susceptibility to electrophilic attack of the 5′-free dipyrrylmethanes was already described by us[1] and later confirmed by others.[3] After 72 hr saponification was complete: nmr 2.7 (m, 8, CH_2CH_2), 3.5 (br, 4, CH_2CO), 3.7 (br, 2, pyrr–CH_2–pyrr), 4.0 (br, 2, CH_2NH_2). The substance was rapidly transformed into porphyrins by manipulation. Addition of an acid resin (IRC-H^+ or IRA 120-H^+) allowed adjustment of the solution to pH 7. This solution could be kept at −10° during 1 week with no decomposition and was used for chemical or enzymatic studies. Ehrlich's reaction was positive in the cold.

2-Aminomethyl-3,3′-(β-carboxyethyl)-4,4′-carboxymethyldipyrrylmethane (5) was obtained as described above for dipyrrylmethane **4**. The dipyrrylmethane **35** (36 mg) was dissolved in 0.4 ml of 2 *N* potassium deuterioxide in 50% perdeuteriomethanol. The saponification was complete after 72 hr. The $C_{5'}$ H (6.0 ppm, 0.20) was not completely exchanged after that period, nmr (δ 0 for DSS) 2.7 (m, 8, CH_2CH_2), 3.5 (br, 4, CH_2CO), 3.75 (br, 2, pyrr–CH_2–pyrr), 3.9 (br, 2, CH_2NH_2). After the solution was adjusted to pH 7 with IRA 120-H^+ resin, it could be freeze-dried and kept without decomposition at −15° during 1 week. Ehrlich's reaction was positive in the cold.

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Registry No.—**4,** 39649-89-3; **5,** 51911-89-8; **6,** 51911-90-1; **7,** 6122-77-6; **8,** 51911-91-2; **9,** 51911-92-3; **10,** 51911-93-4; **11,** 51911-94-5; **12,** 51911-95-6; **13,** 51911-96-7; **14,** 51911-97-8; **15,** 51911-98-9; **17,** 526-51-2; **18,** 17266-35-2; **20,** 51911-99-0; **21,** 38252-54-9; **22,** 50622-64-5; **23,** 51912-00-6; **24,** 38252-61-8; **26,** 50622-78-1; **27,** 50622-66-7; **28,** 50622-68-9; **29,** 51912-01-7; **30,** 51912-02-8; **31,** 51912-03-9; **32,** 51912-04-0; **33,** 51912-05-1; **34,** 51912-06-2; **35,** 51990-01-3; benzyl hydrogen malonate, 616-75-1.

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(17) After this manuscript was submitted for publication, a recent paper[18] by Battersby and coworkers was received which describes the synthesis of the dipyrrylmethanes **4** and **5**. The synthetic approach used is similar to that described in the present paper; the results described in both papers showed no significant differences in the properties of the end products.
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Studies on β-Lactams. XXXVI. Monocyclic Cis β-Lactams *via* Penams and Cephams[1]

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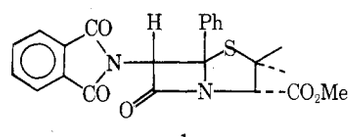
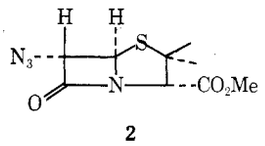
A stereospecific synthesis of monocyclic cis β-lactams has been devised which involves Raney nickel hydrogenolysis of readily accessible penams and cephams. The reaction of various acid chlorides and cyclic imines in presence of a base led to the stereospecific synthesis of a number of 6-substituted penams and 7-substituted cephams with *E* configuration with respect to the β-lactam substituents. These bicyclic β-lactams or their sulfoxides could be desulfurized under mild conditions and in good yields to 1,3,4-trisubstituted cis 2-azetidinones. No convincing rationale is obvious for the exclusive formation of bicyclic β-lactams of *E* configuration by this method.

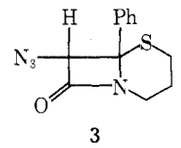
The synthesis of bicyclic β-lactams became a desirable goal from the time it was first suspected that penicillin had a fused thiazolidine-β-lactam structure.[2] The discovery that cephalosporin C is a fused dihydrothiazine β-lactam made the preparation of bicyclic β-lactams even more attractive. Sheehan and coworkers[3] were the first to synthesize penams (for example **1**) by the action of certain acid chlorides on thiazolines in presence of triethylamine.

