Tetrahedron Vol 26, pp 3941 to 3950 Pergamon Press 1970 Printed in Great Britain

PROTON MAGNETIC RESONANCE STUDIES OF COMPOUNDS WITH BRIDGEHEAD NITROGEN ATOMS--XVI[1]

CONFIGURATIONAL AND CONFORMATIONAL STUDIES WITH DERIVATIVES OF 3-THIA-1-AZA BICYCLO[4.4.0] DECANE

T. A. CRABB and R. F. NEWTON

Chemistry Department, Portsmouth Polytechnic

(*Received in the UK* 19 *March* 1970; *Accepted for publication* 16 *April* 1970)

Abstract--A series of substituted 3-thia-1-azabicyclo[4.4.0] decanes have been prepared and their configurations and preferred conformations about the ring fusion assigned from a study of their IR and NMR spectra. A comparison of the spectral data with that obtained on the corresponding 3-oxa-1-azabicyclo [4.4.0] decanes suggests marked deviations from the chair conformation for the 1,3-thiazane ring.

DIFFERENCES between the stereochemistry of the 3-thia-1-azabicyclo [4.4.0] decane (I) and of the closely related 3-oxa-1-azabicyclo[4.4.0]decane (II)[2] system are expected to arise principally from the long C—S bond (1·81 Å) as compared with the C—O bond length of 1·41 Å and also from differences in angles and in torsional interactions involving the heteroatoms. It was with the aim of exploring the consequences of these differences that a series of 3-thia-1-azabicyclo[4.4.0]decanes were synthesized by the route shown in Fig. 1.

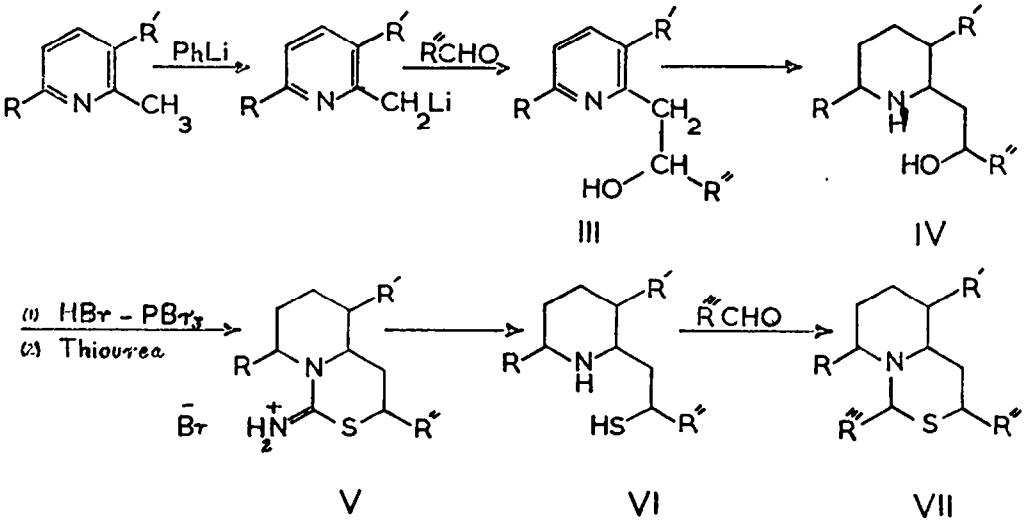
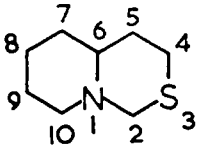
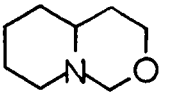


FIG. 1

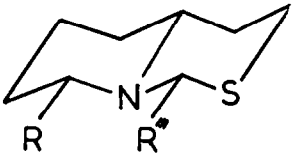
The substituted 2-(β-hydroxyethyl) pyridines (III), prepared by the reaction of the appropriate aldehyde on the substituted picolyl-lithium, were either hydrogenated using Adams catalyst or reduced by sodium and ethanol to give mixtures of the 2-(β-hydroxyethyl) piperidines (IV). These were converted to their bromide hydrobromides by the action of gaseous HBr followed by PBr_3. Refluxing the bromide hydrobromides with thiourea in ethanol afforded the isothiouronium salts (V) which were decomposed to the corresponding 2-(β-mercaptoethyl) piperidines (VI) by refluxing with tetraethylene pentamine in ethanol. The substituted 3-thia-1-azabicyclo[4.4.0]decanes (VII) were then obtained by the action of the appropriate aldehyde on the thiols and the individual racemic isomers by fractional recrystallization of the picrates or by preparative gas–liquid chromatography.



