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THE CONFORMATIONAL BEHAVIOUR OF SOME DIHYDRO-1,4-THIAZINES.—II[1, 2]

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Abstract The conformational properties of 3-substituted 2,3-dihydro-6-methoxycarbonyl-1,4-thiazines have been examined by the NMR method. The 3-Me group shows no conformational preference in either deuteriochloroform or deuteriopyridine. However, the hydroxy-, acetoxy-, methanesulphonyloxy-, chloro- and iodo-methyl groups favour the axial position in these solvents. The methoxycarbonyl group also adopts the axial orientation in deuteriopyridine but prefers the equatorial environment in deuteriochloroform. A correlation between conformation and optical rotation is noted in the case of (3L)-2,3-dihydro-3,6-dimethoxycarbonyl-1,4-thiazine.

RECENTLY the conformational behaviour of (3L)-2,3-dihydro-3,6-dimethoxycarbonyl-1,4-thiazine (**1**) was found to be solvent dependent:[2] in non-polar solvents the sofa conformation (**10B**: R = CO_2Me) is favoured while in polar solvents conformation (**10A**: R = CO_2Me) is preferred. Intramolecular H-bonding between the CO_2Me and NH groups was considered to be important in non-polar solvents, with the result that conformation (**10B**; R = CO_2Me) is stabilized. Moreover, (3DL)-2,3-dihydro-6-methoxycarbonyl-3-(NN-dimethylaminocarbonyl)-1,4-thiazine (**2**), which possesses a stronger intramolecular H-bond than **1**, exists as **10B** (R = $CONMe_2$) irrespective of the nature of the solvent. In polar solvents intramolecular H-bonding of **1** was believed to be unimportant; the destabilization of **10B** (R = CO_2Me) was attributed to $A^{(1,2)}$ strain[3] between the equatorial CO_2Me substituent and the planar solvated NH group.

In an effort to understand more fully the factors which determine the conformational equilibria of the above heterocycles, a series of 3-substituted 2,3-dihydro-6-methoxycarbonyl-1,4-thiazines have been examined. Since the conformational behaviour of derivatives with polar 3-substituents may be complicated by dipolar interactions, it seemed necessary to know how a thiazine possessing a non-polar group at position 3 would behave. In this paper the conformational properties of the 3-methyl derivative are discussed and compared with those of the 3-methoxycarbonyl, 3-hydroxy-, 3-acetoxy-, 3-methanesulphonyloxy-, 3-chloro- and 3-iodo-methyl derivatives.

(3L)-2,3-*Dihydro*-3-*hydroxymethyl*-6-*methoxycarbonyl*-1,4-*thiazine* (**3**) was readily prepared by the selective reduction of the CO_2Me group at position 3 of **1** using lithium borohydride in dry dioxan. A similar reduction was also achieved by diborane in THF but the yield of **3** was less satisfactory. Even sodium borohydride, which is usually slow to reduce esters, was effective; however, if methanol was used as the solvent the optical purity of the alcohol was low, indicating that racemisation was competing with the reduction. Sodium borohydride in dry dioxan gave optically pure **3**.

In acidified acetone the alcohol (**3**) was converted into crystalline (6L)-3-*methoxy*-

carbonyl-9,9-dimethyl-8-oxa-4-thia-1-azabicyclo[4.3.0]*non-2-ene* (**11**; R = CH_2); acidic hydrolysis of the latter regenerated **3**.

Esterification of the alcohol (**3**) with acetic anhydride and methanesulphonyl chloride in pyridine gave good yields of crystalline (3L)-3-*acetoxymethyl*-2,3-*dihydro*-6-*methoxycarbonyl*-1,4-*thiazine* (**4**) and crystalline (3L)-2,3-*dihydro*-3-*methanesulphonyloxymethyl*-6-*methoxycarbonyl*-1,4-*thiazine* (**5**), respectively.

The methanesulphonate (**5**) was readily transformed into crystalline (3L)-2,3-*dihydro*-3-*iodomethyl*-6-*methoxycarbonyl*-1,4-*thiazine* (**7**), when heated with sodium iodide in ethyl methyl ketone. In an attempt to prepare **9**, the iodide (**7**) was treated with zinc in refluxing acetic acid but a complex mixture of products was isolated in only low yield.

