	6-H_{ax}	7-H_{eq}	7-H_{ax}	8-H_{eq}	8-H_{ax}	8a	CH_2	Me	$J_{1eq,1ax}$	$J_{1eq,8a}$	$J_{1ax,8a}$	$J_{3eq,3ax}$
(1)	$CDCl_3$	298	2.88	2.73	3.96	3.72	2.88	2.27							2.52			−10	6.3	10.0	−7.5
(1)	CD_2Cl_2–CS_2	298	2.83	2.67	3.88	3.63	2.87	2.21							2.44			−9.7	6.0	9.7	−7.2
(**1a**)	CD_2Cl_2–CS_2	173	2.96	2.58	3.90	3.32	3.14	*ca.* 2.0							*ca.* 2.0			−9.9	5.5	9.9	−6.3
(**1b**)	CD_2Cl_2–CS_2	173	2.70	2.83	4.19	3.90	2.53	2.37							3.17			−9.9	6.8	9.9	−9.1
(**2**)	$CDCl_3$	298	3.44		4.0	3.27	3.2	2.03	1.66	1.53	1.83	1.20	1.66	1.4	2.09		1.23		6.3		−6.3
(**3**)	$CDCl_3$	298		3.22	3.94	3.67	3.0	2.2	1.66	1.62	1.93	1.35	1.77	1.60	1.92		1.32			6.7	−7.2
(**4**)	$CDCl_3$	298	2.98	2.66	3.96	3.4	3.16	1.75		1.55	1.84	0.94	1.93	1.32	2.08	1.25	0.9	−9.4	5.6	9.4	−6.9
(**5**)	$CDCl_3$	298	2.75	2.83	3.97	4.26	2.55	2.19		1.52	1.66	1.06	1.82	2.06	3.14	1.25	0.9	−11.3	7.5	11.3	−9.1

Table 2. ^{13}C N.m.r. spectra of perhydrothiazolo[3,4-*a*]pyridines

Compd.	Solvent	Temp. (K)	δ C-1	C-3	C-5	C-6	C-7	C-8	C-8a	CH_2	Me
(1)	$CDCl_3$–$CFCl_3$	298	34.7	59.65	50.9	25.35	22.0	29.15	65.1		
(1a)	$CDCl_3$–$CFCl_3$	193	36.5	57.4	53.1	25.0	23.6	30.9	65.0		
(1b)	$CDCl_3$–$CFCl_3$	193	31.1	62.8	46.5	25.0	18.1	25.3	63.9		
(2)	$CDCl_3$	298	44.5	57.6	54.0	25.1	23.8	27.7	68.1		20.3
(2)	$CDCl_3$–$CFCl_3$	298	46.5	58.2	52.4	25.2	22.8	28.4	72.3		18.6
(3)	$CDCl_3$	298	46.2	58.1	52.2	24.9	22.5	28.1	71.9		18.8
(3a)	$CDCl_3$–$CFCl_3$	193	47.7	57.1	53.4	23.5	24.7	29.4	71.8		18.7
(3b)	$CDCl_3$–$CFCl_3$	193	41.8	61.8	47.4	25.1	18.4	25.0	70.6		19.5
(4)	$CDCl_3$	298	36.0	58.2	57.5	37.5	30.2	30.1	65.3	26.7	11.5
(5)	$CDCl_3$	298	31.7	62.6	52.8	37.6	25.6	25.0	64.1	27.1	11.4

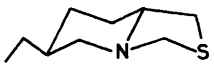
Table 3. ^1H and ^{13}C N.m.r. spectra of *cis*-(8H,9H)- and *trans*-(8H,9H)-9-methylperhydro-3,8-methano-1,3-thiazocines in $CDCl_3$

