Tetrahedron Vol 24, pp 2485 to 2494 Pergamon Press 1968 Printed in Great Britain

PROTON MAGNETIC RESONANCE STUDIES OF COMPOUNDS WITH BRIDGEHEAD NITROGEN ATOMS—IV*

CONFIGURATIONAL AND CONFORMATIONAL STUDIES WITH METHYL SUBSTITUTED 8-THIA-1-AZABICYCLO [4.3.0] NONANES†

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(*Received in the UK 9 October 1967; accepted for publication 23 October 1967*)

Abstract—The preferred conformations of a series of Me substituted 8-thia-1-azabicyclo[4.3.0]nonanes have been assigned on the basis of the 2700–2850 cm^{-1} region of the IR spectra and on the geminal coupling constants of the N—CH_2—S protons.

THE sensitivity of geminal coupling constants to the orientation of lone pairs of electrons on adjacent heteroatoms has recently been the subject of several publications.[1-3] We have demonstrated the application of this effect to conformational analysis in a series of substituted 8-oxa-1-azabicyclo[4.3.0]nonanes.[4-6]

Little work has so far been published on the influence of a S atom on the geminal coupling constant of an adjacent methylene group, and so it seemed of interest to study the NMR spectra and preferred conformations of substituted 8-thia-1-azabicyclo[4.3.0]nonanes. The differences in stereochemistry between this system and the 8-oxa analogue might be expected to be due to the S non-bonding electrons and the increased C—S bond length.

The Me substituted bicyclic compounds were synthesized by the action of formaldehyde on epimeric mixtures of the thiols. The latter were prepared from piperidyl carbinols by the route shown in Fig. 1. From the method of preparation of the piperidyl carbinols, that is catalytic or sodium-ethanol reduction of pyridine carbinols, and assuming the usual stereochemical results obtained in these reductions, the stereochemistry of the predominant isomer in the final epimeric mixture was deduced.[6] Isomerically pure 8-thia-1-azabicyclo[4.3.0]nonanes were obtained by fractional recrystallization of their picrates and by GLC.

The stereochemistry of the 8-thia-1-azabicyclo[4.3.0]nonanes will be similar to that of hydrindane with the additional feature of the conformationally unstable bridgehead N atom. For the *cis*-hydrindane ⇌ *trans*-hydrindane equilibrium ΔG° has been calculated to be only −0·3 Kcals at 25°.[7] Thus one might expect *cis*-3,6-H-3-methyl 8-thia-1-azabicyclo[4.3.0]nonane to exist predominantly as I with a *cis*-fused ring conformation and the Me group equatorial rather than as II with a *trans*-

* Part III. T. A. Crabb and R. F. Newton, *Tetrahedron* **24**, 1997 (1968).

† A shortened version of this paper was presented at the *International Congress of Heterocyclic Chemistry*, Albuquerque, New Mexico, June (1967).

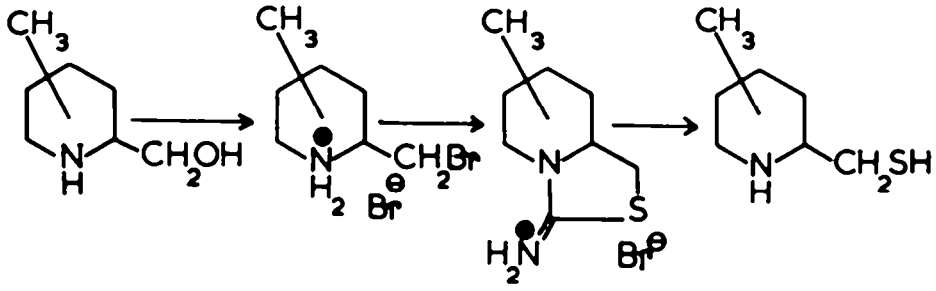

FIG. 1 Preparation of 8-thia-1-azabicyclo[4.3.0]nonanes.

I II

fused ring conformation and the Me group axial. Similar arguments apply to the other Me substituted compounds described in this study.

In order to study the conformational preferences of these compounds, we have used IR and NMR spectroscopy. Previous workers,[8-10] particularly in the alkaloid field, have made great use of the Bohlmann IR criterion first described for the quinolizidines. This states that when the lone pair of electrons on N is *trans*- to at least two axial hydrogens on adjacent C atoms a set of strong bands appear on the low wave number side of the C—H stretching bands between 2800 and 2700 cm^{-1}.

This correlation only applies to compounds having a *trans*-ring fusion as *cis*-conformations do not allow two C—H bonds *trans*-diaxial to the lone pair.