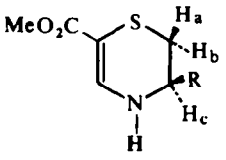
Attempts were made to directly reduce the methanesulphonate (**5**) to **9**: no reaction occurred with sodium borohydride in methanol but a new crystalline substance was isolated in low yield when lithium aluminium hydride in tetrahydrofuran was employed. Micro-analysis and mass spectroscopy revealed that the material was derived from **5** by the replacement of the OSO_2Me group by a Cl atom, and spectroscopic data left no doubt that it was (3L)-3-*chloromethyl*-2,3-*dihydro*-6-*methoxycarbonyl*-1,4-*thiazine* (**8**). This result suggested that **12** was formed in the lithium hydride reaction, and that it was converted into **9** during the hydrochloric acid work-up. Indeed when the reaction was followed by TLC a fast-moving compound was detected which disappeared on addition of acid.

When dissolved in excess methanolic sodium methoxide, **5** was gradually transformed into a compound which possessed a mobility identical to that of the substance formed in the lithium aluminium hydride reaction. The material was purified by alumina chromatography and characterised as (6L)-3-*methoxycarbonyl*-4-*thia*-1-*azabicyclo*[4.1.0]*hept*-2-*ene* (**12**). A second substance, which was found to be (3L)-2,3-*dihydro*-6-*methoxycarbonyl*-3-*methoxymethyl*-1,4-*thiazine* (**6**), was also isolated in low yield; its yield increased when the reaction time was extended and, consequently, it is derived from **12**. Subsequent experiments indicated that the reaction of **5** with sodium hydride in tetrahydrofuran provided a more satisfactory route to the aziridine.

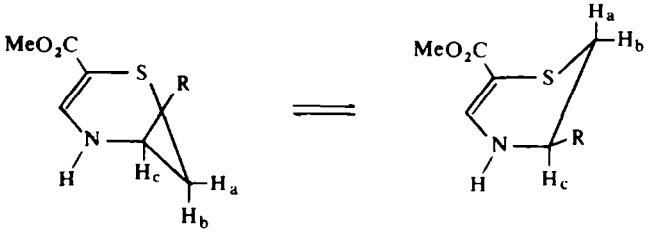
When treated with hydrochloric and acetic acids, the aziridine (**12**) gave good yields of the chloride (**8**) and acetate (**4**), respectively. Furthermore, catalytic hydrogenation of **12** afforded **9** in excellent yield. In these reactions there was no evidence for the formation of products derived by cleavage of the 1–6 bond of **12**.

In the present study NMR spectra were determined at 90 MHz. The abc protons of the 2,3- dihydro-1,4-thiazines appeared as ABX spectra and, in the majority of cases, it was possible to evaluate the coupling constants (accurate to $\pm$ 0·2 Hz) and chemical shifts by the method of Pople *et al.*[4] The values were checked by computer and, if necessary, adjusted until the calculated spectrum matched the recorded spectrum. In the case of **1** in deuterioacetone, **3** and **4** in deuteriochloroform and **4** in deuteriopyridine, "deceptively simple" ABX spectra were obtained; only $|J_{ac} + J_{bc}|$ could be evaluated in these examples.[5] However, since $J_{bc} = 3{\cdot}05 \pm 0{\cdot}25$ Hz, an approximate value of J_{ac} could be estimated. The results are summarised in Table 1.

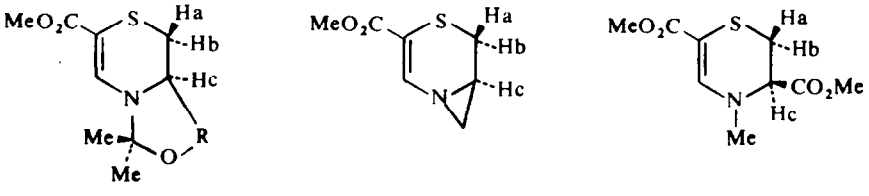
In considering the conformational behaviour of the ester (**1**) and the amide (**2**), compounds (**11**; R = CO) and **13** were previously used as models.[2] The former compound ($J_{ac} = 9{\cdot}6$ and $J_{bc} = 3{\cdot}3$ Hz) was considered to be representative of **10B** and the latter ($J_{ac} = J_{bc} = 3{\cdot}1$ Hz) of **10A**. The coupling constants of the model



1: R = CO_2Me
2: R = $CONMe_2$
3: R = CH_2OH
4: R = CH_2OAc
5: R = CH_2OSO_2Me
6: R = CH_2OMe
7: R = CH_2I
8: R = CH_2Cl
9: R = Me



10A 10B



11 12 13

compounds have been remeasured and the values, which are included in Table 1, were in good agreement with those obtained at 60 MHz. However, some discrepancies were noted when the coupling constants of the ester (**1**) were redetermined. Previously, it was claimed that J_{ac} and J_{bc} were equal (*ca* 4·1 Hz) in pyridine[2] but this is now considered to be incorrect. The revised values are summarised in Table 1.