Compd.	δ_H 2-H_{eq}	2-H_{ax}	4-H_{eq}	4-H_{ax}	5-H_{eq}	5-H_{ax}	7-H_{eq}	7-H_{ax}	8-H	9-H_{ax}	9-Me	J (Hz) $2_{eq},4,2_{ax}$	$4_{eq},4_{ax}$	$4_{eq},5_{ax}$	$4_{eq},5_{eq}$	9-Me
(7)	4.43	4.0	3.03	2.78	1.98	1.44	1.78	1.68	3.6	3.6	1.1	−9.7	−14.3	8.1	4.0	6.9
(6)	4.34	4.01	2.98	2.98	2.35	1.69	1.94	1.81	3.72	9-H_{eq} 3.21	1.43	−9.0				6.9

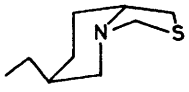
Compd.	δ_C C-1	C-4	C-5	C-6	C-7	C-8	C-9	9-Me
(7)	60.0	58.6	24.4	25.0	34.1	55.7	65.5	20.2
(6)	59.6	52.2	25.2	25.9	30.6	52.7	65.9	13.0

Conformational analysis of *trans*-(1H,8aH)-1-methylperhydrothiazolo[3,4-*a*]pyridine (**3**) suggests that the equilibrium will contain predominantly the *trans*-fused conformer (**3a**) together with a detectable amount of the *S*-inside *cis*-fused conformer (**3b**).

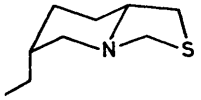
The value of $J_{3ax',3eq'}$ of −7.2 Hz and of $\Delta_{5ax,5eq}$ of 0.8 p.p.m. for (**3**) are intermediate between those for the *cis*- and *trans*-fused conformers (**1a**) and (**1b**) of perhydrothiazolo[3,4-*a*]pyridine (**1**) and indicate a (**3a**) ⇌ (**3b**) equilibrium at 298 K with a predominance of (**3a**). The presence of the *S*-inside *cis*-fused conformer (**3b**) was confirmed by the observed ^{13}C n.m.r. shieldings of C-5 of 1.8 p.p.m. and C-7 of 1.3 p.p.m. relative to the corresponding shifts in *cis*-(1H,8aH)-1-methylperhydrothiazolo[3,4-*a*]pyridine (**2**). The absence of the *S*-outside *cis*-fused conformer (**3c**) is shown by the lack of shielding of C-6 and C-8.



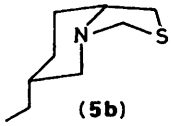
(4a)



(4b)



(5a)



(5b)

The ^{13}C n.m.r. spectrum of *trans*-(1H,8aH)-1-methylperhydrothiazolo[3,4-*a*]pyridine (**3**) at 193 K showed the presence of the two conformers (**3a**) and (**3b**) and the shifts are provided in Table 2. The presence of the *S*-inside *cis*-fused conformer (**3b**) as the minor conformer is confirmed by the shieldings of 5.9, 6.0, and 6.3 p.p.m. for C-1, C-5, and C-7, respectively. Integration of the signals gave an average value of 13% *S*-inside *cis*-fused conformer (**3b**) at 193 K.

Configurational and Conformational Studies of 9-*Methylperhydro*-3,8-*methano*-1,3-*thiazocines*.—The first and third isomers eluted from the chromatographic separation of the compounds produced by the synthesis shown in the Scheme were assigned as the isomers of 9-methylperhydro-3,8-methano-1,3-thiazocines (**7**) and (**6**), respectively on the basis of n.m.r. spectra (Table 3).

The compound (**7**) obtained previously[3] had been assigned the structure (**3b**). Superficially the spectrum is compatible with this structure, *e.g.* the AB system (δ 4.43, 4.0; J_{gem} −9.7 Hz) may be assigned to the C-3 methylene protons, the two multiplets at δ 3.03 and 2.78 to the C-5 methylene protons and the multiplet at δ 3.6 to the pseudoaxial 1-H.

