Studies on Lactams. Part 47.[1] Penicillin and Cephalosporin Analogues with Methylthio-substituents [1]

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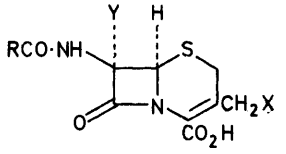
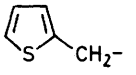
The synthesis, stereochemistry, and rearrangement of several penicillin and cephalosporin analogues with a methylthio-substituent on the ring junction carbon atom are described.

THE discovery [2] of 7-methoxycephalosporins, which are produced by *Streptomyces* and possess substantial gram-negative antibacterial activity, has directed attention toward the synthesis of penicillins and cephalosporins (1a) with methoxy-substituents on the β-lactam ring. The recent synthesis [3] of Cefoxitin, for example, involved the introduction of a 7-methoxy-substituent *via* a 7-methylthiocephalosporin (1b). We report here some

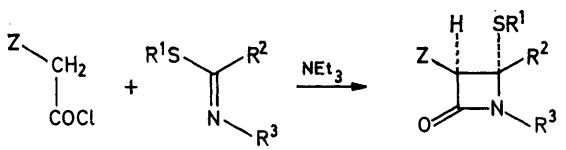


(1) a; Y = OMe, X = OAc or O·CO·NH$_2$
b; Y = SMe, X = OAc, R =



aspects of the synthesis, stereochemistry, and rearrangement of a number of bicyclic β-lactams with exocyclic alkylthio-substituents. In two recent preliminary communications [4,5] we described the synthesis of several unusual analogues of penicillins and cephalosporins in this category. We provide here the details of this work along with its extension to other types of bicyclic β-alkylthio-β-lactams.

Methylthio-azabicyclo[3.2.0]*heptanes and -azabicyclo*-[4.2.0]*octanes*.—We have recently [6] explored the condensation of imines with substituted acetyl chlorides in the presence of triethylamine to give variously substituted β-lactams. When a thioimidate (1) is used as



(1) (2)

the imine component, stereospecific formation of the αβ-*trans*-isomer of the β-lactam (2) occurs.[7]

We have described [8] a convenient preparation of thioimidates that are dihydropyrrole and tetrahydropyridine derivatives [(3)—(7)]. Condensation of these cyclic imines with the appropriate acid chlorides in the presence of triethylamine led to a series of bicyclic β-methylthio-γ-arylmethylene-β-lactams [(8)—(13)]. Interestingly, the azabicyclo-octanes were obtained in higher yield than the azabicycloheptanes.

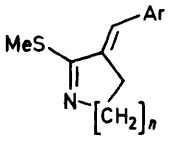
The 5-methylthioazabicycloheptanes (8), (10), and (12) were converted into sulphoxides [(14) and (15)] and sulphones (16)—(18) by successive oxidations with *m*-chloroperbenzoic acid in dichloromethane. The ^{1}H n.m.r. spectra showed progressive downfield shifts of the methylthio-signal upon oxidation. Anisotropic deshielding of the β-lactam proton in (8) upon oxidation to the sulphoxide (14), in deuteriochloroform, was observed. This was also the case for oxidation of the 5-methylthiopenam (24) to the corresponding sulphoxide (21), possibly indicating a *cis*-relationship of the β-lactam proton and the methylthio-substituent. However in dimethyl sulphoxide this deshielding relationship was not observed when the sulphide (12) was converted into the sulphoxide (15). In order to establish definitively the stereochemical relationship of the substituents around the β-lactam ring a single crystal *X*-ray crystallographic study of a typical compound was performed. Rhombohedral crystals of compound (8) were grown from propan-2-ol solution and examined on a Syntex P2$_1$ *X*-ray diffractometer. The space group was $P2_1/c$ as determined from systematic absences ($h0l$: $l = 2n + 1$ absent; $0k0$: $k = 2n + 1$ absent) with $a = 13.30$, $b = 12.14$, $c = 9.01$ Å, $\beta = 94.09°$. Integrated intensities were collected for 2 569 reflections (1 586 observed) by using θ—2θ scans and monochromatised Mo-K_α radiation. The structure was solved by direct methods by Stewart's *X*-Ray '72 system of programs. Isotropic refinement followed by two cycles of anisotropic refinement reduced *R* to 0.075. Further refinement is in progress. An ORTEP drawing of the molecule (8) (Figure 1) shows the methoxy- and methylthio-groups are mutually *cis*. This result was surprising in view of the observed anisotropic deshielding of the β-lactam proton upon formation of the sulphoxide. However,† it

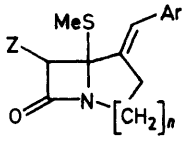
† We thank a referee for this information.

[1] Part 46, M. S. Manhas, S. G. Amin, and A. K. Bose, *Heterocycles*, 1976, **5**, 669.
[2] R. Nagarajan, L. D. Boeck, M. Gorman, R. L. Hamill, C. E. Higgins, M. M. Hoehn, W. M. Stark, and J. G. Whitney, *J. Amer. Chem. Soc.*, 1971, **93**, 2308.
[3] R. Ratcliffe and B. G. Christensen, *Tetrahedron Letters*, 1973, 4653.
[4] A. K. Bose, J. L. Fahey, and M. S. Manhas, *J. Heterocyclic Chem.*, 1973, 791.
[5] A. K. Bose and J. L. Fahey, *J. Org. Chem.*, 1974, **39**, 115.
[6] A. K. Bose, B. Anjaneyulu, S. K. Bhattacharya, and M. S. Manhas, *Tetrahedron*, 1967, **23**, 4769.
[7] A. K. Bose, B. Dayal, H. P. S. Chawla, and M. S. Manhas, *Tetrahedron Letters*, 1972, 2823.
[8] A. K. Bose, J. L. Fahey, and M. S. Manhas, *Tetrahedron*, 1974, **30**, 3.

has been observed that [9] for penicillin *S*-oxides a sulphinyl group *anti* to H-6 can have a greater deshielding effect than one in the *syn*-orientation. By analogy, compounds (8)—(18) are assigned the *Z*-stereostructure shown.