As part of a study of the IR spectra of C_{15}-lupin alkaloids Wiewiórwski and Skolik[11] undertook a qualitative investigation of these bands. They used an α lactam as a reference compound, having no bands in the 2850–2500 cm^{-1} region, termed the T band region, and compared the spectra of alkaloids containing *cis*- and *trans*-fused ring junctions with the references. They were able to show that *cis*-fused conformations do give rise to absorptions in the 2850–2500 cm^{-1} region although of reduced intensity.

As is seen from Table 1 and Fig. 2 an examination of the 2850–2500 cm^{-1} region of the IR spectra of the Me substituted 8-thia-1-azabicyclo[4.3.0]nonanes permits a clear division of the compounds into two groups. The first group all have a strong band at about 2785 cm^{-1} with an ε^a of 115–164 showing these compounds to exist in predominantly *trans*-fused ring conformations. The second group exhibiting absorption at about 2805 cm^{-1} with an ε of 51–60 must then exist in predominantly *cis*-fused ring conformations. The parent unsubstituted compound shows a broad band at 2785 cm^{-1}.

TABLE 1. IR SPECTRA OF 8-THIA-1-AZABICYCLO[4.3.0]NONANES

Compound	cm $^{-1}$	ϵ^a
cis-2,6-H-2-Methyl	2780	164
8-thia-1-azabicyclo[4.3.0]nonane	2703	22
	2689	30
	2647	15
trans-3,6-H-3-Methyl	2785	115
8-thia-1-azabicyclo[4.3.0]nonane	2734	30
	2715	33
	2635	21
cis-4,6-H-4-Methyl	2785	138
8-thia-1-azabicyclo[4.3.0]nonane	2715	35
	2632	21
trans-5,6-H-5-Methyl	2793	115
8-thia-1-azabicyclo[4.3.0]nonane	2728	43
	2704	43
	2622	24
8-thia-1-azabicyclo[4.3.0]nonane	2785	122
	2731	19
	2718	21
	2710	21
	2634	13
cis-3,6-H-3-Methyl	2803	60
8-thia-1-azabicyclo[4.3.0]nonane	2722	16
trans-4,6-H-4-Methyl	2803	60
8-thia-1-azabicyclo[4.3.0]nonane	2724	16
cis-5,6-H-5-Methyl	2821	51
8-thia-1-azabicyclo[4.3.0]nonane	2808	50
	2723	13
	2702	13

[a] ± 7.5 cm $^{-1}$.

Comparison of the area of the T-bands shows that, for example, *cis*-3,6-H-3-methyl 8-thia-1-azabicyclo[4.3.0]nonane has a T-band 55% as intense as that of *trans*-3,6-H-3-methyl 8-thia-1-azabicyclo[4.3.0]nonane whilst the parent unsubstituted compound has a T-band 78% as intense as the latter.

While acknowledging the approximate nature of this quantitative approach and assuming that *cis*-3,6-H and *trans*-3,6-H-3-methyl 8-thia-1-azabicyclo[4.3.0]nonane exist in predominantly *cis*- and *trans*-fused ring conformations respectively the intensity of the T-band of 8-thia-1-azabicyclo[4.3.0]nonane suggests that it contains approximately 50% of the *trans*- and 50% of the *cis*-conformation.

In order to verify this conclusion, we have investigated the NMR spectra of these compounds. A paper on geminal coupling constants (J_{gem}) by Pople and Bothner-By[2] indicated that the value of J_{gem} for a methylene group situated next to a heteroatom should depend on the overlap of the C—H bonds of the methylene group with electron pairs on adjacent heteroatoms. Thus a study of the value of J_{gem} for the methylene group situated between N and S in 8-thia-1-azabicyclo[4.3.0]nonanes would be expected to yield information regarding the preferred conformation of the system.