We introduced the use of α-azidoacyl chlorides for the synthesis of α-azido-β-lactams[4] and several 6-azidopenams[5,7] and 7-azidocephams[6] (for example **2** and **3**) were synthesized in our laboratory in the course of the total synthesis of a 6-epipenicillin ester.[7] Various other penams and cephams have been prepared in different laboratories[8] and



1

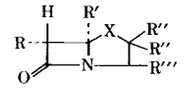




2 **3**

cephalosporins[9] and 4-mercapto-2-azetidinones[10,11] have been synthesized using the "acid chloride method."

Table I.

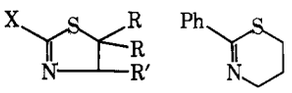


Compd	R	R′	R″	R‴	X	Mp, °C	Yield, %	Formula[a]	Spectral data
6a	MeO	Ph	H	H	S	80–81	90	$C_{12}H_{13}NO_2S$	Ir 1770 cm^{-1}; nmr τ 2.53 (s, 5 H), 5.11 (s, 1 H, 6-H), 5.68 (m, 1 H, 3-H), 6.78 (m, 3 H, 3-1H and 2-2H)
6b	PhO	Ph	H	H	S	132–134	70	$C_{17}H_{15}NO_2S$	Ir 1770 cm^{-1}; nmr τ 2.9 (br, 10 H, 2 Ar), 4.5 (s, 1 H, 6-H), 5.65 (m, 1 H, 3α-H and 2-2H)
6c	N_3	Ph	H	H	S	65–67	70	$C_{11}H_{10}N_4OS$	Ir 2105 (azide), 1773 cm^{-1}; nmr τ 2.55 (s, 5 H), 5.07 (s, 1 H, 6-H), 5.67 (m, 1 H, 3-H), 6.75 (m, 3 H, 3-H and 2-2H)
6d	N_3	Ph	Me	H	S	103–104	87	$C_{13}H_{14}N_4OS$	Ir 2.28 (azide), 1786 cm^{-1}; nmr τ 2.58 (s, 5 H), 4.98 (s, 1 H, 6-H), 5.92 (d, 1 H, 3-H, J = 12.5 Hz), 7.05 (d, 1 H, 3-H, 2-CH_3), 8.56 (s, 3 H, 2-CH_3)
6e	MeO	$C_6H_4CO_2CH_2Ph$-*p*	H	H	S	102–103	70	$C_{20}H_{19}NO_4S$	Ir 1770, 1748 cm^{-1} (ester CO); nmr τ 1.9 (d, 2 H, J = 8 Hz), 2.5 (d, 2 H, J = 8 Hz), 2.6 (br, 5 H), 4.61 (s, 2 H, OCH_2), 5.13 (s, 1 H, 6-H), 5.7 (m, 1 H, 3-H), 6.8 (m, 3 H, 3-H and 2-2H), 6.81 (s, 3 H, OCH_3)
6f	PhO	$C_6H_4CO_2CH_2Ph$-*p*	H	H	S	84–86	63	$C_{25}H_{21}NO_4S$	Ir 1788, 1724 cm^{-1} (ester CO); nmr τ 2 (d, 2 H, J = 8 Hz), 2.9 (br, m, 12 H), 4.48 (s, 1 H, 6-H), 4.7 (s, 2 H, $COCH_2$), 4.67 (m, 1 H, 3-H), 6.86 (m, 3 H, 3-H and 2-2H)
6g	PhO		H	H	S	95	70	$C_{15}H_{13}NO_3S$	Ir 1792 cm^{-1}; nmr τ 2.5–3.11 (m, 6 H), 3.41–3.68 (m, 2 H), 4.47 (s, 1 H), 5.48–5.75 (m, 1 H), 6.43–7.08 (m, 3 H)
6h	PhO	Ph	H	H	SO	108–109	80	$C_{17}H_{15}NO_3S$	Ir 1783 cm^{-1}; nmr τ 2.85 (m, 10 H), 4.25 (s, 1 H, 6-H), 5.66 (m, 1 H, 3-H), 6.65 (m, 3 H, 3-H and 2-2H)
6i	MeO	$C_6H_4CO_2CH_2Ph$-*p*	H	H	SO	180–181	95	$C_{20}H_{19}NO_5S$	Ir 1779, 1730 cm^{-1} (ester CO); nmr τ 1.83 (d, 2 H, J = 8Hz), 2.53 (d, 2 H, J = 8 Hz), 4.6 (s, 2 H, OCH_2), 4.84 (s, 1 H, 6-H), 5.7 (m, 1 H, 3-H), 6.67 (m, 3 H, 3-H and 2-2H), 6.65 (s, 3 H, OCH_3)
6j	MeO	Ph	H	H	SO_2	142–144	80	$C_{12}H_{13}NO_4S$	Ir 1808 cm^{-1}; nmr τ 2.6 (s, 5 H), 4.87 (s, 1 H, 6-H), 5.67 (m, 1 H, 3-H), 6.67 (s, 3 H, OCH_3), 6.6 (br m, 3 H, 3-H and 2-2H)