Methylthio-penams and -cephams.—We have previously [4] described the synthesis of 6-methoxy-5-methylthiopenam (22) from 2-mercaptothiazoline (19), which was methylated [to give (20)] and treated with methoxyacetyl chloride and triethylamine. On the basis of the preceding *X*-ray data compounds (21)—(24) and (27)—(30) are analogously reassigned the stereostructures shown. We also reported [4] that oxidation of (24) at

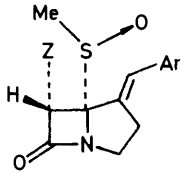


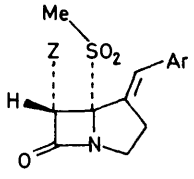


(3) n = 1, Ar = Ph
(4) n = 2, Ar = Ph
(5) n = 1, Ar = 3,4-$(MeO)_2C_6H_3$
(6) n = 2, Ar = 3,4-$(MeO)_2C_6H_3$
(7) n = 1, Ar = 3-$O_2N{\cdot}C_6H_4$

(8) n = 1, Ar = Ph, Z = OMe
(9) n = 2, Ar = Ph, Z = OMe
(10) n = 1, Ar = 3,4-$(MeO)_2C_6H_3$, Z = OPh
(11) n = 2, Ar = 3,4-$(MeO)_2C_6H_3$, Z = OMe
(12) n = 1, Ar = 3-$O_2N{\cdot}C_6H_3$, Z = OPh
(13) n = 1, Ar = Ph, Z = OPh

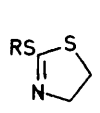
low temperature with *m*-chloroperbenzoic acid occurred selectively on the exocyclic sulphur atom to produce

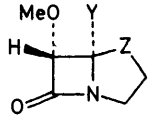


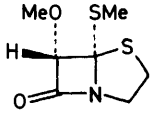


(14) Z = OMe, Ar = Ph
(15) Z = OPh, Ar = 3-$O_2N{\cdot}C_6H_4$

(16) Z = OMe, Ar = Ph
(17) Z = OPh, Ar = 3,4-$(MeO)_2C_6H_4$
(18) Z = OPh, Ar = 3-$O_2N{\cdot}C_6H_3$







(19) R = H
(20) R = Me

(21) Y = S(O)Me, Z = S
(22) Y = S(O)Me, Z = SO
(23) Y = $S(O_2)$Me, Z = SO

(24)

(21). Treatment with 2 equiv. of the oxidant gave a mixture, the ^{1}H n.m.r. spectrum of which indicated that the disulphoxide (22) was the major component. Three equiv. of *m*-chloroperbenzoic acid produced the sulphone–sulphoxide (23) which was resistant to further oxidation.

From the known tetrahydrothiazine (25) [10] we have now prepared the cyclic imine (26) by methylation with methyl iodide. Condensation with methoxy- or phenoxy-acetyl chloride and triethylamine converted (26) into the cepham derivative (27) or (28) in 50—60% yield. A single stereoisomer was formed in each case. The fully oxidised products (29) and (30) were obtained by treatment with 4 equiv. of *m*-chloroperbenzoic acid.

Stereochemistry from Lanthanide-induced Shifts.—Since it was not possible to oxidise the exocyclic sulphur substituent in the cepham series [(9) and (11)] we employed lanthanide-induced shift (l.i.s.) studies to confirm the steric orientation of the methylthio-substituent. The shielding of α-protons in saturated six-membered nitrogen heterocycles is well documented and presumably due to the anisotropy of the *trans*-axial lone pair.[11] The phenomenon may also be viewed as a deshielding by a skew or *cis*-related lone pair.[12] Similar observations have been presented with regard to the shielding of α-protons in *N*-methylpyrrolidines, and it

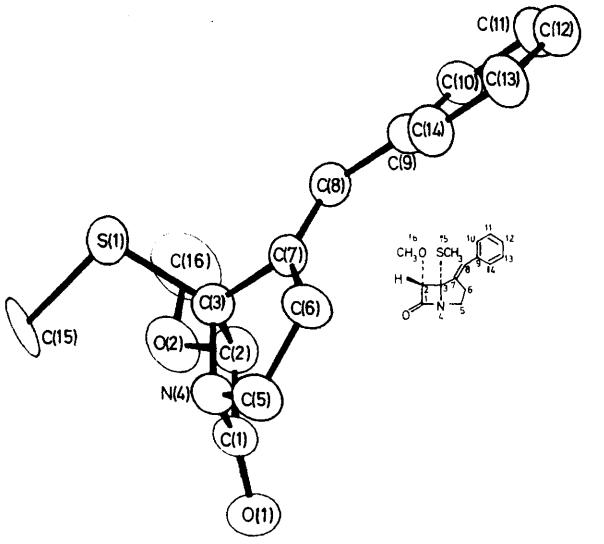
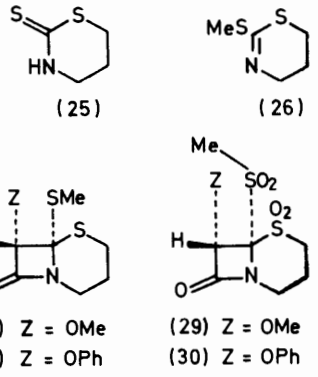