Conformational equilibria were calculated by assuming that **10B** is represented by J_{ac} = 9·8 and **10A** by J_{ac} = 3·3 Hz. The results, which should only be considered to be approximate, are included in Table 2.

In the case of **9**, conformations (**10A**; R = Me) and (**10B**; R = Me) are equally preferred in both deuteriochloroform and deuteriopyridine. The ester (**1**) favours **10A** (R = CO_2Me) (*ca* 70–75%) in deuterioacetone and deuteriopyridine and **10B** (R = CO_2Me) in deuteriochloroform and deuteriobenzene (*ca* 60–65%); intramolecular H-bonding is considered to be important in the latter solvents but not in the former.[2] There is a marked tendency for the alcohol (**3**), the acetate (**4**), the methanesulphonate (**5**), the iodide (**7**) and the chloride (**8**) to adopt the conformation with the 3-substituent axial in both deuteriochloroform and deuteriopyridine. The preference for **10B** appears to decrease in the cases of **4**, **7** and **8** when the solvent is changed from deuterichloroform to deuteriopyridine, possibly because of intramolecular H-bonding in the former solvent. Thus, the high resolution IR spectrum of **7** in chloroform solution (0·01 M) showed peaks at 3455 and 3421 cm^{-1} in the ratio of *ca* 9:1, respectively. The former absorption is ascribed to the NH stretching vibrations of non-associated species and the latter to the corresponding vibrations of intramolecularly H-bonded molecules. Intramolecular H-bonding between OH

TABLE 1. COUPLING CONSTANTS AND CHEMICAL SHIFTS OF THE abc PROTONS OF DIHYDRO-1,4-THIAZINES†

Compound	Solvent	τ_a	τ_b	τ_c	$(\tau_a-\tau_b)$	J_{ab}	J_{ac}	J_{bc}
11 (R = CO)	$CDCl_3$	7·44	6·64	5·80	0·80	−12·6	9·8	3·3
	C_5D_5N	7·28	6·56	5·51	0·72	−12·5	9·7	3·3
13	$CDCl_3$	6·71	7·14	5·72	−0·43	−13·1	3·3	3·0
	C_5D_5N	6·63	7·11	5·47	−0·48	−13·1	3·2	3·0
1	$CDCl_3$	7·16	6·86	5·72	0·30	−12·6	7·4	3·1
	C_6D_6	7·52	7·42	6·36	0·10	−12·8	7·1	3·3
	$(CD_3)_2CO$	7·01		5·52	0	—	ca.5	ca.3
	C_5D_5N	6·75	6·90	5·26	−0·15	−12·8	4·8	3·1
3	$CDCl_3$	7·23	6·30		0	—	ca.3·5	ca.3
4	$CDCl_3$	7·20	6·10		0	—	ca.4·5	ca.3
	C_5D_5N	7·25	6·05		0	—	ca.4	ca.3
5	$CDCl_3$	7·14	7·20	5·94	−0·06	−13·0	3·3	3·3
	C_5D_5N	7·04	7·18	5·80	−0·12	−13·1	3·3	3·3
7	$CDCl_3$	7·07	7·23	6·10	−0·26	−13·2	3·9	2·8
	C_5D_5N	6·96	7·20	5·90	−0·24	−13·2	3·3	2·8
8	$CDCl_3$	7·01	7·19	5·95	−0·18	−12·9	4·1	3·0
	C_5D_5N	6·90	7·18	6·05	−0·28	−13·0	3·7	3·0
9	$CDCl_3$	7·45	7·22	6·30	0·25	−12·7	6·6	3·0
	C_5D_5N	7·45	7·22	6·40	0·23	−12·6	6·4	2·8

† The proton with the larger vicinal coupling constant is assumed to be proton a; this assignment is unambiguous in the majority of cases although when J_{ac} and J_{bc} are similar it is only tentative.