The first clue to the incorrectness of the assignment came from the ^{13}C n.m.r. measurements, in particular the shifts of δ 55.7, 58.6, and 34.1 when compared to the C-1, C-5, and C-8 shifts of the *trans*- and *cis*-fused conformers of perhydrothiazolo[3,4-*a*]pyridine obtained at 193 K. This shows that the ^{13}C shifts of the isomer are not in accord with originally proposed structure (**3b**). Consideration of the reactions indicated in the Scheme suggested (**7**) and (**6**) as possible structures consistent with the new data.

The ^1H n.m.r. signal assignments of the spectrum of *cis*-(8H,9H)-9-methylperhydro-3,8-methano-1,3-thiazocine (**7**) were made after a consideration of electronegativity effects and from decoupling and decoupling difference spectroscopy. The assignments were confirmed and ^{13}C n.m.r. assignments made on the basis of a 2D $^{13}C/^1H$ δ correlation. This showed the AB system (δ 4.43 and 4.0) in the ^1H spectrum assigned to the NCH_2S protons to be coupled to the ^{13}C signal at δ 60.0 which may therefore be assigned to C-2. The broad doublet aligned with the C-4 protons in the F_1 dimension corresponds to the carbon signal at 58.6 p.p.m. in the F_2 dimension. ^1H Decoupling

experiments show a chemical shift difference between the C-5 methylene signals of 0.54 p.p.m. The broad multiplets corresponding to these two proton signals correspond in the F_2 dimension with the methylene carbon signal at 24.4 p.p.m. Both 8-H α to the sulphur and 9-H α to the nitrogen absorb at δ 3.6. These methine protons, distinguished as such by the DEPT technique, are observed in the 2D spectrum as singlets and correspond to carbon signals at δ 55.7 and 65.5 assigned to C-8 and C-9, respectively, by comparison of shifts with those in the spectra of related systems. The 9-Me signals in the ^1H and ^{13}C spectrum are easily distinguishable by chemical shift and multiplicity.

The assignment of the ^1H n.m.r. spectrum of *trans*-(8H,9H)-9-methylperhydro-3,8-methano-1,3-thiazocine (**6**) was aided by decoupling difference spectroscopy and by comparison with the assignments made on the *cis*-(8H,9H)-isomer (**7**).

The small chemical shift differences between 8-H and 9-H preclude assignment of the C-9 configuration on the basis of $J_{9,8}$ values. Conclusive proof however of the configuration and conformation of *trans*-(8H,9H)- and *cis*-(8H,9H)-9-methylperhydro-3,8-methano-1,3-thiazocine came from a comparison of their ^{13}C n.m.r. spectra which showed shielding of C-4, C-7, and Me in the spectrum of (**6**) relative to (**7**) consistent with the pseudoaxial orientation of the methyl group in (**6**) which undergoes γ-axial interactions with C-4 and C-7.

Experimental

^1H N.m.r. spectra were recorded on a Bruker WH-270 spectrometer as 10% solutions in $CDCl_3$ containing tetramethylsilane as the internal standard (sweep width 3 KHz, number of scans 100, accumulation 4 K or 16 K data points, Fourier transform over 8 K data points). Chemical shifts are in p.p.m. downfield from tetramethylsilane and are considered accurate to ±0.02 p.p.m., and the coupling constants to ±0.2 Hz. ^{13}C N.m.r. spectra were recorded by the S.E.R.C. multinuclear n.m.r. service at the City of London Polytechnic at 22.54 MHz with a 2 500 Hz sweep width on a JEOL FX 90Q spectrometer as 10% solutions in $CDCl_3$ containing tetramethylsilane as the internal standard. Each spectrum was acquired over 2 000 pulses. The carbon chemical shifts in p.p.m. downfield from tetramethylsilane are considered accurate to ± 0.05 p.p.m. I.r. spectra were obtained on a Perkin-Elmer 683 dual beam instrument as 0.005M solutions in carbon tetrachloride using 0.2 mm matched cells. Elemental analyses were performed by the Butterworth Microanalytical Service, Teddington, Middlesex. M.p.s are uncorrected.