FIGURE 1 ORTEP Diagram of the molecule (8)

has been proposed that the shielding of α-protons in azacycloalkanes by a *trans* lone pair is a general charac-

[9] A. J. Vlietinck, E. Roets, H. Vanderhaeghe, and S. Toppet, *J. Org. Chem.*, 1974, **39**, 441.
[10] J. Hamer and R. Rathbone, *J. Amer. Chem. Soc.*, 1958, **80**, 3341.
[11] J. B. Lambert and R. G. Kesge, *J. Amer. Chem. Soc.*, 1969, **91**, 7774.
[12] C. C. Price, *Tetrahedron Letters*, 1971, 4527.

teristic.[13] The ^1H n.m.r. spectra of compounds (8)—(13), (24), (27), and (28) reveal that the protons α to the nitrogen afford two multiplets with a shift difference of



30—40 Hz. The low-field proton (H_b) is identified as that proton oriented skew to the lone pair (see Figure 2),

FIGURE 2

and the higher-field proton (H_a) is therefore *trans* to the lone pair.

The l.i.s. is defined in terms of Δ_{Eu}, the induced chemical shift at a 1 : 1 molar ratio of shift reagent to substrate.[14] The Δ_{Eu} values were obtained by extrapolation from appropriate plots. We have shown previously how l.i.s. studies can provide reliable evidence on the steric orientation of protons in the vicinity of the sulphoxide bond of penicillins.[15,16]

The proton spectra were obtained by using a Varian A-60 instrument, and $Eu(fod)_3$ was used as shift reagent in $CDCl_3$. Plots of $Eu(fod)_3$ *vs.* $\Delta\delta$ with molar ratio values of 0.1—0.5 : 1 were used to extrapolate to Δ_{Eu}. The positions of multiplets were defined in terms of the average mid-point. Good straight line plots were found for all the data obtained.

TABLE 1

Δ_{Eu} Values (p.p.m.) for $Eu(fod)_3$ in $CDCl_3$

Compd.	β-lactam H	H_b *	CH_3O	CH_2 + H_a *	CH_3S	C=CH	Ph
(24)	3.55	3.10	1.48	1.25	1.22		
(8)	4.42	3.45	1.43	1.28	1.28	1.08	0.33
(27)	4.20	3.67	1.50	1.17	1.58		

* H_a and H_b are α to the nitrogen atom; CH_2 is adjacent to the ring sulphur atom.

The polyfunctional nature of these compounds indicates that pseudocontact interaction may occur at several sites. A decision amongst the various possibilities can be made by comparison of Δ_{Eu} values. In the penam (24) the methoxy oxygen is not a significant site since the methyl resonance undergoes only a slow shift upon incremental addition of $Eu(fod)_3$. Similarly neither of the sulphur atoms is a significant site, in view of the relatively low Δ_{Eu} values for the adjacent protons. It appears therefore that the europium ion is situated in the region of the amide bond, where it can exert approximately the same effect on H_b and the β-lactam proton, while exerting a lesser effect on the other protons. This appears to indicate that the amide bond presents a more electronegative environment for the lanthanide ion than the various ether and thioether linkages. This complements the observation that thioethers show negligible co-ordination with $Eu(dpm)_3$.[17,18]

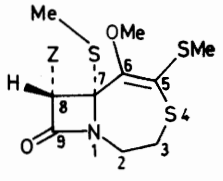
Since the penam (24) and the cepham (27) differ only by a methylene group one would expect the l.i.s. data to show a correlation. Indeed Table 1 shows a close parallelism in behaviour, with, in particular, large values for the β-lactam protons, indicating that the stereochemical orientations of the β-lactam substituents in (24) and (27) are the same. A comparison with data for (8) (structure established unequivocally by *X*-ray data) allows an identical conclusion to be drawn. A similar correlation can be made for (8) and (9), thereby enabling the assignment of steric orientation to (9) without requiring oxidation of the substituent methylthio-group. In molecules [4] such as (31a or b), selective oxidation presents much experimental difficulty, but l.i.s. data (Table 2), which show clear similarities with

TABLE 2

Δ_{Eu} Values (p.p.m.) for $Eu(fod)_3$ in $CDCl_3$

Compd.	β-lactam H	H_b	6-OCH_3	8-OCH_3	5-SCH_3	7-SCH_3
(31a)	4.55	3.88	0.92	1.53	0.38	2.00

those for (8), (23), and (26), enable reassignment of the stereostructure as *Z*. Thus, although in the condens-

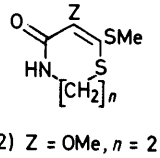


ations of acyclic thioimidates [7] the monocyclic β-lactams formed always have the substituent at C-3 *trans* to the alkylthio group at C-4, in the condensations of the cyclic thioimidates (3)—(7) the stereospecificity exists but the configuration is reversed.