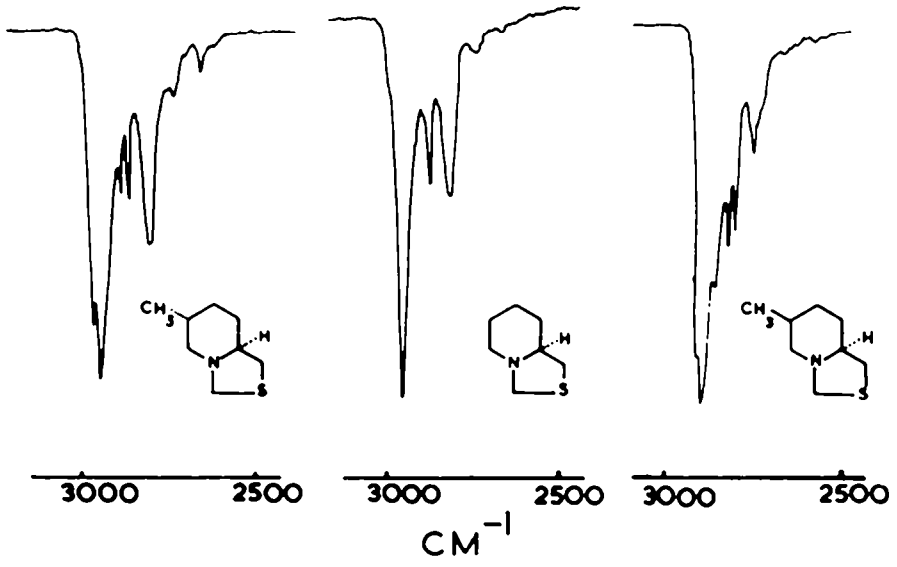

FIG. 2 C—H stretching region of the Infrared spectra.

It can be seen from Tables 2 and 3 that the compounds again fall naturally into two groups. The compounds to which, on the basis of IR spectra, we have assigned predominantly *trans*-fused ring conformations have a J_{gem} −6·0 c/s, those to which we assigned predominantly *cis*-conformations exhibit a J_{gem} of −9·0 c/s. The parent compound shows an intermediate value of J_{gem} = −7·25 c/s. If some linear relationship exists between J_{gem} and conformation these values indicate that the parent compound may exist as an equilibrium mixture of ca. 40% *trans*- and 60% *cis*-conformers at room temperature. This compares with the estimate of 50% of the *trans*- and 50% of the *cis*-fused ring conformation obtained from a similar approach based on the area of the Bohlmann bands in the IR spectra.

The differences in chemical shifts ($\Delta_{H_{9,9'}}$) between the C_9 methylene protons are also indicative of the position of conformational equilibrium. The predominantly *cis*-fused ring compounds all show $\Delta_{H_{9,9'}}$ to be about 0·25 ppm and with the exception of the 2-Me compound the predominantly *trans*-fused ring compounds show $\Delta_{H_{9,9'}}$ of ca. 0·55 ppm. The parent compound closely resembles the *cis*-fused ring compounds with $\Delta_{H9,9'}$ = 0·22 ppm suggesting a much higher percentage of *cis*-fused conformer in the equilibrium mixture than is indicated by IR and by J_{gem} but since so many factors affect chemical shifts, too much reliance cannot be placed upon evidence based upon this parameter.

The large chemical shift differences for protons next to a nitrogen atom have been explained[12] in terms of overlap of the N lone pair and a $\sigma^*C\text{-}H_{ax}$ orbital on the α-C atom which increases the electron density at, and the shielding of, the axial proton. This effect will be maximal when the α-C H bond and the lone pair of the N atom are *trans*-diaxial with respect to each other. Models indicate that this is only possible in compounds having a *trans*-fused ring conformation thus supporting the conformational assignments made. This also permits assignment of the signals arising

TABLE 2. NMR SPECTRA OF *trans*-FUSED COMPOUNDS

Compound	Coupling Constants (c/s)[a]				Chemical Shifts (τ)[b]				
	$J_{H_{6\alpha}H_{6\beta}}$	$J_{H_{7\alpha}H_{7\beta}}$	$J_{H_{6\alpha}H_{9\alpha}}$	$J_{H_{7\beta}H_{9\alpha}}$	$H_{9\beta}$	$H_{9\alpha}$	$H_{7\alpha}$	$H_{7\beta}$	H_2
cis-2,6-H-2-Methyl 8-thia-1-azabicyclo[4.3.0]nonane	−6·0	−9·5	5·6	9·9	5·90	6·80	7·09 (q)	7·43 (t)	
trans-3,6-H-3-Methyl 8-thia-1-azabicyclo[4.3.0]nonane	−6·0	−9·0	5·4	9·5	6·16	6·71	7·14 (q)	7·45 (t)	7·05 (m)
cis-4,6-H-4-Methyl 8-thia-1-azabicyclo[4.3.0]nonane	−6·25	−9·0	5·75	9·75	6·05	6·64	7·06 (q)	7·40 (t)	7·00 (m)
trans-5,6-H-5-Methyl 8-thia-1-azabicyclo[4.3.0]nonane	−6·0	−9·5	5·4	9·4	6·08	6·62	6·98 (q)	7·38 (t)	6·95 (m)

[a] ±0·3 c/s [b] ±0·05 τ.
(t) = triplet; (q) = quartet; (m) = multiplet, all measured from centre.