1-*Methylperhydrothiazolo*[3,4-*a*]*pyridines and* 9-*Methyl*-3,8-*methano*-1,3-*thiazocines*.—A cooled solution of 1-(2-piperidyl)-ethanol (38 g, 0.3 mol) in carbon tetrachloride (150 ml) was saturated with hydrogen bromide gas. The hydrobromide so formed was isolated by removal of the solvent under reduced pressure as a pale white viscous oil. This oil was treated carefully with phosphorus tribromide (81 g; 0.3 mol), and after the completion of the ensuing vigorous exothermic reaction the mixture was heated for 0.5 h on a steam bath. The resultant orange mass was triturated with ether (4 × 200 ml) to give 2-(1-bromoethyl)piperidine hydrobromide as a pale orange waxy solid which upon recrystallisation from absolute alcohol yielded a white solid (52 g, 62%). A solution of this bromide hydrobromide (40 g, 0.15 mol) in absolute ethanol (200 ml) was refluxed with a slight excess of thiourea (11.8 g, 0.155 mol). The isothiouronium salt so formed was dissolved in absolute alcohol (22.6 g, in 200 ml) and converted to the thiol by being boiled under reflux for 1.5 h with a 10% excess of tetraethylenepentamine (22 g). The solvent was removed rapidly under reduced pressure and the viscous residue distilled under reduced pressure.

The yellow oil obtained was a mixture of the thiols (11.4 g, 0.07 mol) and was immediately ring closed by shaking with aqueous formaldehyde (36%; 12 ml) for 1 h. The reaction mixture was basified and extracted with ether (4 × 40 ml). The combined ether extracts were dried (Na_2SO_4) and concentrated and the residue was distilled under reduced pressure to give a mixture of the 1-methylperhydrothiazolo[3,4-*a*]pyridines and the 9-methyl-3,8-methano-1,3-thiazocines (8.2 g, 71%). The separation of all four compounds was achieved by column chromatography over Woelm neutral alumina of activity Grade III.

The mixture (4 g) was dissolved in light petroleum (b.p. 40—60 °C) (10 ml) placed at the top of the alumina column (450 g) and eluted with light petroleum (b.p. 40—60 °C). The first eluted compound was cis-(8H,9H)-9-*methylperhydro*-3,8-*methano*-1,3-*thiazocine* (**7**), b.p. 78—80 °C at 3 mmHg (Found: C, 61.0; H, 9.4; N, 8.9. $C_8H_{15}NS$ requires C, 61.1; H, 9.6; N, 8.9%). The second eluted compound was cis-(1H,8aH)-1-*methylperhydrothiazolo*[3,4-a]*pyridine* (**2**), b.p. 81—83 °C at 3.5 mmHg (Found: C, 61.4; H, 9.4; N, 9.0%). The third eluted isomer was trans-(8H,9H)-9-*methylperhydro*-3,8-*methano*-1,3-*thiazocine* (**6**), b.p. 90—93 °C at 8 mmHg (Found: C, 61.2; H, 9.3; N, 8.9. $C_8H_{15}NS$ requires C, 61.1; H, 9.6; N, 8.9%). The fourth eluted isomer was trans-(1H,8aH)-1-*methylperhydrothiazolo*[3,4-a]-*pyridine* (**3**) b.p. 94—95 °C at 8 mmHg (Found: C, 61.3; H, 9.5; N, 8.7%).