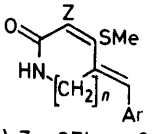
[13] E. Breuer and D. Melumad, *J. Org. Chem.*, 1973, **38**, 1601.
[14] P. V. Demarco, T. K. Elzey, R. B. Lewis, and E. Wenkert, *J. Amer. Chem. Soc.*, 1970, **92**, 5736.
[15] A. K. Bose, B. Dayal, H. P. S. Chawla, and M. S. Manhas, *Tetrahedron Letters*, 1972, 3599.
[16] A. K. Bose, B. Dayal, H. P. S. Chawla, and M. S. Manhas, *Tetrahedron*, 1972, **28**, 5977.
[17] D. R. Crump, J. K. M. Sanders, and D. H. Williams, *Tetrahedron Letters*, 1970, 4949.
[18] H. Yanagawa, T. Kato, and Y. Kitahara, *Tetrahedron Letters*, 1973, 2137.

L.i.s. [Eu(fod)$_3$] studies on the sulphoxides (14) and (22) present a different picture. In this case, owing to the dipolar nature of the sulphoxide group, the europium ion is situated close to the sulphoxide oxygen.

Rearrangements of Methylthio-azabicycloheptanes and -azabicyclo-octanes.—During studies on the penicillin analogue (24) we discovered that trifluoroacetic acid induces a ready rearrangement to the 1,4-thiazepine derivative (32). Reactions of the cephalosporin analogues (27) and (28) with trifluoroacetic acid led to the ring-expanded products (33) and (34) in nearly quantitative yield. The 5-methylthio-azabicycloheptanes (12)



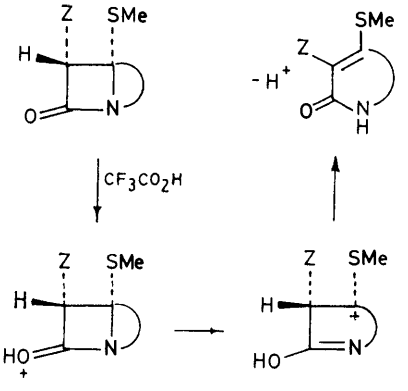
(32) Z = OMe, n = 2
(33) Z = OMe, n = 3
(34) Z = OPh, n = 2



(35) Z = OPh, n = 2, Ar = Ph
(36) Z = OPh, n = 2, Ar = 3-O_2N·C_6H_4
(37) Z = OMe, n = 3, Ar = 3,4-$(MeO)_2C_6H_3$

and (13) underwent a rapid exothermic reaction with trifluoroacetic acid to give high yields of (36) and (35). A similar ^{1}H n.m.r. experiment with compound (11) indicated complete rearrangement. The final spectrum was consistent with expected rearranged structure (37). It is likely that the rearrangement proceeds by initial protonation of the β-lactam carbonyl group, followed by rearrangement to a carbocation that loses a proton (Scheme).

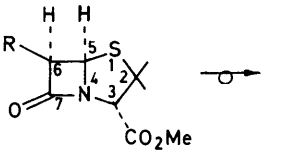
Penicillin is well known for its susceptibility to various types of rearrangement.[19,20] The formation of a seven-membered ring by rearrangement of methyl 6β-phthalimidopenicillanate [(39) ⟶ (40)] and similar compounds



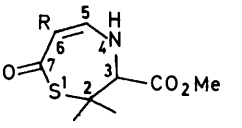
SCHEME

during base-catalysed epimerisation has been reported.[21] However, in this rearrangement the N–C(5) bond is not cleaved.

The amide function in the rearrangement products (32)—(34) can be converted into thioamide with phosphorus pentasulphide, and then methylated to give a cyclic thioimidate suitable for β-lactam formation. We

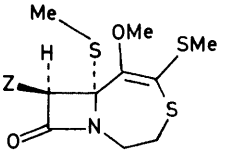


(39)

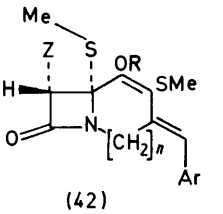


(40)
R = phthalimido

have reported[4] the preparation of a few such bishomologues of cephalosporin of type (41). The availability of compounds (35)—(37) now permits the synthesis of azabicyclo-nonanes and -decanes of type (42). Thus the chemistry described here may lead to various large ring analogues of penicillin. Work along these lines is in progress. Further verification of the stereochemistry of the thia-azabicyclononane (41) by *X*-ray studies is also in progress.



(41)



(42)

EXPERIMENTAL

M.p.s were obtained with a Mel-Temp apparatus. ^{1}H N.m.r. spectra were recorded with a Varian A-60A instrument (60 MHz) with tetramethylsilane as internal standard. Mass spectra were obtained with a Perkin-Elmer RMU-7 spectrometer. Elemental analyses were performed by Bernhardt, Max-Planck Institute, Mülheim, West Germany. Florisil (Fischer) was used for chromatography. All solvents were reagent grade. Distillation of solvents was carried out in the presence of phosphorus pentaoxide. Dichloromethane and chloroform extracts were dried over anhydrous sodium or magnesium sulphate.