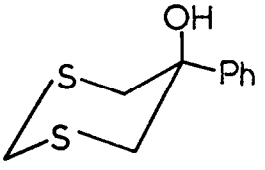
I



II



VIII



IX

RESULTS AND DISCUSSION

3-Thia-1-azabicyclo[4.4.0]decane (I) shows pronounced absorption (Bohlmann[3] bands) in the 2800–2600 cm^{-1} region of its IR spectrum (Table 1) indicating the predominance of the *trans* fused ring conformation (VIII, R = R‴ = H). Its NMR spectrum (Table 2) exhibited one strikingly different feature from that of the related oxa-compound (II) in that the high field part of the C2 methylene AB showed additional splitting (J = 1·6 Hz) whereas in the NMR spectrum of II the low field part of the quartet appeared as broadened signals. Although equatorial-axial and axial-axial four bond couplings occur, the most positive values of ^4J are normally observed between protons in a W-relationship.[4] It is reasonable therefore to assign the high field signals of the AB quartet in the spectrum of I to the C2Heq protons so that the ^4J is by a W path between H2eq and H4eq. A coupling of 1·85 Hz has been observed[5] between H2eq and H4eq in 5-hydroxy-5-phenyl-1,3-dithian (IX).

The higher field absorption of H2eq than H2ax in I, in contrast to the situation in II and in most cyclohexane derivatives, is in agreement with previous chemical shift

data on methylene protons adjacent to sulphur in a 6-membered ring and has been interpreted[6] in terms of differences between C—S and C—C bond anisotropies.

Additional support for the correctness of this assignment of signals in I comes from a study of the NMR spectrum of 2-phenyl-3-thia-1-azabicyclo[4.4.0]decane (VII, R = R′ = R″ = H, R‴ = Ph).

TABLE 1. IR SPECTRA (2800–2600 cm^{-1} REGION) OF 3-THIA-1-AZABICYCLO[4.4.0] DECANES

Compound	Ring fusion†	cm^{-1}	ε_a*
I	*trans*	2782	75
		2738	32
		2720	32
VIII (R = H, R‴ = Ph)	*trans*	2787	70
		2743	42
		2720	25
VIII (R = Me, R‴ = H)	*trans*	2773	86
X (X = S)	*trans*	2791	60
		2737	25
		2720	24
XI (X = S)	*trans*	2792	77
		2733	25
		2720	25
XII (R = H)	*trans*	2785	70
		2735	27
		2720	25
XII (R = Ph)	*trans*	2795	40
		2748	27
XIV (R = H)	*cis*	2790	14
		2720	12
XIV (R = Ph)	*cis*	2800	16

* Apparent extinction coefficient.
† Predominant conformation.

This compound exhibits marked Bohlmann bands and since it was the only isomer obtained by condensing benzaldehyde with 2-(β-mercaptoethyl) piperidine its configuration and preferred conformation must be as in VIII (R = H, R‴ = Ph). A comparison of the NMR data (Table 2) for this compound and I and for II and its 2-phenyl derivative show a deshielding by the phenyl group of the H2ax proton in the oxa-series of 0·70 ppm and in the thia-series of 0·68 ppm. The close correspondence between these deshieldings suggests similar stereochemistry for both systems and also confirms the assignment of the low field H2 signals in I to H2ax.

The *cis*-10,6-*H* configuration may be assigned to the 10-methyl-3-thia-1-azabicyclo[4.4.0]decane since it was synthesized by the route shown in Fig. 1 from *cis*-6-methyl-2-(β-hydroxyethyl) piperidine.[2] The marked Bohlmann bands in the IR confirm the *trans* fused conformation depicted in VIII (R = Me, R‴ = H). A comparison, however, of the change in the C2 methylene chemical shifts on going from I to the 10-Me compound with the change in the analogous pair of oxa compounds

TABLE 2. CHEMICAL SHIFTS (τ) AND COUPLING CONSTANTS (Hz) FOR THE C2 METHYLENE PROTONS IN 3-THIA-1-AZABICYCLO [4.4.0] DECANES AND IN THE RELATED 3-OXA SYSTEM

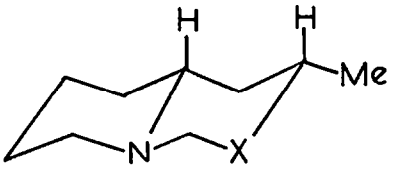
Compound 3-thia-1-azabicyclo [4.4.0.]decane	Ring fusion[c]	Chemical shifts H2e	H2a	J_{2e2a}	J_{2e4e}	Compound 3-oxa-1-azabicyclo [4.4.0]decane	Ring fusion[c]	Chemical shifts H2e	H2a	J_{2e2a}
I	*trans*	6·40	6·09	−12·0	1·6	II	*trans*	5·82	6·48	−8·0
cis-2,6-*H*-2-Phenyl	*trans*	—	5·41	—	—	*cis*-2,6-*H*-2-Phenyl	*trans*	—	5·78	—
cis-10,6-*H*-10-Methyl	*trans*	6·09	6·98	−11·8	1·3	*cis*-10,6-*H*-10-Methyl		5·42	6·73	−8·0
trans-7,6-*H*-7-Methyl[b]	*trans*	6·45	6·15	−12·2	1·8	—			—	
cis-7,6-*H*-7-Methyl[b]	*cis*	6·24	5·59	−12·8	2·6	*cis*-7,6-*H*-7-Methyl	*cis*	5·73	5·97	−9·7
trans-4,6-*H*-4-Methyl	*trans*	6·70	6·06	−12·2	0·5	*trans*-4,6-*H*-4-Methyl	*trans*	6·13	6·13	−8·0
cis-4,6-*H*-4-Methyl	*trans*	6·44	6·14	−12·2	—	*cis*-4,6-*H*-4-Methyl	*trans*	5·75	6·36	−8·0