6k	MeO	$C_6H_4CO_2CH_2Ph$-*p*	H	H	SO_2	113–114	90	$C_{20}H_{19}NO_6S$	Ir 1776, 1709 cm^{-1} (ester CO); nmr τ 1.97 (d, 2 H, J = 8 Hz), 2.48 (d, 2 H, J = 8 Hz), 2.6 (s, 5 H, phenyl), 4.61 (m, 2 H, OCH_2), 5.83 (m, 1 H, 3-H), 6.7 (s, 3 H, OCH_3), 6.65 (m, 3 H, 3β-H and 2-2H)
7a	MeO	H	H	CO_2Et	S	61–63	11	$C_9H_{13}NO_4S$	Ir 1770, 1739 cm^{-1} (ester CO); nmr τ 4.85 (d, 1 H, 6 H, J = 1.5 Hz), 4.95 (m, 1 H, 3-H), 5.47 (d, 1 H, 5-H, J = 1.5 Hz), 5.73 (q, 2 H, OCH_2, J = 7 Hz), 6.45 (s, 3 H, OCH_3), 6.53 (m, 2 H, 2-2H), 8.7 (t, 3 H, CH_3, J = 7 Hz)
7b	MeO	Ph	Me	CO_2CHPh_2	S	110–111	90	$C_{28}H_{27}NO_4S$	Ir 1739 (ester CO), 1770 cm^{-1}; nmr τ 2.3 (m, 2 H), 2.7–2.75 (m, 13 H, aromatic), 5.22 (s, 1 H, 6-H), 5.32 (s, 1 H, 3-H), 6.95 (s, 3 H, OCH_3), 8.33 (s, 3 H, 2-CH_3), 9.02 (s, 3 H, 2-CH_3)

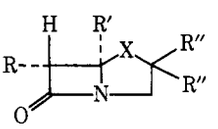
[a] All of the solid penams described in this table gave satisfactory (within ±0.4% of the theoretical value) C, H, and N analyses. In most of the cases they were also analyzed for S.

Recently we have discussed some aspects of the mechanism and stereochemistry[12] of the reaction of imines, acid chlorides, and bases to give β-lactams. We report here on some studies where the imine component in this type of reaction was either a thiazoline (**4**) or a dihydrothiazine (**5**).[13] The 6-substituted penams (**6, 7**) and the 7-substituted cephams (**8**) were obtained by the general reaction shown in eq 1. Some of the penams and cephams were converted to the corresponding sulfoxides and sulfones for characterization purposes because of better crystallinity of these derivatives.



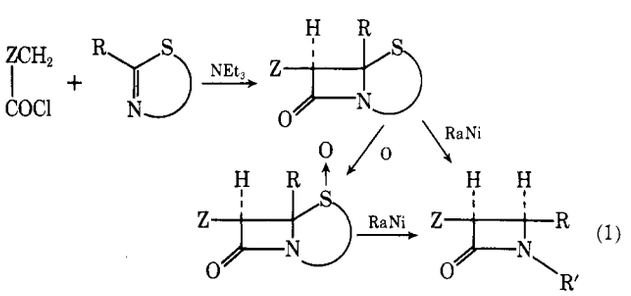
4 **5**

a, R = H; R′ = H; X = Ph
b, R = H; R′ = CO_2H; X = Ph
c, R = Me; R′ = CO_2Et; X = Ph
d, R = Me; R′ = CO_2H; X = Ph
e, R = Me; R′ = H; X = Ph
f, R = H; R′ = H; X = $C_6H_4CO_2CH_2Ph$-*p*
g, R = H; R′ = H; X = 
h, R = Me; R′ = CO_2CHPh_2; X = Ph
i, R = H; R′ = CO_2Et; X = H