4-Benzylidene-6-methoxy-5-methylthio-1-azabicyclo[3.2.0]*-heptan-7-one* (8).—A solution of 3-benzylidene-3,4-dihydro-5-methylthio-2*H*-pyrrole (18.3 g, 0.09 mol) and triethylamine (18.2 g, 0.18 mol) in distilled dichloromethane (250 ml) was stirred at room temperature under nitrogen while a solution of methoxyacetyl chloride (9.8 g, 0.09 mol) in distilled dichloromethane (200 ml) was added dropwise. The resulting solution was stirred for 20 h, washed with aqueous 20% hydrochloric acid (4 × 200 ml), saturated aqueous sodium hydrogen carbonate (4 × 200 ml), and water (200 ml), dried, and evaporated to leave a brown oil that solidified on scratching and was crystallised from propan-2-ol to give the *product* (8) (16.0 g, 68%), m.p. 73—74°, $\nu_{max.}$ (Nujol) 1 780 (CO) and 1 590 cm^{-1} (C=C), δ ($CDCl_3$) 2.20 (3 H, s, CH_3S), 2.8—3.4 (3 H, m, CH_2 and CH), 3.66 (3 H, s, CH_3O), 3.7—4.2 (1 H, m, CH), 4.41 (1 H, s, β-lactam H), 6.59 (1 H, t, *J* 2 Hz, C=CH), and 7.25 (5 H, s,

[19] R. D. G. Cooper and D. O. Spry in 'Cephalosporin and Penicillins, Chemistry and Biology,' ed. E. H. Flynn, Academic Press, New York, 1972.
[20] M. S. Manhas and A. K. Bose, '*beta*-Lactams: Natural and Synthetic,' Part 1, Wiley–Interscience, New York, 1971.
[21] O. K. J. Kovacs, B. Ekström, and B. Sjöberg, *Tetrahedron Letters*, 1969, 1863; B. G. Ramsey and R. J. Stoodley, *J.C.S. Chem. Comm.*, 1973, 450; A. Vlietinck, E. Roets, P. Claes, and H. Vanderhaege, *Tetrahedron Letters*, 1972, 285.

Ph); M^+ 275 (Found: C, 65.45; H, 5.85; N, 5.05; S, 11.55. $C_{15}H_{17}NO_2S$ requires C, 65.45; H, 6.25; N, 5.1; S, 11.65%).

5-Benzylidene-7-methoxy-6-methylthio-1-azabicyclo[4.2.0]*-octan-8-one* (9).—A similar reaction of methoxyacetyl chloride and (4) on a 0.146 mol scale gave the *product* (9) (75%), m.p. 98—99° (from ethyl acetate), $\nu_{max.}$ (Nujol) 1 760 (CO) and 1 600 cm^{-1} (C=C), δ ($CDCl_3$) 1.5—2.0 (2 H, m, CH_2), 2.15 (3 H, s, CH_3S), 2.2—3.5 (3 H, m, CH_2 and CH), 3.70 (3 H, s, CH_3O), 3.7—4.0 (1 H, m, CH), 4.70 (1 H, s, β-lactam H), 6.50br (1 H, s, CH), and 7.0—7.4 (5 H, m, Ph), M^+ 289 (Found: C, 66.55; H, 6.85; N, 5.0. $C_{16}H_{19}NO_2S$ requires C, 66.4; H, 6.6; N, 4.85%).

5-Methylthio-6-phenoxy-4-veratrylidene-1-azabicyclo[3.2.0]*-heptan-7-one* (10).—A similar reaction of phenoxyacetyl chloride and (5) on a 0.020 mol scale gave the *product* (10) (33%), m.p. 154—155° (from benzene), $\nu_{max.}$ (Nujol) 1 780 (CO) and 1 600 cm^{-1} (C=C), δ ($CDCl_3$) 2.25 (3 H, s, CH_3S), 3.0—3.2 (3 H, m, CH_2 and CH), 3.85 (4 H, s, CH_3O and CH), 5.20 (1 H, s, β-lactam H), and 6.6—7.5 (9 H, m, aromatic and C=CH), M^+ 397 (Found: C, 66.55; H, 5.65; N, 3.6; S, 8.1. $C_{22}H_{23}NO_4S$ requires C, 66.45; H, 5.85; N, 3.55; S, 8.05%).

6-Methylthio-7-phenoxy-5-veratrylidene-1-azabicyclo[4.2.0]*-octan-8-one* (11).—As in previous examples, phenoxyacetyl chloride and (6) on a 0.100 mol scale gave the *product* (11) (67%), m.p. 119—120° (from propan-2-ol), $\nu_{max.}$ (Nujol) 1 760 (CO) and 1 600 cm^{-1} (C=C), δ ($CDCl_3$) 1.6—2.0 (2 H, m, CH_2), 2.18 (3 H, s, CH_3S), 2.5—2.9 (2 H, m, CH_2), 3.0—3.4 (1 H, m, CH), 3.4—3.9 (1 H, m, CH), 3.80 (6 H, s, 2 OMe), 5.43 (1 H, s, β-lactam H), 6.38 (1 H, t, *J* 1 Hz, C=CH), 6.5—6.7 (3 H, m, aromatic), and 7.19 (5 H, s, Ph), M^+ 411 (Found: C, 67.15; H, 6.15; N, 3.5; S, 7.85. $C_{23}H_{25}NO_4S$ requires C, 67.15; H, 6.1; N, 3.4; S, 7.8%).

5-Methylthio-4-(3-nitrobenzylidene)-6-phenoxy-1-azabicyclo-[3.2.0]*heptan-7-one* (12).—As in previous examples, phenoxyacetyl chloride and (7) on a 0.100 mol scale gave the *product* (12) (60%), m.p. 164—165° (from t-butyl alcohol), $\nu_{max.}$ (Nujol) 1 780 (CO), 1 600 (C=C), and 1 530 cm^{-1} (NO_2), δ [$(CD_3)SO$] 2.20 (3 H, s, CH_3S), 2.8—3.5 (3 H, m, CH_2 and CH), 3.7—4.2 (1 H, m, CH), 5.73 (1 H, s, β-lactam H), and 6.8—8.5 (10 H, m, aromatic and C=CH), M^+ 382 (Found: C, 62.8; H, 4.95; N, 7.45. $C_{20}H_{18}N_2O_4S$ requires C, 62.8; H, 4.75; N, 7.3%).