[a] NMR data other than that pertaining to the C2 methylene protons is given in the Experimental.
[b] Measured at 100MHz, all other compounds at 60MHz
[c] Predominant conformation

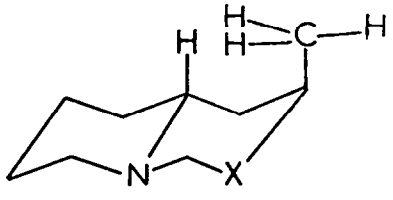
shows that introduction of an equatorial Me group into the *trans* fused conformation of I results in a deshielding of H2eq (recognised by additional splitting of signals due to ^4J) by 0·31 and a shielding of H2ax by 0·89 ppm in contrast to the shift changes for the corresponding protons in the oxa series of 0·40 and 0·25 ppm. The deshielding of H2eq by the peri-Me group, noted in the 3-oxa-1-azabicyclo[4.4.0]decane[2] and related systems[7] and attributed[8] to a van der Waals interaction, was expected in VIII (R = Me, R''' = H). However, the shielding by 0·89 ppm of H2ax by the equatorial 10Me group was quite unexpected and implies a marked deviation of the thiazane ring in VIII (R = Me, R''' = H) from the chair geometry.

Since the torsional interactions in non-chair conformations of 1,3-thiazane should be less than in comparable conformations of 1,3-oxazanes (torsional barrier in MeOMe = 2·72 kcal/mole and in MeSMe = 2·13 kcal/mole) and because the S containing ring in I is larger than the O containing ring in II it seems likely that in VIII (R = Me, R''' = H) the unfavourable peri-interaction in the chair–chair conformation can be relieved by a deformation of the thiazane ring with a consequent change in the shielding of the C2 methylene protons.

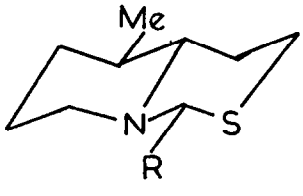
Further evidence for the occurrence of significant variation from the chair-conformation of the thiazane system, in some cases, came from a study of the NMR spectra of the isomeric 4-methyl-3-thia-1-azabicyclo[4.4.0]decanes. The oxa analogues both exist predominantly in the *trans* fused conformation and the presence of Bohlmann bands in the IR spectra showed that this was also the predominant conformation for the 4-Me-thia-aza compounds. One of the isomers showed almost identical C2 methylene NMR parameters to those in the unsubstituted parent compound (I) and was accordingly assigned the *cis*-4,6-*H* configuration and the preferred conformation (X, X = S) with an equatorial Me group (cf the similar C2 methylene NMR parameters for II and for *cis*-4,6-*H*-4-methyl-3-oxa-1-azabicyclo[4.4.0]decane (X, X = 0).



X



XI



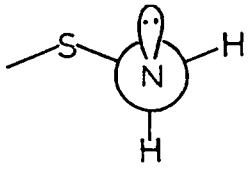
XII

The C2Hax chemical shift in XI (X = 0) is 0·35 ppm to lower field in XI (X = 0) than in II in agreement with the known[9] deshielding of a proton by a *syn*-axial Me group. In XI (X = S) however, the C2Hax proton absorbs at almost the same field as in I and comparison of normal Dreiding models of XI (X = S) and XI (X = 0) permits a rationalisation of this observation.

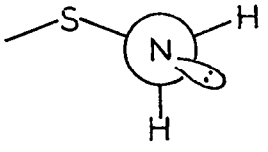
The long C—S bonds places the axial Me group in XI (X = S) further from H2ax than in XI (X = 0) consequently reducing the deshielding effect of the Me group on H2ax in the sulphur compound. In addition, the models indicate the Me-H6ax distance in XI (X = S) to be less than in XI (X = 0) and therefore one would expect this *syn*-axial interaction to be relieved in the thia-aza compound by a bending out from the ring of the Me group removing it even further from H2ax. As indicated above these types of deformation are energetically less demanding in the thia-aza than in the oxa-aza system because of differences in torsional barriers and the larger "looser" ring in the former system.