6

a, R = MeO; R′ = Ph; R″ = H; X = S
b, R = PhO; R′ = Ph; R″ = H; X = S
c, R = N_3; R′ = Ph; R″ = H; X = S
d, R = N_3; R′ = Ph; R″ = Me; X = S
e, R = MeO; R′ = $C_6H_4CO_2CH_2Ph$-*p*; R″ = H; X = S
f, R = PhO; R′ = $C_6H_4CO_2CH_2Ph$-*p*; R″ = H; X = S
g, R = PhO; R′ =  ; R″ = H; X = S
h, R = PhO; R′ = Ph; R″ = H; X = SO
i, R = MeO; R′ = $C_6H_4CO_2CH_2Ph$-*p*; R″ = H; X = SO
j, R = MeO; R′ = Ph; R″ = H; X = SO_2
k, R = MeO; R′ = $C_6H_4CO_2CH_2Ph$-*p*; R″ = H; X = SO_2



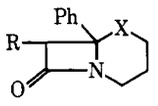
(1)

In the synthesis of penams the yield of β-lactams was low when X = H in the thiazoline (**4**);[7,14] the yield increased sharply when X = aryl or ester.[5,15] In general, cephams were formed in higher yield than the corresponding penams.

In the synthesis of monocyclic β-lactams by the "acid chloride method" it is usual to get a mixture of both cis and trans stereomers—often the trans isomer predominates.[12,16] In one case, however, only the cis β-lactam was formed.[17]

The synthesis of bicyclic β-lactams from thiazolines and

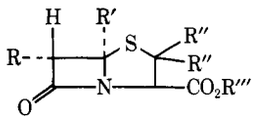
Table II.



Compd	R	X	Mp, °C	Yield, %	Formula[a]	Spectral data
8a	MeO	S		63		Ir 1770 cm^{-1}; nmr τ 2.59 (s, 5 H), 5.31 (s, 1 H), 5.72–5.90 (m, 1 H), 6.94 (s, 3 H), 6.78–7.42 (m, 3 H), 8.0–8.33 (m, 2 H)
8b	PhO	S	130–131	81	$C_{18}H_{17}NO_2S$	Ir 1770 cm^{-1}; nmr τ 2.3–3.45 (m, 10 H), 4.6 (s, 1 H), 5.66–6.0 (m, 1 H), 6.7–7.27 (m, 3 H), 8.0–8.3 (m, 2 H); M^+ at *m/e* 311
8c	MeO	SO	130	80	$C_{13}H_{15}NO_3S$	Ir 1751 cm^{-1}; nmr τ 2.62 (s, 5 H), 4.90 (s, 1 H), 5.76–6.06 (m, 1 H), 6.51–7.67 (m, 4 H), 6.80 (s, 3 H), 8.32–8.68 (m, 1 H)
8d	PhO	SO	138–139	88	$C_{18}H_{17}NO_3S$	Ir 1776 cm^{-1}; nmr τ 2.77–3.33 (m, 10 H), 4.20 (s, 1 H), 5.70–6.03 (m, 1 H), 6.50–7.67 (m, 4 H), 8.3–8.82 (m, 1 H); M^+ at *m/e* 327

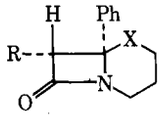
[a] The compounds described in this table gave satisfactory (within ±0.4% of the theoretical value) C, H, and N analyses.

dihydrothiazines was characterized by stereospecificity—a single stereoisomer was formed in each instance. In the case of the 5-unsubstituted penam (**7a**) the size of the coupling (J = 2 Hz) between H-5 and H-6 indicated the trans stereochemistry of the β-lactam, but for the other penams and cephams the stereochemistry was not so obvious. The compounds (**6a, 6e, 6j, 6k, 6l, 8a**), however, were found to belong to a special category—the signal for the methoxy protons appeared at τ 6.65–6.94, that is at ~0.45–0.70 ppm higher field than usual. This upfield shift is indicative of the cis relationship between the methoxy group and the aromatic ring and "*E*" stereochemistry as in this configuration the methoxy protons lie in the shielding cone of the phenyl ring. The nmr spectra of the other penams and cephams do not reveal their stereochemistry. Therefore, we took recourse to desulfurization of these compounds with Raney nickel. Reductive desulfurization has been reported to proceed with retention of configuration.[18] We reconfirmed this in two different ways. Firstly, we desulfurized the trans β-lactam **9** with deuterated Raney nickel. The product (**10**) showed ~70% deuterium incorporation by