4-Benzylidene-5-methylthio-6-phenoxy-1-azabicyclo[3.2.0]*-heptan-7-one* (13).—As in previous examples, phenoxyacetyl chloride and (3) on a 0.100 mol scale gave the product (13) (50%), m.p. 122—124° (from propan-2-ol), $\nu_{max.}$ (Nujol) 1 780 (CO) and 1 600 cm^{-1} (C=C), δ ($CDCl_3$) 2.20 (3 H, s, CH_3S), 2.8—3.4 (3 H, m, CH_2 and CH), 3.8—4.3 (1 H, m, CH), 4.95 (1 H, s, β-lactam H), and 6.6—7.5 (11 H, m, aromatic and C=CH), M^+ 337.

4-Benzylidene-6-methoxy-5-methylsulphinyl-1-azabicyclo-[3.2.0]*heptan-7-one* (14).—A solution of the methylthioazabicycloheptane (8) (2.75 g, 0.010 mol) in dichloromethane (100 ml) was stirred at −78 °C while 70% *m*-chloroperbenzoic acid (2.5 g, 0.010 mol) in dichloromethane (110 ml) was added dropwise over 15 min. The mixture was allowed to warm to room temperature and stirred for 1 h. The solvent was removed to leave a brown oil that was passed through a Florisil column (chloroform as solvent). Evaporation left an oil which was triturated with ether to give a white solid; this was crystallised from benzene–ether (1 : 20) to give the *product* (14) (0.30 g, 10%), m.p. 122—123°, $\nu_{max.}$ (Nujol) 1 770 (CO) and 1 600 cm^{-1} (C=C), δ ($CDCl_3$) 2.45 (3 H, s, CH_3S), 3.0—3.5 (3 H, m, CH_2 and CH), 3.63 (3 H, s, CH_3O), 3.6—4.2 (1 H, m, CH), 4.68 (1 H, s, β-lactam H), 7.0 (1 H, t, *J* 1 Hz, C=CH), and 7.40 (5 H, s, Ph), M^+ 291 (Found: C, 61.85; H, 6.05; N, 4.5. $C_{15}H_{17}NO_3S$ requires C, 61.85; H, 5.9; N, 4.8%).

5-Methylsulphinyl-4-(3-nitrobenzylidene)-6-phenoxy-1-azabicyclo[3.2.0]*heptan-7-one* (15).—A solution of the methylthioazabicycloheptane (12) (1.85 g, 0.005 0 mol) in dichloromethane (150 ml) was stirred at −78 °C while 70% *m*-chloroperbenzoic acid (1.0 g, 0.005 0 mol) in dichloromethane (40 ml) was added dropwise. The mixture was allowed to warm slowly to room temperature, stirred for 1.5 h, and evaporated to leave a yellow oil. This was triturated to give a white solid that was crystallised from benzene to give the *product* (15) (1.0 g, 50%), m.p. 153—154°, $\nu_{max.}$ (Nujol) 1 780 (CO), 1 600 (C=C), and 1 520 cm^{-1} (NO_2), δ [$(CD_3)_2SO$] 2.64 (3 H, s, CH_3S), 3.0—3.4br (3 H, m, CH_2 and CH), 3.8—4.2br (1 H, m, CH), 5.64 (1 H, s, β-lactam H), and 6.8—8.3 (10 H, m, aromatic and C=CH), M^+ 398 (Found: C, 60.2; H, 4.8; N, 7.0. $C_{20}H_{18}N_2O_5S$ requires C, 60.3; H, 4.55; N, 7.0%).

5-Methylsulphonyl-6-phenoxy-4-veratrylidene-1-azabicyclo-[3.2.0]*heptan-7-one* (17).—A solution of the methylthioazabicycloheptane (10) (0.50 g, 0.001 3 mol) and tetrahydrofuran (100 ml) was stirred at room temperature while 85% *m*-chloroperbenzoic acid (0.52 g, 0.002 6 mol) in tetrahydrofuran (30 ml) was added. After 2 h the solvent was removed and the solid produced triturated with ether and filtered off to give the product (17) (0.47 g, 81%), m.p. 166—169°, $\nu_{max.}$ (Nujol) 1 780 (C=O) and 1 600 cm^{-1} (C=C), δ (6 H, s, 2 MeO), 3.8—4.2 (1 H, m, CH), 5.30 (1 H, s, β-lactam H), and 6.8—7.6 (9 H, m, aromatic and C=CH).

5,6-Dihydro-2-methylthio-4H-1,3-thiazine (26).—A solution of tetrahydro-1,3-thiazine-2-thione (36.8 g, 0.28 mol) and methyl iodide (42.0 g, 0.30 mol) in tetrahydrofuran (550 ml) was stirred at room temperature. After 2 h the product was removed as a yellow crystalline precipitate (72.3 g, 94%), m.p. 156—158°, $\nu_{max.}$ (Nujol) 1 590 cm^{-1} (C=N). This hydriodide was neutralized with triethylamine (60 g); extraction with chloroform, drying, and evaporation gave the free base as a yellow oil, $\nu_{max.}$ (film) 1 600 cm^{-1} (C=N).