Two isomers of 7 methyl 3-thia-1-azabicyclo[4.4.0]decane were obtained and their configurations assigned from a consideration of their method of synthesis.[10] The isomer prepared from the 3-methyl-2-(β-hydroxyethyl) piperidine obtained by sodium-ethanol reduction of the corresponding pyridine ethanol was assigned the *trans*-7,6-*H* configuration whereas that obtained from the 3-methyl-2-(β-hydroxyethyl) piperidine (from catalytic reduction of the pyridine) was assigned the *cis*-7,6-*H* configuration.

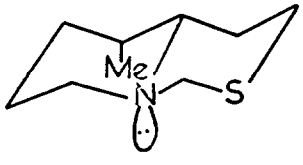
The *trans*-7,6-*H*-7-methyl-thia-aza compound is expected to exist in the *trans*-fused conformation XII (R = H) with the Me group equatorial and in confirmation of this marked bands were observed in the 2800–2700 cm^{-1} region of its IR spectrum. In addition, the NMR parameters of the C2 methylene protons in this compound and in I were very similar; the equatorial 7-Me group being too far from the C2 group to exert a direct shielding effect.



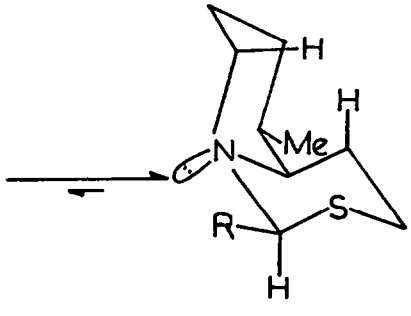
XIIa



XIVa



XIII



XIV

The *cis*-7,6-*H*-7-methyl compound might be expected to exist as an equilibrium mixture containing appreciable amounts of the *cis* fused ring conformation XIV (R = H) in equilibrium with the *trans* fused ring conformation XIII, since conformation XIII is destabilized by two gauche-butane, one gauche-propylamine and one "rabbit-ear" effect[11] between the lone pairs of electrons on N and S whereas XIV (R = H) is destabilized by three gauche-butane and one gauche-propane-thiol interaction and although the magnitude of some of these interactions is unknown analogies with other systems suggests that the free energy of the *cis* conformation might be less than that of the *trans* conformation.

In fact, the absence of Bohlmann bands in the IR spectrum of *cis*-7,6-*H*-7-methyl-3-thia-1-azabicyclo[4.4.0]decane showed the *cis* conformation (XIV, R = H) to predominate at room temperature.

For comparison purposes, *cis*-7,6-*H*-7-methyl-3-oxa-1-azabicyclo[4.4.0]decane was synthesized and the presence of only weak bands in the 2800–2700 cm^{-1} region of its IR spectrum showed that the *cis* fused ring conformation was also the predominant one in CCl_4 solution at room temperature. The *J* gem (C2 methylene) of −9·7 Hz was 0·3 Hz more positive than the corresponding value for *trans*-10,6-*H*-10-methyl-3-oxa-1-azabicyclo[4.4.0]decane showing that the 7 Me compound contains more of the *trans* fused ring conformation in equilibrium with the *cis* than does the 10 Me compound.

Although the difference in *J* gem (C2 methylene protons) between *cis* and *trans* fused 3-oxa-1-azabicyclo[4.4.0]decanes is 2·0 Hz the difference in *J* gem for the two 7,6-*H*-7-methyl-3-thia-1-azabicyclo[4.4.0]decanes is only 0·6 Hz. A much more negative J_{gem} for the *cis* fused thia-aza system of ca. −14·0 Hz was actually expected since the lone pair−C2 methylene geometry in XII and in XIV (R = H) differ only in the orientation of the N lone pair (XIIIa and XIVa), the S lone pair orbitals* having the same orientation with respect to the CH_2 in both conformations. The change in *J* for a nitrogen lone pair changing its orientation from gauche to both methylene CH bonds (XIIa) to anti coplanar (XIVa) is ca. 2·5 Hz.[1] *J* for XIV (R = H) should then be 2·5 Hz more negative than the value (−12 Hz) observed for the *trans* fused conformation XII.

An examination of a Dreiding model of XIV (R = H) permits a rationalisation of its "too large" a J_{gem}. The normal model shows that there is a significant non bonded interaction between C5Hax and C10Hax and that the magnitude of this interaction can readily be reduced by rotation about the C5–C6 bond. However this rotation brings the N lone pair from its position of bisecting the C2 methylene (XIVa) towards an eclipsing position which should result in a more positive J_{gem}.[13]

Treatment of the epimeric 3-methyl-2-(β-hydroxyethyl) piperidines with benzaldehyde gave only one compound in each case. That from the *trans*-2,3-*H*-piperidine showed marked Bohlmann bands in the IR spectrum consistent with the *trans* fused conformation XII (R = Ph) and H2ax proton absorbed at 5·17 τ, ca. 1 ppm to lower field than in XII (R = H).