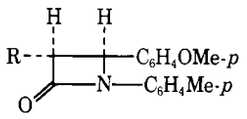
7

a, R = MeO; R′ = H; R″ = H; R‴ = Et
b, R = MeO; R′ = Ph; R″ = Me; R‴ = $CHPh_2$



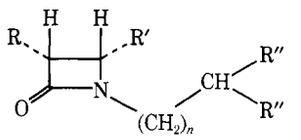
8

a, R = MeO; X = S
b, R = PhO; X = S
c, R = MeO; X = SO
d, R = PhO; X = SO

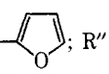


9, R = $PhCH_2S$
10, R = D

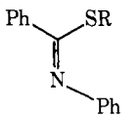
mass spectroscopy and trans relationship of the protons at C-3 and C-4 was preserved. Secondly, Raney nickel desulfurization of **8a** led to the monocyclic β-lactam **11c** which was found to be cis by nmr spectroscopy as would be expected on the basis of its *E* stereochemistry.



11

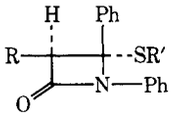
a, R = PhO; R′ =  ; R″ = H; n = 1
b, R = MeO; R′ = Ph; R″ = H; n = 2
c, R = PhO; R′ = Ph; R″ = H; n = 2

Application of the desulfurization technique to the other penams (**6g**) and cephams (**8b**) or their sulfoxides (**6i**,[18] **8c, 8d**) also gave cis β-lactams—thus demonstrating their *E* configuration in each case. The currently held views[12,19] regarding the mechanism of β-lactam formation from acid chlorides and imines do not provide any convincing rationale for the exclusive formation of bicyclic β-lactams of *E* configuration from thiazolines and dihydrothiazines. It may be added that monocyclic β-lactams **13** from thioimidates, such as **12**, also show the same stereospecificity.

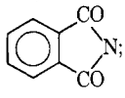


12

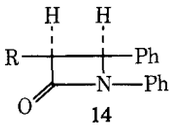
a, R = CH_3
b, R = CH_2Ph
c, R = $CH_2C_6H_4NO_2$-*p*



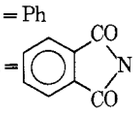
13

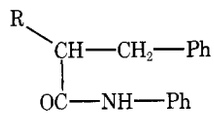
a, R = PhO; R′ = Me
b, R = PhO; R′ = CH_2Ph
c, R = PhO; R′ = $CH_2C_6H_4NO_2$-*p*
d, R = MeO; R′ = Me
e, R = Ph; R′ = Me
f, R =  ; R′ = Me

Raney nickel desulfurization to cis β-lactams **14** was observed to form side products (**15**) in some cases.



14

a, R = PhO
b, R = OMe
c, R = Ph
d, R = 



15

a, R = H
b, R = OMe

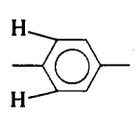
Monocyclic cis β-lactams derived from penicillins are currently attracting considerable attention for the partial synthesis of cephalosporins.[20,21] A few monocyclic β-lactams have also been discovered in nature.[22] In view of these developments, our method for preparing variously substituted monocyclic *cis*-β-lactams by the desulfurization of readily synthesized penams and cephams is of potential value to medicinal chemists. There is an added interest in monocyclic β-lactams since we have recently discovered that some of them show antibiotic activity.[1a]

Experimental Section

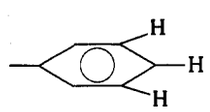
The ir spectra were recorded on a Perkin-Elmer Infracord spectrophotometer calibrated with polystyrene film at 1603 cm^{-1}. The pmr spectra were obtained on a Varian A-60A spectrometer operating at 60 MHz using TMS as an internal standard. The mass spectra were measured on a Hitachi Perkin-Elmer RMU-7 mass spectrometer at 70 eV using an all glass heated inlet system. Thin layer chromatography (tlc) was performed on silica G plates and spots were developed with iodine vapors or aqueous $KMnO_4$ solution. Elemental analyses were performed by A. Bernhardt, Max Planck Institute, Mülheim, W. Germany. Melting points were determined in open capillary tubes and are uncorrected.

4-Carboxy-2-phenyl-2-thiazoline (4b). This compound was synthesized by the method of Sheehan and coworkers:[23] mp 123–124°; nmr ($CDCl_3$) τ 0.44 (s, 1 H), 2.10 (m, 2 H), 2.54 (m, 3 H), 4.58 (t, 1 H), 6.28 (d, 2 H).