1,5,6,7-Tetrahydro-4-methylthio-5-(3-nitrobenzylidene)-3-phenoxyazepin-2-one (36).—A solution of the methylthioazabicycloheptane (12) (3.0 g, 0.007 9 mol) in trifluoroacetic acid (10 ml) was stirred for 30 min and evaporated *in vacuo* to leave a brown oil. Trituration with ether gave a pale green solid (2.7 g, 90%), m.p. 225—230°. Crystallization from benzene–hexane gave a white *powder*, m.p. 230—232°, $\nu_{max.}$ (Nujol) 3 300, 3 200 (NH), 1 650 (C=O), 1 600 (C=C), 1 560 (NH bend), and 1 520 cm^{-1} (NO_2), δ ($CF_3{\cdot}CO_2H$) 2.47 (3 H, s, CH_3S), 3.2—3.6 (2 H, m, CH_2), 3.6—4.1 (2 H, m, CH_2), and 6.9—8.9 (11 H, m, aromatic, C=CH, and NH) (Found: C, 63.0; H, 4.85; N, 7.25. $C_{20}H_{18}N_2O_4S$ requires C, 62.8; H, 4.75; N, 7.3%).

4-Benzylidene-6-methoxy-5-methylsulphonyl-1-azabicyclo-[3.2.0]*heptan-7-one* (16).—A solution of the methylthioazabicycloheptane (8) (2.75 g, 0.010 mol) in dichloromethane (100 ml) was stirred at room temperature while 70% *m*-chloroperbenzoic acid (5.0 g, 0.010 mol) in dichloromethane (80 ml) was added. After 1 h the solvent was evaporated off to give a white solid. Trituration with ether gave material that was crystallised from ether–benzene (20 : 1) to yield the *product* (16) (0.70 g, 23%), m.p. 145—146°, $\nu_{max.}$ (Nujol) 1 770 (CO) and 1 600 cm^{-1} (C=C), δ ($CDCl_3$) 3.17 (3 H, s, CH_3S), 3.0—3.5 (3 H, m,

CH_2 and CH), 3.72 (3 H, s, CH_3O), 3.7—4.1 (1 H, m, CH), 4.6 (1 H, s, β-lactam H), 7.03 (1 H, t, *J* 1 Hz, C=CH), and 7.4 (5 H, s, Ph) (Found: C, 58.65; H, 5.7; N, 4.65. $C_{15}H_{17}NO_4S$ requires C, 58.65; H, 5.6; N, 4.55%).

5-Methylsulphonyl-4-(3-nitrobenzylidene)-6-phenoxy-1-azabicyclo[3.2.0]heptan-7-one (18).—A solution of the methylthioazabicyclo[3.2.0]heptane (12) (1.85 g, 0.005 0 mol) in dichloromethane (150 ml) was stirred at room temperature while a 70% solution of *m*-chloroperbenzoic acid (2.0 g, 0.010 mol) in dichloromethane (50 ml) was added. After 1.5 h the solvent was removed to give a white solid; this was triturated with ether then crystallised from ethyl acetate to yield the *product* (18) (1.5 g, 75%), m.p. 203—205°; $\nu_{max.}$ (Nujol) 1 780 (CO), 1 600 (C=C), and 1 520 cm^{-1} (NO_2), δ [$(CD_3)_2SO$] 3.20 (3 H, s, CH_2S), 3.0—3.6 (3 H, m, CH_2 and CH), 3.7—4.1 (1 H, m, CH), 5.3 (1 H, s, β-lactam H), 6.8—7.6 (9 H, m, aromatic and C=CH) (Found: C, 58.3; H, 4.65; N, 7.0. $C_{20}H_{18}N_2O_6S$ requires C, 57.95; H, 4.4; N, 6.7%).

5-Benzylidene-1,5,6,7-tetrahydro-4-methylthio-3-phenoxyazepin-2-one (35).—A solution of 4-benzylidene-5-methylthio-6-phenoxy-1-azabicyclo[3.2.0]heptan-7-one (13) (1.1 g, 0.003 3 mol) and trifluoroacetic acid (15 ml) was stirred for 30 min, evaporated, and triturated with ether to give a pale yellow crystalline *solid* (1.0 g, 91%), m.p. 193—195°; $\nu_{max.}$ (Nujol) 3 330 (NH), 1 650 (CO), 1 605 (C=C), and 1 560 cm^{-1} (NH), δ ($CDCl_3$) 2.25 (3 H, s, CH_3S), 2.8—3.3 (2 H, m, CH_2), 3.4—3.8 (2 H, m, CH_2), 6.8—7.8 (12 H, m, aromatic, C=CH and NH) (Found: C, 71.45; H, 5.9; N, 4.05. $C_{20}H_{19}NO_2S$ requires C, 71.2; H, 5.7; N, 4.15%), M^+ 337.

6-Methoxy-5-methylsulphinyl-4-thia-1-azabicyclo[3.2.0]heptan-7-one (21).—A solution of 6-methoxy-5-methylthio-4-thia-1-azabicyclo[3.2.0]heptan-7-one (2.05 g, 0.010 mol) in dichloromethane (150 ml) was stirred at −78 °C while 70% *m*-chloroperbenzoic acid (2.5 g, 0.010 mol) in dichloromethane (100 ml) was added dropwise. The resulting solution was allowed to warm to room temperature, stirred for 1 h, and evaporated to a white solid; this was triturated with ether then crystallised from chloroform–hexane (2 : 1) to give *product* (21) (1.0 g, 45%), m.p. 170—172°, $\nu_{max.}$ (Nujol) 1 790 cm^{-1} (CO), δ ($CDCl_3$) 2.80 (3 H, s, CH_3S), 3.65 (3 H, s, CH_3O), 3.3—4.0 (3 H, m, CH_2 and CH), 4.0—4.4 (1 H, m, CH), and 4.99 (1 H, s, β-lactam H) (Found: C, 37.9; H, 4.7. $C_7H_{11}NO_3S_2$ requires C, 38.0; H, 5.0%).