The isomeric hydroxyethylpiperidine gave a 2-phenylthia-aza compound which was assigned the stereochemistry XIV (R = Ph) since it showed no absorption in the

* As pointed out by Eliel[12] in connection with 1,3-dithianes the lone pairs on S in the thia-aza compounds probably do not occupy strictly axial-equatorial positions since the hybridisation of the sulphur bonds is not sp^3. This, however, does not affect the present argument.

2800–2700 cm^{-1} region of the IR. The absorption (4·63τ) of the H2ax proton was also ca. 1 ppm to lower field than in XIV (R = H).

EXPERIMENTAL

Elemental analyses were carried out by Dr. F. Pascher and E. Pascher. M.ps are uncorrected. IR spectra were recorded on a Perkin–Elmer 457 grating instrument as 0·2M solns in CCl_4 using 0·2 mm matched cells. The NMR spectra were determined on a Perkin–Elmer R.10 spectrometer and a Varian H.A. 100 spectrometer as 10% solns in CCl_4 with TMS as internal reference.

Preparation of 3-*thia*-1-*azabicyclo* [4.4.0] *decanes*

General procedure. A cooled soln of the 2-(β-hydroxyethyl) piperidine (15 g) in CCl_4 (150 ml) was saturated with dry gaseous HBr. The solvent was removed *in vacuo* and the syrupy hydrobromide was treated with PBr_3 (17 g). A vigorous exothermic reaction ensued and dense clouds of HBr were evolved. When the reaction ceased the crude product was triturated with ether and then recrystallized from abs EtOH to give the bromide hydrobromide. The bromide hydrobromide (20 g) was refluxed with thiourea (5·5 g) in abs EtOH (250 ml) for 5 hr. The isothiouronium salt was not isolated but tetraethylenepentamine (15 g) was added to the reaction mixture which was refluxed for a further hr. The solvents were removed *in vacuo* and the residual viscous oil distilled under high vacuum to give the corresponding 2-(β-mercaptoethyl) piperidine. This thiol (5 g) was shaken with 40% aqueous formaldehyde soln (5 ml) for ½ hr. The soln was basified with NaOHaq and ether extracted 3 times. The extract was dried (Na_2SO_4), concentrated and distilled to give the 3-thia-1-azabicyclo [4.4.0] decane.

3-*Thia*-1-*azabicyclo* [4.4.0] *decane.* 2-(β-Bromoethyl) piperidine hydrobromide (42 g, 77%) was obtained from 2-(β-hydroxyethyl) piperidine (30 g) as a white crystalline solid m.p., 162–164°. (Found: C, 30·80; H, 5·30; N, 4·88; Br, 59·07. $C_7H_{15}NBr_2$ requires: C, 30·76; H, 5·53; N, 5·12; Br, 58·57%). The bromide hydrobromide (40 g) was converted to the isothiouronium salt which was not isolated but reacted to give 2-(β-mercaptoethyl) piperidine (9·6 g, 38%) as a colourless mobile oil b.p., 107–109°/12 mm, which solidified on standing to a low melting white solid. 3-Thia-1-azabicyclo [4.4.0] decane (4·8 g, 88%) was obtained from 2-(β-mercaptoethyl) piperidine (5 g) as a colourless mobile oil b.p., 82–84°/6 mm $n_D^{26\cdot0}$1·5263. It formed a picrate as yellow needles from EtOH m.p., 141–142°. (Found: C, 43·67; H, 4·78; N, 14·63; S, 8·27. $C_{14}H_{18}N_4O_7S$ requires: C, 43·52; H, 4·66; N, 14·51; S, 8·28%).

cis-2,6-H-2-*Phenyl*-3-*thia*-1-*azabicyclo* [4.4.0] *decane.* This compound (5·0 g, 65%) was obtained from 2-(β-mercaptoethyl) piperidine (5·0 g) by refluxing with a slight excess of benzaldehyde in benzene using a Dean and Stark water separator. It was a white solid b.p., 137–139°/0·2 mm and formed white needles from ether m.p., 62–64°. (Found: C, 71·93; H, 8·26; N, 6·05. $C_{14}H_{19}SN$ requires: C, 72·07; H, 8·21; N, 6·00%).