2-Phenyl-2-thiazoline (4a). 4-Carboxy-2-phenyl-2-thiazoline (**4b,** 32 g, 0.154 mol) was heated under reduced pressure (1.5 mm). When the bath temperature was raised to 180°, evolution of carbon dioxide started and the desired product began to distil over which was collected at 95–100° (1.5 (1.5 mm) [lit.[24] bp 105–107° (2 mm), 275–280° (740 mm)]: yield 28.5%; nmr ($CDCl_3$) τ 2.05 (m, 2 H, a), 2.55 (m, 3 H, b), 5.56 (t, 2 H, 4-CH_2), 6.66 (t, 2 H, 5-CH_2).

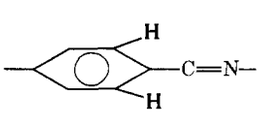


a

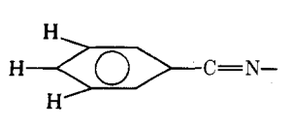


b

5,5-Dimethyl-2-phenyl-2-thiazoline (4e). 5,5-Dimethyl-2-phenyl-2-thiazoline-4-carboxylic acid (**4d,** 46.0 g, 0.195 mol) obtained by the hydrolysis of ethyl 5,5-dimethyl-2-phenyl-2-thiazoline-4-carboxylate (**4c**)[25] was heated to 120° (0.25 mm). Effervescence due to the evolution of carbon dioxide was noticed and 5,5-dimethyl-2-phenyl-2-thiazoline (**4e**) was collected at 120° (0.25 mm) (35.5 g, 76%): ν_{max} 1610 cm^{-1} (C=N); nmr ($CDCl_3$) τ 2.11 (m, 2 H, c), 2.59 (m, 3 H, d), 5.9 (s, 2 H, 4-CH_2), 8.51 (s, 6 H, 5-$2CH_3$); mass spectrum M^+ at *m/e* 191.

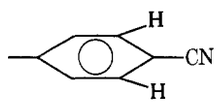


c

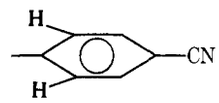


d

Benzyl 4-Cyanobenzoate. 4-Cyanobenzoic acid (34 g, 0.231 mol) was suspended in 200 ml of anhydrous ether in a 1-l. flask equipped with a dropping funnel. A solution (600 ml) of 28.04 g of phenyldiazomethane[26] was added. The yellowish pink color of the phenyldiazomethane solution disappeared immediately on reaction. After the addition of the phenyldiazomethane solution was completed, the reaction mixture was refluxed for 16 hr. Evaporation of the solvent gave the crude ester (55 g) which was dissolved in 300 ml of methylene chloride. This solution was washed successively with 50 ml of saturated $NaHCO_3$ and 2 × 100 ml of water, dried ($MgSO_4$), and stripped of the solvent to give the product (53 g, 96.5%). This material was used for subsequent reactions without further purification: mp 44–46°; ν_{max} 2252 (–CN), 1760 cm^{-1} (ester carbonyl); nmr ($CDCl_3$) τ 1.93 (d, 2 H, e), 2.45 (d, 2H, f), 2.6 (br, 5 H, phenyl), 4.67 (s, 2 H, CH_2); mass spectrum M^+ at *m/e* 234.

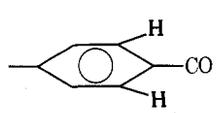


e

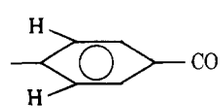


f

2-(*p*-Benzyloxycarbonylphenyl)-2-thiazoline (4f). In a 500-ml round-bottom flask equipped with a condenser and a drying tube were placed benzyl 4-cyanobenzoate (59 g, 0.25 mol) and cysteamine (20 g, 0.25 mol). The mixture was heated for 18 hr at 150° without solvent and the melt was cooled and extracted with 300 ml of methylene chloride. Evaporation of the solvent from the extract left a viscous material (78 g) which was passed through a column of Florisil (80 g, mesh 60–100) and eluted with benzene–hexane (1:1) mixture. The first 200 ml of the eluant gave the desired compound (59 g, 80%). This material was used without purification for the next operation. A portion was purified by distillation under reduced pressure, the fraction distilling at 210° (0.5 mm) which was essentially pure title compound solidified on standing: mp 67–69°; ir (Nujol) ν_{max} 1709 (ester carbonyl), 1610 cm^{-1} (C=N); nmr ($CDCl_3$) τ 1.87 (d, 2 H, $J_{A_2B_2}$ = 8 Hz, g), 2.11 (d, 2 H, $J_{A_2B_2}$ = 8 Hz, h), 2.61 (s, 5 H, phenyl), 4.63 (s, 3 H, OCH_2), 5.51 (t, 2 H, J = 8 Hz, 4-2H), 6.6 (t, 2 H, J = 8 Hz, 5-2H); mass spectrum M^+ at *m/e* 297.