6-Methoxy-5-methylsulphonyl-4-thia-1-azabicyclo[3.2.0]heptan-7-one 4-Oxide (23).—A solution of 6-methoxy-5-methylthio-4-thia-1-azabicyclo[3.2.0]heptan-7-one (2.1 g, 0.010 mol) in dichloromethane (100 ml) was mixed with 70% *m*-chloroperbenzoic acid (9.9 g, 0.043 mol) in dichloromethane (100 ml). After stirring for 1 h the solvent was removed and the resulting solid triturated with ether, then crystallised from benzene to give the *product* (23) (0.8 g, 30%), m.p. 167—168°, $\nu_{max.}$ (Nujol) 1 800 cm^{-1} (CO), δ [$(CD_3)_2SO$] 3.29 (3 H, s, CH_3S), 3.4—3.8 (3 H, m, CH_2 and CH), 3.60 (3 H, s, CH_3O), 3.8—4.5 (1 H, m, CH), and 5.00 (1 H, s, β-lactam H) (Found: C, 33.35; H, 4.4; N, 5.6. $C_7H_{11}NO_5S_2$ requires C, 33.2; H, 4.4; N, 5.55%).

7-Methoxy-6-methylthio-5-thia-1-azabicyclo[4.2.0]octan-8-one (27).—A solution of the thiazine (26) (14.7 g, 0.100 mol) and triethylamine (20.2 g, 0.200 mol) in distilled dichloromethane (200 ml) was stirred at room temperature under nitrogen while a solution of methoxyacetyl chloride (10.9 g, 0.100 mol) in distilled dichloromethane (150 ml) was added dropwise over 1 h. The mixture was stirred overnight, washed four times with aqueous 20% hydrochloric acid, three times with saturated aqueous sodium hydrogen carbonate, and once with water, dried, and evaporated to give a yellow solid. This was crystallised from benzene to give the *product* (27) (12.9 g, 59%), m.p. 103—105°, $\nu_{max.}$ (Nujol) 1 770 cm^{-1} (CO), δ ($CDCl_3$) 1.7—2.0 (2 H, m, CH_2), 2.1 (3 H, s, CH_3S), 2.3—3.5 (3 H, m, CH_2 and CH), 3.62 (3 H, s, CH_3O), 3.7—4.2 (1 H, m, CH), and 4.52 (1 H, s, β-lactam H), M^+ 219 (Found: C, 44.0; H, 5.83; N, 6.35. $C_8H_{13}NO_2S_2$ requires C, 43.8; H, 5.95; N, 6.4%).

6-Methylthio-7-phenoxy-5-thia-1-azabicyclo[4.2.0]octan-8-one (28).—A similar reaction, but with phenoxyacetyl chloride, on a 0.10 mol scale, gave the *product* (28) (14.5 g, 52%), m.p. 138—139° (from ethyl acetate), $\nu_{max.}$ (Nujol) 1 770 cm^{-1} (CO), δ ($CDCl_3$) 1.8—2.0 (2 H, m, CH_2), 2.05 (3 H, s, CH_3S), 2.5—3.5 (3 H, m, CH_2 and CH), 3.7—4.2 (1 H, m, CH), 5.3 (1 H, s, β-lactam H), and 6.8—7.5 (5 H, m, Ph), M^+ 281 (Found: C, 55.5; H, 5.45; N, 5.05. $C_{13}H_{15}NO_2S_2$ requires C, 55.5; H, 5.35; N, 5.0%).

7-Methoxy-6-methylsulphonyl-5-thia-1-azabicyclo[4.2.0]octan-8-one 5,5-Dioxide (29).—*m*-Chloroperbenzoic acid (70%; 8.4 g, 0.04 mol) in chloroform (100 ml) was added to a solution of 7-methoxy-6-methylthio-5-thia-1-azabicyclo[4.2.0]octan-8-one (2.2 g, 0.010 mol) in chloroform (50 ml). After stirring for 16 h the mixture was evaporated to a solid. This was triturated with ether, then crystallised from benzene to give the *product* (29) (1.4 g, 64%), m.p. 176—177°, $\nu_{max.}$ (Nujol) 1 800 cm^{-1} (CO), δ [$(CD_3)_2SO$] 2.0—2.5 (2 H, m, CH_2), 3.0—4.1 (4 H, m, $CH_2 \cdot CH_2$), 3.3 (3 H, s, CH_3SO_2), 3.6 (3 H, s, CH_3O), and 5.47 (1 H, s, β-lactam H) (Found: C, 33.65; H, 4.55; N, 5.0. $C_8H_{13}NO_6S_2$ requires C, 33.9; H, 4.6; N, 4.95%).

6-Methylsulphonyl-7-phenoxy-5-thia-1-azabicyclo[4.2.0]octan-8-one 5,5-Dioxide (30).—A similar reaction on a 0.100 mol scale of (27) gave the *product* (30) (3.0 g, 87%), m.p. 205—207° (from ethyl acetate), $\nu_{max.}$ (Nujol) 1 800 cm^{-1} (CO) (Found: C, 45.55; H, 4.6; N, 4.15. $C_{13}H_{15}NO_6S_2$ requires C, 45.2; H, 4.4; N, 4.05%).

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