TABLE 3. NMR SPECTRA OF *cis*-FUSED COMPOUNDS

Compound	Coupling Constants (c/s)[a]				Chemical shifts (τ)[b]			
	$J_{H_{6\alpha}H_{6\beta}}$	$J_{H_{6\alpha}H_{7\alpha}}$	$J_{H_{6\alpha}H_{7\beta}}$	$J_{H_{6\alpha}H_{9\alpha}}$	$H_{9\beta}$	$H_{9\alpha}$	$H_{2\alpha}$	$H_{2\beta}$
cis-3,6-H-3-Methyl 8-thia-1-azabicyclo[4.3.0]nonane	−8·5	−10·0	4·0	10·5	5·89	6·11	7·52 (q)	7·85 (t)
trans-4,6-H-4-Methyl 8-thia-1-azabicyclo[4.3.0]nonane	−9·0	−11·0	4·0	11·0	5·85	6·10	7·50 (q)	7·82 (t)
cis-5,6-H-5-Methyl 8-thia-1-azabicyclo[4.3.0]nonane	−9·0	—	—	—	5·85	6·11	7·55 (m)	
8-Thia-1-azabicyclo[4.3.0]nonane	−7·25	–		—	6·11	6·33		

[a] ±0·3 c/s [b] ±0·05 τ.
(t) = triplet; (q) = quarter; (m) = multiplet, measured from centre.

from the C_9 methylene protons in the *trans*-fused ring compounds. One of the proton absorbs in the normal region (ca. 6 τ) for thiazolidines[13] and this must be the C_9-H_β proton since the abnormally shielded protons giving signals at ca. 6·6–6·8 τ must be those in a near *trans*-diaxial relationship with the N lone pair, i.e. the C_9–H_α protons. Since in the preferred *cis*-fused ring conformation neither of the C_9 methylene protons in no way approach being *trans*-diaxially orientated with respect to the N lone pair of electrons, abnormal shielding is absent and both protons absorb normally at ca. 6 τ.

The 2-Me compound is exceptional with $\Delta_{H_9H_9'} = 0{\cdot}90$ and this must be due to the close proximity of the Me group to the C_9 methylene. A similar effect was noted in the 8-oxa analogues.[6]

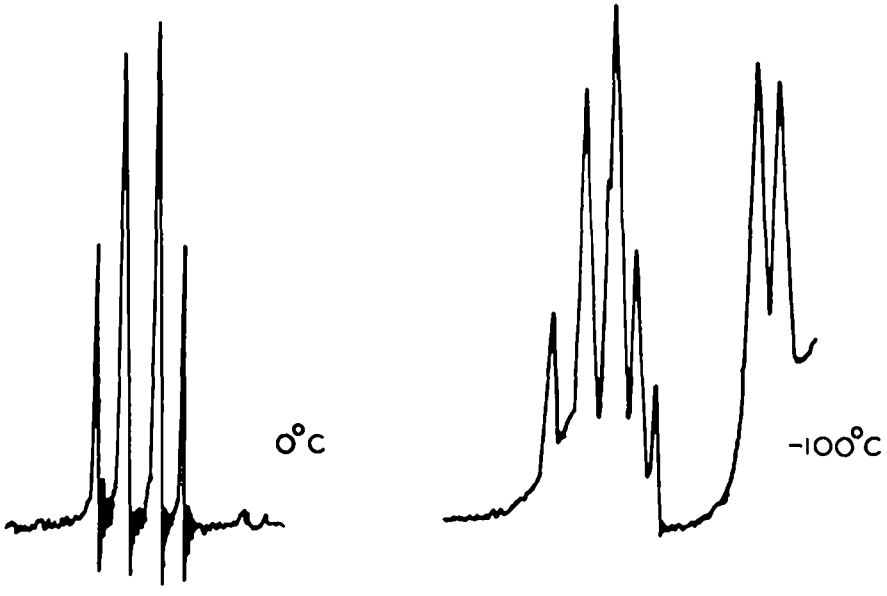

FIG. 3 Effect of temperature on the C_9 methylene quartet of 8-thia-1-azabicyclo[4.3.0]nonane.

Variable temperature NMR experiments on the parent compound have justified the above made assumptions concerning the nature of the conformational equilibrium present (Fig. 3). At 0°C in CS_2 the C_9 methylene signals appear as a quartet having $J_{gem} = -7{\cdot}25$ c/s and $\Delta_{H_9H_9'} = 0{\cdot}24$ ppm. As the temperature is decreased this quartet begins to break down, at $-60°$ the signal is broad, at $-80°$ a new spectrum has begun to emerge and at $-100°$ the original quartet has completely disappeared and two new quartets are in evidence. One quartet has $J = -9{\cdot}5$ c/s and $\Delta_{H_9H_9'} = 0{\cdot}29$ ppm, and this corresponds to the *cis*-conformation, the H_9H_9, quartet in, for example, *trans*-4,6-H-4-methyl 8-thia-1-azabicyclo[4.3.0]nonane (CCl_4 solution) has $J = -9{\cdot}0$ c/s and $\Delta_{H_9H_9'} = 0{\cdot}29$ ppm. The other quartet has $J = -6{\cdot}0$ c/s and $\Delta_{H_9H_9'} = 0{\cdot}63$ ppm and corresponds to the *trans*-fused conformer; in, for example, *cis*-4,6-H-4-methyl 8-thia-1-azabicyclo[4.3.0]nonane (CCl_4 soln) $J = -6{\cdot}0$ c/s and $\Delta_{H_9H_9'} = 0{\cdot}62$ ppm.