TABLE 2. CONFORMATIONAL EQUILIBRIA OF DIHYDRO-1,4-THIAZINES

Compound	Solvent	Conformation (**10A**)	:	Conformation (**10B**)
1	$CDCl_3$	35	:	65
	C_6D_6	40	:	60
	$(CD_3)_2CO$	ca.70	:	30
	C_5D_5N	75	:	25
3	$CDCl_3$	ca.95	:	5
4	$CDCl_3$	ca.80	:	20
	C_5D_5N	ca.90	:	10
5	$CDCl_3$	100	:	0
	C_5D_5N	100	:	0
7	$CDCl_3$	90	:	10
	C_5D_5N	100	:	0
8	$CDCl_3$	90	:	10
	C_5D_5N	95	:	5
9	$CDCl_3$	50	:	50
	C_5D_5N	50	:	50

groups and I atoms is well established[6] and, for example, *o*-iodophenol shows $\Delta\nu$ = 93 cm^{-1} between the free and bonded OH groups. The iodide (**7**) exhibits $\Delta\nu$ = 34 cm^{-1}; a smaller frequency difference is to be expected when an OH group is replaced by an NH group.

The above results clearly show that the presence of a polar group at position 3 can have a dramatic effect on the conformational equilibria of 2,3-dihydro-6-methoxycarbonyl-1,4-thiazines. Such substituents generally display a much greater tendency to adopt the axial environment than the methyl group although this behaviour can be reversed if the substituents can undergo intramolecular H-bonding with the NH group.

The conformational free energies of a large number of functional groups have been estimated in monosubstituted cyclohexanes, enabling the substituents to be classified according to their steric requirements.[7] For example, the non-bonded interactions of the methyl group ($-\Delta G^\circ = 1{\cdot}7$ kcal mole^{-1}) are greater than those of the methoxycarbonyl group ($-\Delta G^\circ = 1{\cdot}1$ kcal mole^{-1}). Moreover, since the conformational free energies of the methyl and ethyl substituents are very similar, the non-bonded interactions of the hydroxy-, acetoxy-, methanesulphonyloxy-, chloro- and iodomethyl groups are not expected to differ greatly from those of the methyl group. Consequently $A^{(1,2)}$ strain[3] does not satisfactorily account for the present results. The axial preference is clearly associated with the presence of a polar group at position 3 and, especially in the case of the methanesulphonate (**5**) and the chloride (**8**), the magnitude of the effect is appreciable (*ca* 1·7 kcal mole^{-1} or greater). A possible explanation of this behaviour is that a dipolar attraction exists between the S atom and the polar 3-substituent, perhaps involving the electrophilic C atom of the latter. There is some analogy for such a 1,4-interaction in tetrahydro-1,4-thiapyrones.[8]

Axial protons generally absorb at higher field than their equatorial counterparts. Such chemical shift differences have often been used to diagnose the conformational preferences of carbocyclic and heterocyclic six-membered rings.[9] As can be seen from Table I there appears to be a correlation between ($\tau_a - \tau_b$) and conformation in dihydro-1,4-thiazines; a positive value of ($\tau_a - \tau_b$) is indicative of **10B** and a zero or negative value of **10A**. Moreover, in the case of the ester (**1**), a decrease in the value of ($\tau_a - \tau_b$) is accompanied by an increase in the proportion of **10A** present at equilibrium.

It was earlier reported that the ester (**1**) displayed large changes in optical rotation with solvent; thus, $[\alpha]_D$ values of +86°, +128°, +150° and +214° were observed in chloroform, benzene, acetone and pyridine, respectively.[2] Evidently, an increase in the optical rotation of **1** is indicative of a greater preference for conformation (**10A**). Lemieux and Pavia have recently noted a similar phenomenon in the case of methyl 2-deoxy-α-L- and methyl 3-deoxy-β-L-*erythro*-pentopyranoside.[10]

EXPERIMENTAL

For general details see Part I.[2] High resolution NMR spectra were determined in *ca* 0·2 M soln using a Brucker spectrospin spectrometer at 90 MHz. The ABX systems were expanded using a scale factor of 1 Hz cm^{-1}; peak positions were determined by holding the pen at the centre of each peak and noting the frequency on the counter. The average of two scans was usually taken. Coupling constants and chemical shifts were evaluated from the spectra by the method of Pople *et al.*[4] and the values were checked using a three-spin computer programme,[11] kindly provided by Dr. R. M. Acheson of Oxford University. Calculations were performed on an English Electric KDF9 computer.

Adsorption chromatography was carried out using silica gel (Mallinckrodt) or aluminium oxide (Savoury and Moore). TLC was performed on Gelman chromatography medium ITLC type SA in $CHCl_3$-EtOAc (9:1); compounds were detected with I_2 vapour.