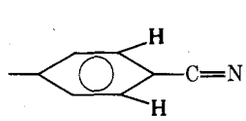


g

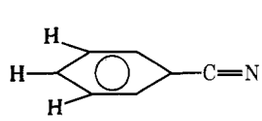


h

Benzhydryl 5,5-Dimethyl-2-phenyl-2-thiazoline-4-carboxylate (4h). In a 500-ml round-bottom flask equipped with a condenser and a drying tube was taken a solution of 6 g (0.025 mol) of **4d** in 200 ml of anhydrous ether. Freshly prepared diphenyldiazomethane[27] (5.95 g, 0.0255 mol) in 200 ml of ether was then added dropwise at room temperature with constant stirring. After the addition of the diphenyldiazomethane, the solution was refluxed for 48 hr and then the solvent was evaporated to give essentially the pure product (10 g). An analytical sample of the thiazoline ester was prepared by crystallization from methylene chloride–petroleum ether: mp 114–116°; ir ν_{max}^{Nujol} 1745 (ester C=O), 1605 cm^{-1} (C=N); nmr ($CDCl_3$) τ 2.13 (m, 2 H, i), 2.65 (br, 13 H, j and two phenyls), 2.97 (s, 1 H, Ph_2CH), 5.05 (s, 1 H, 4-H), 8.27 (s, 3 H, 5-CH_3), 9.73 (s, 3 H, 5-CH_3); mass spectrum M^+ at *m/e* 401.



i

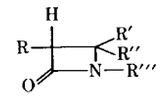


j

Anal. Calcd for $C_{25}H_{23}NO_2S$: C, 74.81; H, 5.73; N, 3.49; S, 7.98. Found: C, 74.63; H, 5.75; N, 3.67; S, 7.97.

Ethyl 2-Thiazoline-4-carboxylate (4i). Through a solution of L-cysteine ethyl ester hydrochloride (50 g) in 500 ml of methanol was passed ammonia gas at room temperature at moderate rate for 15 min. The precipitated ammonium chloride was filtered off. Evaporation of methanol under reduced pressure gave L-cysteine ethyl ester which was dissolved in 200 ml of absolute ethanol containing 50 mg of *p*-toluenesulfonic acid and the solution was refluxed. To this refluxing solution was added 150 ml of triethyl orthoformate dropwise over a period of 0.5 hr. The reaction mixture was refluxed for an additional 3 hr. The solvent was then evaporated under reduced pressure and the viscous residue was dissolved in 200 ml of methylene chloride and washed with 3 × 75 ml of water and dried ($MgSO_4$). Evaporation of CH_2Cl_2 yielded the *N*-formylcysteine ethyl ester as a viscous oil (29 g) which was not

Table III.