A possible reason for the high proportion of *cis*-fused ring conformer in the equilibrium mixture of 8-thia-1-azabicyclo[4.3.0]nonane is the unfavourable dipole-dipole interaction which exists between the heteroatoms in the *trans*-fused ring conformer and which is relieved in the *cis*-fused ring conformer.

In simple substituted thiazolidines J_{gem} is found to be ca. $-9{\cdot}5$ c/s[13] and this suggests a similarity between the stereochemistry of these compounds and that of the 5-membered ring in the predominantly *cis*-fused ring conformers which have the same value of J. The more positive value of J of -6 c/s for the *trans*-fused ring conformation indicates a 5-membered ring in which the S lone pair orbitals eclipse the C_9 methylene group, and these orbitals must also eclipse the C_7 methylene since $J_{H_{77}}$ is found to be $-9{\cdot}0$ to $-9{\cdot}5$ c/s, a more positive value than J_{gem} in cyclopentane derivatives in which J is normally -12 c/s.[1]

The remaining features of the NMR spectra of these compounds resembled those of the oxa-analogues,[6] except that overlapping of peaks and comparable magnitudes of coupling constants and chemical shifts in certain cases made extraction of many coupling constants impossible. As is seen in Table 2, for the *trans*-fused ring compounds $J_{7\beta 6_a}$ was 9·5 to 9·9 c/s and $J_{7_a 6_a}$ was 5·4 to 5·75 c/s. Assignment of signals to 7β and 7α protons was made on the assumption that $J_{7\beta 6_a} > J_{7_a 6_a}$.

In the 100 Mc spectra of the 3-Me and 4-Me *cis*-fused ring compounds the signals arising from the C_2 methylene protons were readily analysed, giving $J_{2_a 2_e} = -10$ to -11 c/s, $J_{2_a 3_e} = 4$ c/s, $J_{2_a 3_a}$ = ca. 11 c/s and $J_{2_e 3_e}$ = ca. 0 c/s, these values being similar to the coupling constants between the C_4 and C_5 protons observed in dioxans[14] suggesting a chair conformation for the 6-membered ring. The small chemical shift $\Delta_{2_a 2_e}$ of ca. 0·3 ppm might then arise from the shielding effect of the *cis*-fused 5-membered ring but may also be due to slight distortion of the geometry of the 6-membered ring. In the 100 Mc spectrum of the *cis*-fused 5-Me compound the C_2 methylene protons appeared as a multiplet between 7·43 and 7·60 τ and no coupling constants were obtainable.

EXPERIMENTAL

All elemental analyses were carried out by Dr. F. Pascher and E. Pascher, Micro-analytical Laboratory, Bonn, Germany. M.ps are uncorrected. IR spectra were recorded on a Perkin-Elmer 237 grating instrument as 0·2M solns in CCl_4 using 0·1 mm matched cells and on a Unicam S.P. 100 as 0·1M solns in CCl_4 using 0·5 mm matched cells.

The NMR spectra were determined on a Perkin–Elmer R.10 and Varian HA-60 and HA-100 spectrometers as 10% solns in CCl_4. The variable temp experiments were carried out using CS_2 solns.

Preparation of methyl substituted 8-thia-1-azabicyclo[4.3.0]nonanes

General procedure. A cooled soln of the Me substituted piperidyl carbinol in CCl_4 was saturated with HBr gas. The solvent was removed *in vacuo* to give the hydrobromide as a viscous yellow liquid. This was treated with PBr_3 and shaken. A vigorous exothermic reaction took place and dense fumes of HBr were evolved. When the reaction ceased the mixture was heated for ½ hr on a water bath. Trituration of the orange mass with ether and recrystallization from abs EtOH yielded the bromide hydrobromide as a white crystalline solid.