(3L)-2,3-*Dihydro*-3-*hydroxymethyl*-6-*methoxycarbonyl*-1,4-*thiazine* (**3**)

(a) The ester **1** (2·17 g, 0·01 mole) was dissolved in dry dioxan (15 ml) and $LiBH_4$ (0·218 g, 0·01 mole) was added. The mixture was stirred at room temp until starting material was not detected on TLC (*ca* 3 hr) and H_2O was then added. Metal ions were removed by IR 120 (H^+) and the solvent was evaporated off. The residue was dissolved in MeOH and the solution concentrated (repeated 3 times) to leave **3** (1·89 g, 100%) as a syrup.

The alcohol **3** (0·567 g, 3 mmole) was dissolved in acetone (30 ml) containing a few drops of conc H_2SO_4 and after 8 hr the soln was diluted with H_2O and extracted with $CHCl_3$. The organic layer was washed with H_2O, dried ($MgSO_4$) and evaporated to leave crude **11** (R = CH_2), which was purified by silica gel chromatography (0·365 g, 53%); m.p. 94° (ether-light petroleum); $[\alpha]_D$ + 139° (0·15% in $CHCl_3$); ν_{max}^{KBr} 1685 (unsat C=O) and 1585 cm^{-1} (C=C); λ_{max}^{EtOH} 256 (ε, 2900) and 320 nm (ε, 11,500); τ (60 MHz) ($CDCl_3$) 8·61 and 8·51 (each 3H, s, *gem*-Me), 7·66 (1H, dd, J_{ab} = 12·5 and J_{ac} = ~ 7 Hz, 5β-H), 6·99 (1H, dd, J_{ab} = 12·5 and J_{bc} = 2·9 Hz, 5α-H), 6·6–5·9 (2H, m, 7-CH_2), 6·28 (3H, s, CO_2Me) and 2·27 (1H, s, 2-H). [Found: C, 52·25; H, 6·6; N, 6·3%; *M*, 229 (mass spectrum, mol ion). $C_{10}H_{15}NO_3S$ requires: C, 52·4; H, 6·55; N, 6·1%; *M*, 229].

The isopropylidene derivative **11** (R = CH_2; 0·229 g, 1 mmole) was heated under reflux with N-HCl (15 ml) for 15 min; the soln was neutralised with $NaHCO_3$ and extracted with $CHCl_3$. The dried ($MgSO_4$) organic layer was evaporated to leave pure **3** (0·16 g, 85%) as a syrup; $[\alpha]_D$ + 154° (0·6% in $CHCl_3$); ν_{max}^{film} 3320 (OH and NH), 1665 (unsat C=O), 1600 (C=C) and 1515 cm^{-1} (amide II); ν_{max}^{EtOH} 258 (ε, 2600) and 310 nm (ε, 11,400); τ (60 MHz) ($CDCl_3$) 7·23 (2H, d, separation = 3·3 Hz, 2-CH_2), 6·4–6·0 (3H, m, 3-H and CH_2O), 4·2br (1H, NH) and 2·25 (1H, d, *J* = 7 Hz, 5-H) (when D_2O was added to the soln the signal at τ 4·2 disappeared and that at 2·25 collapsed to a singlet).

(b) The ester **1** (2·17 g, 0·1 mole) was dissolved in THF (50 ml) containing excess diborane. After 3 hr, when no starting was detected on TLC, the soln was diluted with H_2O and extracted with $CHCl_3$. The extract was dried ($MgSO_4$) and concentrated, and the crude product was fractionated by alumina chromatography to give **3** (0·76 g, 40%). A sample of **3** was converted into **11** (R = CH_2); m.p. 93–94°; $[\alpha]_D$ +133° (0·15% in $CHCl_3$).

(c) The ester **1** (2·17 g, 0·01 mole) was dissolved in MeOH (35 ml) and $NaBH_4$ (0·76 g, 0·02 mole) was added; further reducing agent (0·76 g, 0·02 mole) was added after 24 hr. After 48 hr acetone was added and the soln was diluted with H_2O and extracted with $CHCl_3$. The organic layer was dried ($MgSO_4$) and evaporated to leave **3**, which was converted into **11** (R = CH_2; 1·1 g, 48%); m.p. 98–100°; $[\alpha]_D$ + 10° (0·2% in $CHCl_3$).

(d) The ester **1** (0·65 g, 3 mmole) was dissolved in dry dioxan (20 ml) and $NaBH_4$ (0·76 g, 2 mmole) was added. The suspension was stirred at room temp until no starting material was detected on TLC (*ca* 6 days). Work-up as in (a) gave **3** (0·47 g, 83%), which was converted into **11** (R = CH_2); m.p. 93°; $[\alpha]_D$ +135° (0·2% in $CHCl_3$).