cis-10,6-H-10-*Methyl*-3-*thia*-1-*azabicyclo* [4.4.0] *decane.* 6-Methyl 2-(β-bromoethyl) piperidine hydrobromide (31·7 g, 65%) was obtained from 6-methyl-2-(β-hydroxyethyl) piperidine (23 g) as a white crystalline solid m.p., 202–204°. (Found: C, 33·44; H, 5·97; N, 4·89; Br, 55·88. $C_8H_{17}NBr_2$ requires: C, 33·45; H, 5·92; N, 4·88; Br, 55·75%). The isothiouronium salt (25 g, 97%) was obtained from the bromide hydrobromide (25 g) as white needles m.p., 158–160° from EtOH. Decomposition of the isothiouronium salt (25 g) yielded 6-methyl-2-(β-mercaptoethyl) piperidine (54· g, 29%) as a colourless mobile oil b.p., 70–74°/4 mm. *cis*-10,6-*H*-10-Methyl-3-thia-1-azabicyclo [4.4.0] decane (2·9 g, 80%) was obtained from 6-methyl-2-(β-mercaptoethyl) piperidine (3·0 g) as a colourless mobile oil b.p., 131–133°/18 mm $n_D^{19\cdot0}$1·5325. It formed a picrate as yellow needles from EtOH m.p., 175–177°. (Found: C, 44·64; H, 5·01; N, 14·15. $C_{15}H_{20}N_4O_7S$ requires: C, 45·00; H, 5·04; N, 14·00%); NMR: centre of C-Me doublet 9·10 τ, "J_{CH-Me}" 6·2 Hz.

cis-7,6-H-7-*Methyl*-3-*thia*-1-*azabicyclo* [4.4.0.] *decane.* 3-Methyl 2-(β-hydroxyethyl) pyridine (20 g), prepared according to the method of Finkelstein and Elderfield,[14] glacial AcOH (200 ml) and PtO_2 (1 g) were shaken with H_2 at 60 p.s.i. until the theoretical amount of H_2 had been absorbed. The soln was filtered, basified with NaOHaq and ether extracted 3 times. The dried (Na_2SO_4) ether extract was concentrated to give an epimeric mixture of 3-methyl-2-(β-hydroxyethyl) piperidine (19·5 g, 93%) as white needles m.p., 95–97° from ether. An epimeric mixture of 3-methyl-2-(β-bromoethyl) piperidine hydrobromide (24 g, 82%) was obtained from 3-methyl-2-(β-hydroxyethyl) piperidine (15 g) as a white crystalline solid m.p., 137–138°. (Found: C, 33·70; H, 5·92; N, 4·90; Br, 56·14. $C_8H_{17}NBr_2$ requires: C, 33·45; H, 5·92; N, 4·88; Br, 55·75%). The isothiouronium salt prepared from the bromide hydrobromide (21·5 g) was not isolated but immediately converted to an epimeric mixture of 3-methyl-2-(β-mercaptoethyl) piperidine (8·6 g, 71%) as a colourless oil, b.p. 104–106°/8 mm. An epimeric mixture of the *cis*- and *trans*-7,6-*H*-7-methyl-3-thia-1-

azabicyclo [4.4.0.] decanes (5·9 g, 82%) was obtained from 3-methyl-2-(β-mercaptoethyl) piperidine (6·0 g) as a colourless mobile oil b.p., 126–128°/11 mm. The NMR spectrum indicated that the mixture contained 90% *cis*-7,6-*H*- and 10% *trans*-7,6-*H*-7-methyl-3-thia-1-azabicyclo [4.4.0.] decane. The bicyclic compound (3 g) in abs EtOH (100 ml) was reacted with picric acid (4 g) in EtOH (50 ml). The resultant picrate (6·2 g) was fractionally recrystallized from abs EtOH and finally yielded the picrate of epimerically pure *cis*-7,6-*H*-7-methyl-3-thia-1-azabicyclo [4.4.0.] decane (5·1 g) as light yellow plates m.p., 162–164°. (Found: C, 45·03; H, 4·95; N, 13·97. $C_{15}H_{20}N_4O_7S$ requires: C, 45·00; H, 5·04; N, 14·00%). The picrate (4·7 g) was strongly basified with NaOH aq and immediately filtered and the filtrate extracted 6 times with ether. The ethereal soln was dried (Na_2SO_4) concentrated and distilled to give *cis*-7,6-*H*-7-methyl-3-thia-1-azabicyclo [4.40.] decane (1·1 g, 57%) as a colourless mobile oil b.p., 131–132°/19 mm; $n_D^{24°}$ 1·5415; NMR: centre of C-Me doublet 9·18 τ, "$J_{CH\text{-}Me}$" 7·0 Hz.