The bromide hydrobromide in abs EtOH was refluxed for 5 hr with a slight excess of thiourea and the resulting isothiouronium salt was precipitated by the addition of ether. This was recrystallized from abs EtOH to give the pure isothiouronium salt as a white crystalline solid. Excess tetra-ethylene pentamine was added to a soln of the isothiouronium salt in abs EtOH. The mixture was refluxed for 1 hr and the alcohol was removed *in vacuo*. The remaining viscous oil was distilled under high vacuum. The thiols were obtained as low melting white solids or colourless oils. The thiol was shaken for ½ hr with a slight excess of 40%

formaldehyde soln, the soln was basified with NaOH aq and ether extracted, the ether was dried over Na_2SO_4 and evaporated. The crude formal was distilled under vacuum to give an epimeric mixture of the Me substituted 8-thia-1-azabicyclo[4.3.0]nonane as a colourless oil. Pure epimers were obtained by fractional recrystallization of their picrates, which were reconverted to the formals by treatment with NaOH. In some cases the epimeric formals were separated by gas chromatography.

8-Thia-1-azabicyclo[4.3.0]*nonane*. 2-Bromomethylpiperidine hydrobromide (72 g, 65%) was obtained from 2-piperidyl carbinol (54 g) as white needles m.p., 190–191° from EtOH (Lit.[15] m.p., 192–193°). (Found: C, 27·72; H, 5·11; N, 5·49; Br, 62·01. Calc. for $C_6H_{12}NBr_2$: C, 27·80; H, 5·02; N, 5·40; Br, 61·77%). Conversion of this gave the isothiouronium salt (54 g, 71%) as a white crystalline solid m.p., 151–153° (Lit.[15] 153°). The isothiouronium salt (40 g) yielded 2-mercaptomethylpiperidine (14 g, 68%) as a white solid m.p., 54–55° (Lit.[15] m.p., 55–56°). 2-Mercaptomethylpiperidine (11·0 g) gave 8-thia-1-azabicyclo[4.3.0]-nonane (10·5 g, 87%) as a colourless oil b.p., 124–126°/0·65 mm, $n_D^{22.5}$ 1·5350. Picrate m.p., 204–205° as yellow plates from EtOH. (Found: C, 42·17; H, 4·44; N, 15·18; S, 8·69. $C_{13}H_{16}N_4O_7S$ requires: C, 41·94; H, 4·33; N, 15·05; S, 8·61%).

cis-2,6-H-2-Methyl 8-thia-1-azabicyclo[4.3.0]*nonane*. 6-Methyl 2-bromomethylpiperidine hydrobromide (58 g, 58%) was obtained from 6-methyl 2-piperidyl carbinol (50 g) as white needles m.p., 235–236° from EtOH. (Found: C, 30·71; H, 5·39; N, 4·88; Br, 59·09. $C_7H_{14}NBr_2$ requires: C, 30·88; H, 5·18; N, 4·96; Br, 58·82%). The isothiouronium salt (51 g, 96%) was obtained from the bromide (58 g) as a white crystalline solid m.p., 220–221° from EtOH. The isothiouronium salt (50 g) was decomposed with tetra-ethylene pentamine, the alcohol was removed *in vacuo* and excess formaldehyde was added to the remaining syrup. The mixture was basified with NaOH aq until a ppt began to appear and then ether extracted 3 times. The ether soln was dried over Na_2SO_4, the ether evaporated and the crude formal distilled. *cis*-2,6-H-2-Methyl 8-thia-1-azabicyclo[4.3.0]nonane (10·5 g, 33%) was obtained as a colourless oil b.p., 130–132°/0·65 mm $n_D^{22.5}$ 1·5085, picrate m.p., 188·189° as yellow needles from EtOH. (Found: C, 43·53; H, 4·78; N, 14·57; S, 8·28. $C_{14}H_{18}N_4O_7S$ requires: C, 43·52; H, 4·70; N, 14·50; S, 8·28%).

cis- and trans-3,6-H-3-Methyl 8-thia-1-azabicyclo[4.3.0]*nonane*. An epimeric mixture of the 5-methyl 2-bromomethylpiperidine hydrobromides (58 g, 72%) was obtained as white needles from 5-methyl 2-piperidyl carbinol (40 g) obtained by catalytic reduction of 5-methyl 2-pyridyl carbinol. Recrystallization of a small amount of this gave the two epimeric bromides. *trans-5,6-H-5-Methyl 2-bromomethylpiperidine hydrobromide* was obtained as a white crystalline solid m.p., 145–146° from EtOH. (Found: C, 30·34; H, 5·39; N, 5·01; Br, 58·17. $C_7H_{14}NBr_2$ requires: C, 30·88; H, 5·18; N, 4·96; Br, 58·82%). *cis-5,6-H-5-Methyl 2-bromomethylpiperidine hydrobromide* was obtained as white needles from EtOH m.p., 192–193°. (Found: C, 30·64; H, 5·39; N, 4·82; Br, 59·04. $C_7H_{14}NBr_2$ requires: C, 30·88; H, 5·18; N, 4·96; Br, 58·82%).