(3L)-3-*Acetoxymethyl*-2,3-*dihydro*-6-*methoxycarbonyl*-1,4-*thiazine* (**4**)

The alcohol **3** (0·17 g, 0·9 mmole) was dissolved in pyridine (10 ml) and Ac_2O (0·15 g, 1·5 mmole) was added. The mixture was left overnight, acidified with dil HCl and extracted with $CHCl_3$. The organic layer was washed with H_2O, dried ($MgSO_4$) and evaporated to afford the crude acetate **4** (0·198 g, 95%), which was purified by silica gel chromatography. Sublimation at 100° under reduced pressure afforded an analytical sample of **4**: m.p. 74–75°; $[\alpha]_D$ + 160° (0·25% in $CHCl_3$); ν_{max}^{KBr} 3325 (NH), 1745 (acetyl C=O), 1655 (unsat C=O), 1585 (C=C) and 1515 cm^{-1} (amide II); λ_{max}^{EtOH} 256 (ε, 2460) and 307 nm (ε, 10,500); τ (60 MHz) ($CDCl_3$) 7·92 (3H, s, COMe), 7·23 (2H, d, separation = 3·8 Hz, 2-CH_2), 6·28 (3H, s, CO_2Me), 6·2–5·6 (3H, m, 3-H and CH_2O), 4·6br (1H, NH) and 2·35 (1H, d, *J* = 3 Hz, 5-H) (addition of D_2O to the soln caused the signal at τ 4·6 to disappear and that at 2·35 to collapse to a singlet. [Found: C, 46·95; H, 5·8; N, 6·0%; *M* 231 (mass spectrum, mol ion). $C_9H_{13}NO_4S$ requires C, 46·75; H, 5·65; N, 6·05%; *M*, 231).

(3L)-2,3-*Dihydro*-3-*methanesulphonyloxymethyl*-6-*methoxycarbonyl*-1,4-*thiazine* (**5**)

The alcohol **3** (1·0 g, mmole) was dissolved in pyridine (20 ml) and methanesulphonyl chloride (0·69 g, 6 mmole) was added. After standing overnight at room temp, the mixture was acidified with dil HCl and extracted with $CHCl_3$. The organic layer was washed with water, dried ($MgSO_4$) and evaporated to a residue (1·20 g, 85%), which was recrystallised from $CHCl_3$-ether; m.p. 85–86°; $[\alpha]_D$ + 230° (0·2% in $CHCl_3$); ν_{max}^{KBr} 3330 (NH), 1660 (unsat C=O), 1600 (C=C) and 1515 cm^{-1} (amide II); λ_{max}^{EtOH} 256 (ε, 2600) and 307 nm (ε, 10,400); τ (60 MHz) $CDCl_3$) 7·15 (2H, d, separation = 3 Hz, 2-CH_2), 6·92 (3H, s, SO_2Me), 6·28 (3H, s, CO_2Me), 5·7 (3H, m, 3-H and CH_2O), 4·5br (1H, NH) and 2·27 (1H, d, *J* = 7 Hz, 5-H) (addition of D_2O to the soln caused the signal at τ 4·5 to disappear and that at 2·27 to collapse to a singlet). [Found:

C,35·85; H,4·7; N,5·2%; *M*, 267·0232 (mass spectrum, mol ion). $C_8H_{13}NO_5S$ requires C,35·95; H,4·85; N,5·25%; *M* 267·0235].

(3L)-2,3-*Dihydro*-3-*iodomethyl*-6-*methoxycarbonyl*-1,4-*thiazine* (7)

The methanesulphonate **5** (0·20 g, 0·75 mmole) and NaI (0·13 g, 0·8 mmole) were heated in ethyl methyl ketone under reflux for 22 hr, when the reaction was essentially complete by TLC. The mixture was diluted with H_2O and extracted with $CHCl_3$. The organic layer was dried ($MgSO_4$) and evaporated to leave **7** (0·22 g, 98%), which was recrystallized from $CHCl_3$-light petroleum: m.p. 125–126°; $[\alpha]_D$ +54° (0·2% in $CHCl_3$); ν_{max}^{KBr} 3260 (NH), 1650 (unsat C=O), 1590 (C=C) and 1510 cm^{-1} (amide II); λ_{max}^{EtOH} 257 (ε, 3280) and 314 nm (ε, 11,850); τ (90 MHz) ($CDCl_3$) 7·23 (1H, dd, J_{ab} = 13 and J_{bc} = 3 Hz, 2α-H), 7·07 (1H, dd, J_{ab} = 13 and J_{ac} = 4 Hz, 2β-H), 6·70 (1H, 2 dd, J = 9·5, J' = 6 and J'' = 7 Hz, CH_2I), 6·25 (3H, s, CO_2Me), 6·0 (1H, m, 3–H), 4·6br (1H, NH) and 2·42 (1H, d, J = 7 Hz, 5-H) (addition of D_2O to the soln caused the signal at τ 4·6 to disappear and that at 2·42 to collapse to a singlet). [Found: C, 28·0; H, 3·4; N, 4·5%; *M*, 298·9488 (mass spectrum, mol ion). $C_7H_{10}INO_2S$ requires: C, 28·1; H, 3·35; N, 4·7%; *M*, 298·9488].