trans-7,6-H-7-*Methyl*-3-*thia*-1-*azabicyclo* [4.4.0.] *decane*. 3-Methyl 2-(β-hydroxyethyl) pyridine (25 g) was dissolved in abs EtOH (400 ml) and Na (50 g) was added at such a rate as to maintain reflux. When all the Na had dissolved the reaction mixture was cooled in ice and acidified with conc HCl. Excess EtOH was removed *in vacuo* and the reaction mixture was strongly basified with NaOH aq and ether extracted 3 times. The extract was dried (Na_2SO_4) concentrated and distilled to give an epimeric mixture of 3-methyl-2-(β-hydroxyethyl) piperidine (13·5 g, 50%) as a low melting white solid b.p., 88–94°/0·5 mm. The bromide hydrobromide prepared from this alcohol (13·5 g) was not isolated but was converted first to the isothiouronium salt and finally to an epimeric mixture of 3-methyl-2-(β-mercaptoethyl) piperidine (6·7 g, 47%) which was obtained as a colourless mobile oil b.p., 74–76°/0·6 mm. An epimeric mixture of *cis*- and *trans*-7, 6-*H*-7-methyl-3-thia-1-azabicyclo [4.4.0.] decane (5·0 g, 80%) was obtained from the epimerically impure 3-methyl-2-(β-mercaptoethyl) piperidine (5·5 g) as a colourless mobile oil b.p., 91–92°/0·7 mm. The NMR spectrum of the mixture indicated the presence of 10% *cis*-7, 6-*H*- and 90% *trans*-7, 6-*H*-7-methyl-3-thia-1-azabicyclo [4.4.0.] decane. This mixture (4·5 g) in abs EtOH (50 ml) was added to picric acid (6·0 g) in EtOH (100 ml). Fractional recrystallization of the resultant picrate eventually yielded the epimerically pure picrate of *trans*-7,6-*H*-7-methyl-3-thia-1-azabicyclo [4.4.0.] decane (7·7 g) as yellow needles m.p., 120–123°. (Found: C, 45·25; H, 4·95; N, 14·15. $C_{15}H_{20}N_4O_7S$ requires: C, 45·00; H, 5·04; N, 14·00%).

The picrate (7·4 g) was decomposed as above to give *trans*-7,6-*H*-7-methyl-3-thia-1-azabicyclo [4.4.0.] decane (1·9 g, 64%) as a colourless mobile oil b.p., 129–130°/19 mm; $n_D^{24°}$ 1·5378; NMR: centre of Me doublet 9·05 τ, "J_{CH-Me}" 6·0 Hz.

cis-2,6-H, cis-7,6-H-2-*Phenyl*-7-*methyl*-3-*thia*-1-*azabicyclo* [4.4.0.] *decane*. The thiol (2·2 g) prepared from catalytically reduced 3-methyl-2-(β-hydroxyethyl) piperidine, was dissolved in dry benzene (150 ml) and refluxed with benzaldehyde (1·5 g) using a Dean and Stark water separator. When the reaction was complete excess benzene was removed *in vacuo* and the crude product distilled. *cis*-2,6-*H*, *cis*-7,6-*H*-2-Phenyl-7-methyl-3-thia-1-azabicyclo [4.4.0.] decane (3·1 g, 93%) was obtained as a viscous slightly yellow oil b.p., 139–142°/0·3 mm $n_D^{25°}$ 1·5814. (Found: C, 73·39; H, 8·39; N, 5·60; S, 12·64. $C_{15}H_{21}SN$ requires: C, 72·84; H, 8·56; N, 5·66; S, 12·94%); NMR: centre of Me doublet 9·15 τ, "J_{CH-Me}" 6·9 Hz, H2ax 4·63 τ.

cis-2,6-H, trans-7,6-H-2-*Phenyl*-7-*methyl*-3-*thia*-1-*azabicyclo* [4.4.0.] *decane*. The thiol (0·75 g) prepared from Na-EtOH reduced 3-methyl-2-(β-hydroxyethyl) pyridine, was reacted with benzaldehyde (0·5 g) as above. *cis*-2,6-*H*, *trans*-7,6-*H*-2-Phenyl-7-methyl-3-thia-1-azabicyclo [4.4.0.] decane (0·96 g, 78%) was obtained as a viscous slightly yellow oil b.p., 140–142°/0·35 mm. (Found: C, 73·41; H, 8·30; N, 5·69; S, 12·82. $C_{15}H_{21}SN$ requires: C, 72·84; H, 8·56; N, 5·66; S, 12·94%); NMR: centre of Me doublet 8·98 τ, "J_{CH-Me}" 6·0 Hz, H2ax 5·17 τ.