6-*Ethylperhydrothiazolo*[3,4-a]*pyridines*.—6-Ethylperhydrothiazolo[3,4-*a*]pyridine was prepared in the same manner as for 1-methylperhydrothiazolo[3,4-*a*]pyridine (see above). Upon treatment with hydrogen bromide gas in carbon tetrachloride (100 ml) 5-ethyl-2-piperidylmethanol (35 g, 0.245 mol) yielded the hydrobromide salt. Treatment of this with phosphorus tribromide (23.6 ml, 68 g) followed by trituration with ether (4 × 200 ml) gave 2-bromomethyl-5-ethylpiperidine hydrobromide as a pale orange waxy solid which crystallised from ethanol as a white solid (45 g, 64%). The bromide hydrobromide (28.7 g, 0.1 mol) in ethanol (150 ml) was refluxed with thiourea (8 g) for 5 h to produce the isothiouronium salt. Evaporation of the solvent gave the crude salt which was not isolated pure due to its hygroscopic nature. Instead it was decomposed by refluxing an ethanolic solution for 1.5 h with tetraethylenepentamine (26 g). The residue obtained upon removal of the solvent was distilled under reduced pressure to yield a mixture of 5-ethyl-2-piperidylmethanethiols (11.4 g, 70%), b.p. 150—152 °C at 0.9 mmHg. This mixture of thiols (11.4 g, 0.07 mol) was immediately ring closed with aqueous formaldehyde (11 ml). After the reaction mixture had been basified and extracted with ether (4 × 40 ml), the solvent was removed and the residue was distilled under reduced pressure to give a mixture of the 5-ethylperhydrothiazolo[3,4-*a*]pyridines (9.5 g, 77%) as a yellow oil, b.p. 76—80 °C at 0.5 mmHg.

Isomer separation was achieved by column chromatography over Woelm neutral alumina (grade III). The 6-ethylperhydrothiazolo[3,4-*a*]pyridines (5 g) were dissolved in light petroleum (b.p. 40—60 °C) (15 ml) and this solution was placed on top of the alumina column (500 g). This sample was eluted with light petroleum (b.p. 40—60 °C). The first 1.5 l of light petroleum were discarded. The polarity of the eluant was increased by addition of 2.5% ether and after 20 fractions (15 ml) the eluant was detected. The progress of elution was monitored by ^1H n.m.r. spectroscopy. The following 110 fractions (15 ml) upon evaporation yielded the cis-(6H,8aH)-6-*ethylperhydrothiazolo*[3,4-a]*pyridine* (Found: C, 63.5; H, 9.8; N, 8.3. $C_9H_{18}NS$ requires C, 63.2; H, 9.9; N, 8.2%). The next 120 fractions yielded an isomeric mixture but the following 100 fractions upon

evaporation gave the trans-(6H,8aH)-6-*ethylperhydrothiazolo*-[3,4-a]*pyridine* (Found: C, 63.2; H, 9.6; N, 8.0%).

Acknowledgements

This work was carried out with the support of the Procurement Executive, Ministry of Defence. We thank the S.E.R.C. for the ^{13}C n.m.r. spectra.

References

1 Part 53, T. A. Crabb, O. G. Roch, and B. Wood, *Magn. Reson. Chem.*, 1987, **25**, 707.
2 T. A. Crabb and R. F. Newton, *Tetrahedron*, 1968, **24**, 2485.
3 T. A. Crabb and P. A. Jupp, *Org. Magn. Reson.*, 1980, **13**, 63.
4 T. A. Crabb and R. F. Newton, *J. Heterocycl. Chem.*, 1966, **3**, 418.
5 T. Taguchi and S. Kasuga, *Chem. Pharm. Bull.*, 1965, **13**, 241.
6 T. A. Crabb and A. R. Katritzky, *Adv. Heterocycl. Chem.*, 1985, **36**, 1.
7 H. Booth and J. H. Little, *Tetrahedron*, 1967, **23**, 291.
8 H. Booth, *Tetrahedron*, 1966, **22**, 615.
9 M. Karplus, *J. Am. Chem. Soc.*, 1963, **85**, 2870.
10 L. Banting, T. A. Crabb, and A. N. Trethewey, *Magn. Reson. Chem.*, 1987, **25**, 352.

Received 2nd *June* 1987; *Paper* 7/969