Reaction of the methanesulphonate (**5**) *with* $LiAlH_4$

The methanesulphonate **5** (0·30 g, 1·12 mmole) was dissolved in dry THF (10 ml) and $LiAlH_4$ (0·43 g, 1·12 mmole) was added. The reaction was followed by TLC and a component with a mobility much greater than that of the starting material appeared. After *ca* 12 hr EtOAc (1 ml) and dil HCl were added to the mixture. The mixture was extracted with $CHCl_3$ and the extract was dried ($MgSO_4$). Evaporation of the solvent left a syrup (0·2 g) which, on TLC, contained one major component with a mobility slightly greater than that of **5**. The component, which proved to be **8**, was isolated in crystalline form (0·084 g, 36%) after silica gel chromatography: m.p. 125–126° ($CHCl_3$ light petroleum); $[\alpha]_D$ + 192° (0·2% in $CHCl_3$). ν_{max}^{KBr} 3280 (NH), 1650 (unsat C=O), 1595 (C=C) and 1520 cm^{-1} (amide II); λ_{max}^{EtOH} 256 (ε, 2900) and 307 nm (ε, 11,600); τ (90 MHz) ($CDCl_3$) 7·19 (1H, dd, J_{ab} = 13 and J_{bc} = 3Hz, 2α-H), 7·01 (1H, dd, J_{ab} = 13 and J_{ac} = 4 Hz, 2β-H), 6·35 (3H, s, CO_2Me), 6·3 (3H, m, 3-H and CH_2Cl), 4·6br (1H, NH) and 2·45 (1H, d, J = 7 Hz, 5-H) (addition of D_2O to the soln caused the signal at τ 4·6 to disappear and that at 2·45 to collapse to a singlet). [Found: C,40·3; H,4·85; Cl,17·1; N,6·7%; *M*, 207 (mass spectrum, mol ion). $C_7H_{10}ClO_2NS$ requires: C,40·5; H,4·8; Cl,17·1; N,6·75%; *M*, 207].

(6L)-3-*Methoxycarbonyl*-4-*thia*-1-*azabicyclo*[4.1.0]*hept*-2-*ene* (**12**)

(a) The methanesulphonate **5** (1·00 g, 3·7 mmole) was dissolved in MeOH (30 ml) and 1·5 N-NaOMe in MeOH (10 ml) was added. The mixture was left overnight when TLC indicated the presence of a component which had a mobility much greater than that of the starting material. The soln was diluted with H_2O and extracted with $CHCl_3$; the organic layer was dried ($MgSO_4$) and evaporated to a syrup (0·7 g), which was fractionated by alumina chromatography to give the aziridine **12** (0·50 g, 78%) and the methyl ether **6** (0·125 g, 16%).

The aziridine **12** was a syrup: $[\alpha]_D$ +573° (0·15% in $CHCl_3$); ν_{max}^{film} 1700 (unsat C=O) and 1570 cm^{-1}; τ (60 MHz) ($CDCl_3$) 8·54 (1H, d, J = 3 Hz, *endo* 7-H), 8·21 (1H, dd, J_{ab} = 12·6 and J_{ac} = 7·6 Hz, 5β-H), 7·52 (1H, d, J = 4·5 Hz, *exo* 7–H), 7·2 (1H, m, 6-H), 6·67 (1H, dd, J_{ac} = 12·6 and J_{bc} = 5·7 Hz, 5α-H) and 2·25 (1H, s, 2-H). [Found: *M*, 171·0361 (mass spectrum, mol ion). $C_7H_9NO_2S$ requires *M*, 171·0354].