An epimeric mixture of the isothiouronium salts (51 g, 95%) was obtained from an epimeric mixture of the bromides (57 g) as a white solid from EtOH. After refluxing with tetra-ethylene pentamine and removing the EtOH, excess formaldehyde was added to the reaction mixture which was worked up as above to give an epimeric mixture of *cis-* and *trans*-3,6-H-3-methyl 8-thia-1-azabicyclo[4.3.0]nonane (13·6 g, 43%) as a colourless oil b.p., 121–122°/32 mm.

The formal (11·2 g) in abs EtOH (200 ml) was added to a soln of picric acid (16·4 g) in EtOH (200 ml). The resulting picrate (26·5 g) was filtered off and fractionally recrystallized to give the epimerically pure picrate of *cis*-3,6-H-3-methyl 8-thia-1-azabicyclo[4.3.0]nonane as yellow needles m.p., 160–161°. (Found: C, 43·68; H, 4·72; N, 14·40; S, 8·27. $C_{14}H_{18}N_4O_7S$ requires: C, 43·52; H, 4·70; N, 14·50; S, 8·28%).

Excess cold NaOH aq was added to the picrate (5·0 g) and the mixture was immediately ether extracted 3 times. The ether soln was dried (Na_2SO_4) and the ether evaporated. The residue was distilled to give cis-3,6-H-3-*methyl 8-thia-1-azabicyclo*[4.3.0]*nonane* (1·75 g, 86%) as a colourless oil b.p., 112–116°/13 mm, $n_D^{22.5}$ 1·5304.

Concentration of the mother liquors yielded an epimeric mixture of picrates (5·1 g) m.p. 140–142°. Further concentration yielded the nearly pure picrate of *trans*-3,6-H-3-methyl 8-thia-1-azabicyclo[4.3.0] nonane (8·0 g). This was recrystallized 3 times to give the pure picrate of *trans*-3,6-H-3-methyl 8-thia-1-azabicyclo[4.3.0]nonane (4·5 g) as yellow plates m.p., 154–155°. (Found: C, 43·56; H, 4·74; N, 14·66, S, 8·48. $C_{14}H_{18}N_4O_7S$ requires: C, 43·52; H, 4·70; N, 14·50; S, 8·28%).

The picrate (3·0 g) was decomposed as before to give pure trans-3,6-H-3-*methyl 8-thia-1-azabicyclo*-[4.3.0]*nonane* (0·95 g, 78%) as a colourless oil b.p., 128–130°/35 mm, $n_D^{25.5}$ 1·5213.

cis- and trans-4,6-H-4-Methyl 8-thia-1-azabicyclo[4.3.0]*nonane*. An epimeric mixture of the 4-methyl 2-bromomethylpiperidine hydrobromides (24 g, 63%) was obtained as white needles from 4-methyl piperidyl 2-carbinol (18 g) itself prepared by catalytic hydrogenation of 4-methyl 2-pyridyl carbinol.

The isothiouronium salt (21 g, 88%) was obtained from the bromide (24 g) as a white solid from EtOH. Refluxing this with tetraethylene pentamine and distilling the syrupy residue yielded an epimeric mixture of the thiols (8·6 g, 65%) as a colourless oil b.p., 78–80°/1·4 mm. Reaction of this with formaldehyde yielded an epimeric mixture of *cis*- and *trans*-4,6-H-4-methyl 8-thia-1-azabicyclo[4.3.0]nonane (8·1 g, 87%) as a colourless oil b.p., 128–130°/28 mm. Separation was achieved on an Aerograph Autoprep gas chromatogram using a 20% apiezon column and hydrogen carrier gas. cis-4,6-H-4-*Methyl* 8-*thia*-1-*azabicyclo*[4.3.0]-*nonane* was a colourless oil b.p., 122–124°/21 mm, $n_D^{22.5}$ 1·5200. The picrate was obtained as yellow needles m.p., 162–163° from EtOH. (Found: C, 43·73; H, 4·76; N, 14·54; S, 8·24. $C_{14}H_{18}N_4O_7S$ requires: C, 43·52; H, 4·70; N, 14·50; S, 8·28%). trans-4,6-H-4-*Methyl* 8-*thia*-1-*azabicyclo*[4.3.0]*nonane* was obtained as a colourless oil b.p., 127–129°/28 mm, $n_D^{25.5}$ 1·5277. The picrate formed yellow needles m.p., 159–160° from EtOH. (Found: C, 43·76; H, 4·75; N, 14·54; S, 8·36. $C_{14}H_{18}N_4O_7S$ requires: C, 43·52; H, 4·70; N, 14·50; S, 8·28%).