cis- *and* trans-4,6-H-4-*Methyl*-3-*thia*-1-*azabicyclo* [4.4.0.] *decane*. An epimeric mixture of the 1-(α-piperidyl)-2-propanols (15 g) was converted to the bromide hydrobromide (28·5 g, 98%) which was obtained as white needles m.p., 168–170°. (Found: C, 33·47; H, 5·95; N, 4·80; Br, 55·86. $C_8H_{17}NBr_2$ requires: C, 33·45; H, 5·92; N, 4·88; Br, 55·75%). The bromide hydrobromide (22 g) gave the isothiouronium salt (18 g, 77%) as white crystalline solid from EtOH, m.p. 171–173°. Decomposition of the isothioronium salt (18 g) yielded an epimeric mixture of the 1-(α-piperidyl)-2-mercaptopropanes (6·9 g, 35%) as a low melting white solid b.p., 78–80°/3 mm. An epimeric mixture of *cis*- and *trans*-4,6-H-4-methyl-3-thia-1-azabicyclo [4.4.0.] decane (9·9 g, 93%) was obtained from 1-(α-piperidyl)-2-mercaptopropane (10 g) as a colourless mobile oil b.p., 135–136°/18 mm. The epimeric mixture was separated by preparative GLC on an Aerograph Autoprep instrument using a 20% Apiezon L column and H_2 carrier gas. *cis*-4,6-*H*-4-(methyl-3-thia-1-azabicyclo [4.4.0.] decane was the first isomer off the column as a colourless mobile oil b.p., 68–70°/0·65 mm; $n_D^{19°}$ 1·5298; NMR: centre of Me doublet 8·84 τ, "$J_{CH\text{-}Me}$" 6·5 Hz. It formed a picrate as yellow

needles from EtOH m.p., 179–180°. (Found: C, 45·14; H, 5·05; N, 13·99. $C_{15}H_{20}N_4O_7S$ requires: C, 45·00; H, 5·01; N, 14·00%). *trans*-4,6-H-4-Methyl-3-thia-1-azabicyclo [4.4.0.] decane was the second fraction off the column and was a colourless mobile oil b.p., 66–68°/0·45 mm; $n_D^{19·0}$1·5348; NMR: centre of Me doublet 8·54 τ, "$J_{CH—Me}$" 7·0 Hz. The picrate formed yellow needles from EtOH m.p., 172–174°. (Found: C, 45·07; H, 5·08; N, 13·94. $C_{15}H_{20}N_4O_7S$ requires: C, 45·00; H, 5·01; N, 14·00%).

cis-7.6-H-7-*Methyl*-3-*oxa*-1-*azabicyclo* [4.4.0.] *decane*. 3-Methyl 2-(β-hydroxyethyl) piperidine (1·1 g) obtained by catalytic reduction of the corresponding pyridylethanol was shaken with 40% aqueous formaldehyde soln (1·5 ml) for 10 min. The mixture was basified with NaOH and ether extracted 3 times. The extract was dried (Na_2SO_4) concentrated and distilled. *cis*-7,6-*H*-7-Methyl-3-oxa-1-azabicyclo [4.4.0.] decane (1·1 g, 91%) was obtained as a colourless mobile oil b.p., 111–113°/30 mm, $n_D^{25°}$1·4829. The picrate formed yellow crystals from EtOH m.p., 171–173. (Found: C, 46·94; H, 5·08; N, 14·59. $C_{15}H_{20}O_8N_4$ requires: C, 46·87; H, 5·25; N, 14·58%); IR spectra (cm^{-1}, ε_a): 2763 (32), 2723 (25), 2700 (20); NMR: centre of Me doublet 9·15 τ, "$J_{CH—Me}$" 6·8 Hz.

REFERENCES

1. Part XV. P. J. Chivers and T. A. Crabb, *Tetrahedron* **26**, 3389 (1970)
2. T. A. Crabb and R. F. Newton, *Ibid.* **24**, 4423 (1968)
3. F. Bohlmann, *Chem. Ber.* **91**, 2157 (1958)
4. M. Barfield and B. Chakrabarti, *Chem. Revs.* **69**, 757 (1969)
5. W. A. Thomas, *Annual Review of NMR Spectroscopy* Vol. I, p. 80. Academic Press, London and New York (1968)
6. E. Campaigne, N. F. Chamberlain and B. E. Edwards, *J. Org. Chem.* **27**, 135 (1962)
7. T. A. Crabb and R. F. Newton, *Tetrahedron* **24**, 1997 (1968)
8. R. J. Abraham and J. S. E. Holker, *J. Chem. Soc.* 806 (1963)
9. H. Booth, *Tetrahedron* **22**, 615 (1966)
10. B. Belleau and S. McLean, *Technique of Organic Chemistry* Part II, Vol. XI; pp. 1023 and 1031 Interscience (1963)
11. R. O. Hutchins, L. D. Kopp and E. L. Eliel, *J. Am. Chem. Soc.* **90**, 7174 (1968)
12. E. L. Eliel and R. O. Hutchins, *Ibid.* **91**, 2703 (1969)
13. J. A. Pople and A. A. Bothner-By, *J. Chem. Phys.* **42**, 1339 (1965)
14. J. Finkelstein and R. C. Elderfield, *J. Org. Chem.* **4**, 365 (1939)