The ether **6** was recrystallized from $CHCl_3$-light petroleum; m.p. 84–86°; $[\alpha]_D$ + 168° (0·25% in $CHCl_3$); ν_{max}^{KBr} 3350 (NH), 1650 (unsat C=O), 1600 (C=C) and 1535 cm^{-1} (amide II); λ_{max}^{EtOH} 259 (ε, 2540) and 310 nm (ε, 11,070); τ (60 MHz) ($CDCl_3$) 7·30 (2H, d, separation = 4 Hz, 2-CH_2), 6·66 (3H, s, OMe), 6·6 (2H, m, CH_2O), 6·32 (3H, s, CO_2Me), 6·3 (1H, m, 3-H), 4·8br (1H, NH) and 2·42 (1H, d, J = 7 Hz, 5-H) (addition of D_2O to the soln caused the signal at τ 4·8 to disappear and that at 2·42 to collapse to a singlet). [Found: C, 47·2; H, 6·45; N, 6·95%; *M*, 203·0635 (mass spectrum, mol ion). $C_8H_{13}NO_3S$ requires: C, 47·3; H, 6·4; N, 6·9%; *M*, 203·0616].

(b) The methanesulphonate **5** (0·534 g, 2 mmole) was dissolved in dry THF (10 ml), NaH (0·144 g, 6 mmole) was added and the mixture was stirred overnight. MeOH (2 ml) was added, the soln was diluted with H_2O and extracted with $CHCl_3$. The organic layer was dried ($MgSO_4$) and evaporated to give **12** (0·308 g, 90%); $[\alpha]_D$ + 580° (0·2% in $CHCl_3$).

Reaction of the aziridine (**12**) *with* NaOMe

The methanesulphonate **5** (0·214 g, 0·8 mmole) was dissolved in MeOH and 1·5 N-NaOMe in MeOH (1·5 ml) was added. TLC indicated that the aziridine **12**, which was formed after 15 hr, was slowly replaced

by the ether **16** and after 11 days no **12** remained. The soln was then diluted with H_2O and extracted with $CHCl_3$; the extract was dried ($MgSO_4$) and evaporated to afford **6** (0·054 g, 33%); m.p. 84–86° (from $CHCl_3$-light petroleum).

Reaction of the aziridine (**12**) *with* HOAc

The aziridine **12** (0·06 g, 0·35 mmole) was dissolved in EtOH (1 ml) and glacial HOAc (0·024 g, 0·4 mmole) was added. After 3 hr the soln was diluted with H_2O and extracted with $CHCl_3$. The organic layer was dried ($MgSO_4$) and evaporated to a syrup (0·062 g, 78%); a crystalline sample of the acetate **4** was obtained by sublimation; m.p. 74–75°; $[\alpha]_D$ + 158° (0·2% in $CHCl_3$).

Reaction of the aziridine (**12**) *with* HCl

The aziridine **12** (0·171 g, 1 mmole) was dissolved in MeOH (5 ml) and N-HCl (1 ml, 1 mmole) was added. The soln was diluted with H_2O and extracted with $CHCl_3$: the organic layer was dried ($MgSO_4$) and evaporated to give the chloride **8** (0·16 g, 77%); m.p. 125–126°; $[\alpha]_D$ + 200° (0·2% in $CHCl_3$).

(3L)-2,3-*Dihydro*-6-*methoxycarbonyl*-3-*methyl*-1,4-*thiazine* (**9**)

The aziridine **12** (0·36 g, 2·1 mmole) was dissolved in MeOH (9 ml) containing a suspension of 10% Pd-C (0·045 g) and hydrogenated overnight. The catalyst was removed by filtration and the soln was evaporated to give **9** (0·35 g, 96%); m.p. 104–106° (from $CHCl_3$-light petroleum); $[\alpha]_D$ + 159° (0·2% in $CHCl_3$); ν_{max}^{KBr} 3300 (NH), 1645 (unsat C=O), 1590 (C=C) and 1510 cm^{-1} (amide II); λ_{max}^{EtOH} 261 (ε, 2840) and 312 nm (ε, 11,060); τ (90 MHz) ($CDCl_3$) 8·70 (3H, d, J = 6 Hz, C-Me), 7·46 (1H, dd, J_{ab} = 12·7 and J_{ac} 6·6 Hz, 2β-H), 7·22 (1H, dd, J_{ab} = 12·7 and J_{bc} = 3Hz, 2α-H), 6·30 (3H, s, CO_2Me), 6·3 (1H, m, 3–H), 4·9br (1H, NH) and 2·42 (1H, d, J = 7 Hz, 5-H) (addition of D_2O to the soln caused the signal at τ 4·9 to disappear and that at 2·42 to collapse to a singlet). [Found: C, 48·25; H, 6·4; N, 7·8%; M 173 (mass spectrum, mol ion). $C_7H_{11}NO_2S$ requires: C, 48·0; H, 6·35; N, 8·1%; M, 173].

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