cis-5,6-H-5-*Methyl* 8-*thia*-1-*azabicyclo*[4.3.0]*nonane*. An epimeric mixture of 3-methyl 2-bromomethylpiperidine hydrobromide (40 g, 68%) was obtained from 3-methyl 2-piperidyl carbinol (30 g) itself obtained by catalytic reduction of 3-methyl 2-pyridyl carbinol. Recrystallization of a small amount of this gave epimerically pure cis-3,6-H-3-*methyl* 2-*bromomethylpiperidine hydrobromide* as white needles m.p., 192–195° from EtOH. (Found: C, 30·70; H, 5·36; N, 5·31; Br, 58·77. $C_7H_{14}NBr_2$ requires: C, 30·88; H, 5·18; N, 4·96; Br, 58·82%). The isothiouronium salt (36 g, 97%) was obtained from the bromide (40 g) as white crystals from EtOH. Refluxing with tetra-ethylene pentamine and treatment of the crude product with excess formaldehyde yielded an epimeric mixture of *cis*- and *trans*-5,6-H-5-methyl 8-thia-1-azabicyclo-[4.3.0]nonane (7·1 g, 39%) as a colourless mobile oil b.p., 80–82°/0·9 mm. The epimeric mixture (5·1 g) in EtOH (100 ml) was added to picric acid (7·45 g) in EtOH (100 ml). Repeated fractional recrystallization gave the pure picrate of *cis*-5,6-H-5-methyl 8-thia-1-azabicyclo[4.3.0]nonane (7·0 g) as yellow needles m.p., 181–183°. (Found: C, 44·00; H, 4·86; N, 14·36; S, 8·06. $C_{14}H_{18}N_4O_7S$ requires: C, 43·52; H, 4·70; N, 14·50; S, 8·28%)

The picrate (7·0 g) was decomposed to give cis-5,6-H-5-*methyl* 8-*thia*-1-*azabicyclo*[4.3.0]*nonane* (2·0 g, 70%) as a colourless mobile oil b.p., 81–83°/0·85 mm, $n_D^{26.0}$ 1·5296.

trans-5,6-H-5-*Methyl* 8-*thia*-1-*azabicyclo*[4.3.0]*nonane*. An epimeric mixture of 3-methyl 2-bromomethylpiperidine hydrobromide (35 g, 60%) was obtained from 3-methyl 2-piperidyl carbinol (30 g) obtained by Na and EtOH reduction of 3-methyl 2-pyridyl carbinol. Recrystallization of a small amount gave epimerically pure trans-3,6-H-3-*methyl* 2-*bromomethylpiperidine hydrobromide* as white needles m.p., 201–202° from EtOH. (Found: C, 30·84; H, 5·27; N, 5·18; Br, 58·65. $C_7H_{14}NBr_2$ requires: C, 30·88; H, 5·18; N, 4·96; Br, 58·82%). An epimeric mixture of *cis*- and *trans*-5,6-H-5-methyl 7,8-tetramethylene-9-iminothiazolidine hydrobromide (34 g, 97%) was obtained from the bromide (35 g) as white crystals from EtOH. Recrystallization of a small amount gave epimerically pure trans-5,6-H-5-*methyl* 7,8-*tetramethylene*-9-*iminothiazolidine hydrobromide* as white crystals m.p., 205–207°. An epimeric mixture of *cis*- and *trans*-5,6-H-5-methyl 8-thia-1-azabicyclo[4.3.0]nonane (6·0 g, 23%) was obtained as above as a colourless oil b.p., 95–97°/25 mm. This mixture (5·8 g) in EtOH was added to a soln of picric acid (8·5 g) in EtOH. Repeated fractional recrystallization gave the pure picrate of *trans*-5,6-H-5-methyl 8-thia-1-azabicyclo-[4.3.0]nonane (6·7 g) as yellow plates m.p., 175–177° (Found: C, 43·26; H, 4·75; N, 14·62; S, 8·36. $C_{14}H_{18}N_4O_7S$ requires: C, 43·52; H, 4·70; N, 14·50; S, 8·28%). The picrate (6·5 g) was decomposed to give trans-5,6-H-5-*methyl* 8-*thia*-1-*azabicyclo*[4.3.0]*nonane* (1·85 g, 70%) as a colourless mobile oil b.p., 114–116°/18 mm, $n_D^{25.5}$ 1·5179

Acknowledgement—We are indebted to Mr. D. N. Henty and S. Vary for running the variable temperature NMR experiment.

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