Compd	R	R′	R″	R‴	Stereochemistry	Mp, °C	Yield, %	Formula[a]	Spectral data[b]
9	$PhCH_2S$	C_6H_4OMe-*p*	H	C_6H_4Me-*p*	Trans	118–119	56	$C_{24}H_{23}NO_2S$	Ir 1727 cm^{-1}; nmr τ 2.79–3.27 (m, 13 H), 5.45 (d, 1 H, J = 2 Hz), 6.08 (s, 1 H), 6.11 (d, 1 H, J = 2 Hz), 6.25 (s, 3 H), 7.75 (s, 3 H)
11a	PhO		H	C_2H_5	Cis	109–110	60	$C_{15}H_{15}NO_3$	Ir 1748 cm^{-1}; nmr τ 2.5–3.15 (m, 6 H), 345–3.62 (m, 2 H), 4.50 (d, 1 H, J = 4.5 Hz), 4.81 (d, 1 H, J = 4.5 Hz), 6.25, 7.10 (m, 2 H), 8.89 (t, 3 H)
11b	MeO	Ph	H	C_3H_7-*n*	Cis	Colorless oil	50		Ir 1745 cm^{-1}; nmr τ 5.29 (d, 1 H, J = 4 Hz), 5.39 (d, 1 H, J = 4 Hz), 5.39 (d, 1 H, J = 4 Hz), 7.0 (s, 3 H)
11c	PhO	Ph	H	C_3H_7-*n*	Cis	109–110	40	$C_{18}H_{19}NO_2$	Ir 1745 cm^{-1}; nmr τ 2.57–3.21 (m, 10 H), 4.46 (d, 1 H, J = 4.5 Hz), 4.98 (d, 1 H, J = 4.5 Hz), 6.3–7.31 (m, 2 H), 8.3–8.75 (m, 2 H), 9.1 (t, 3 H, J = 7 Hz)
13a	PhO	SCH_3	Ph	Ph		192	64	$C_{22}H_{19}NO_2S$	Ir 1770 cm^{-1}; nmr τ 2.15–3.18 (m, 15 H, aromatic), 4.40 (s, 1 H, 3-H), 7.88 (s, 3 H, SCH_3); M^+ at *m/e* 361
13b	PhO	SCH_2Ph	Ph	Ph		154–155	71	$C_{28}H_{23}NO_2S$	Ir 1764 cm^{-1}; nmr τ 2.1–3.22 (m, 20 H), 4.57 (s, 1 H), 6.19 (s, 2 H)
13c	PhO	$SCH_2C_6H_4NO_2$-*p*	Ph	Ph		138–139	81	$C_{28}H_{22}N_2O_4S$	Ir 1767 cm^{-1}; nmr τ 1.90–3.30 (m, 19 H), 4.5 (s, 1 H), 6.06 (AB q, 2 H, J = 13 Hz)
13d	MeO	SCH_3	Ph	Ph		126	90	$C_{17}H_{17}NO_2S$	Ir 1748 cm^{-1}; nmr τ 2.11–2.02 (m, 10 H), 5.12 (s, 1 H, 3-H), 6.75 (s, 3 H, OCH_3), 7.94 (s, 3 H, SCH_3)
13e	Ph	SMe	Ph	Ph		169–170	76	$C_{22}H_{19}NOS$	Ir 1745 cm^{-1}; nmr τ 2.03–2.97 (m, 10 H), 4.95 (s, 1 H, 3-H), 7.82 (s, 3 H, SCH_3)
13f		SMe	Ph	Ph		208–209	69	$C_{24}H_{18}N_2O$	Ir 1787, 1757, 1720 cm^{-1}; nmr τ 2.03–3.0 (m, 14 H), 4.26 (s, 1 H, 3-H), 7.82 (s, 3 H, SCH_3)

14a[c]	PhO	Ph	H	Ph	Cis	192–193	50	$C_{21}H_{17}NO_2$	Ir 1757 cm^{-1}; nmr τ 4.46 (d, 1 H, J = 5 Hz), 4.64 (d, 1 H, J = 5 Hz)
14b[c]	MeO	Ph	H	Ph	Cis	141–142	60		Ir 1754 cm^{-1}; nmr τ 2.63–3.0 (m, 10 H), 4.8 (d, 1 H, J = 5 Hz), 5.20 (d, 1 H, J = 5 Hz), 5.28 (d, 1 H, J = 5 Hz), 6.81 (s, 3 H)
14c[d]	Ph	Ph	H	Ph	Cis	184–185	57		Ir 1742 cm^{-1}; nmr τ 2.47–3.0 (m, 15 H), 4.17 (d, 1 H, J = 6 Hz), 4.99 (d, 1 H, J = 6 Hz)
14d		Ph	H	Ph	Cis	218–219	61	$C_{23}H_{16}N_2O_3$	Ir 1781, 1760, 1722 cm^{-1}; nmr τ 2.42–2.95 (m, 14 H), 4.34 (d, 1 H, J = 5 Hz), 5.5 (d, 1 H, J = 5 Hz)

[a] All of the new β-lactams described in this table gave satisfactory (within ±0.4% of the theoretical value) C, H, and N analyses. [b] Infrared spectra in Nujol; the band at 1745–1805 cm^{-1} is due to β-lactam CO. Nmr spectra in $CDCl_3$. M^+ peak for nominal mass reported for compounds **6a–k, 7a, b.** [c] Reference 12a. [d] Reference 28.

purified further: ν_{max} 3300 (amide NH), 1739 (ester C=O), 16.75 cm^{-1} (amide C=O).

N-Formylcysteine ethyl ester (34 g) was distilled from 100-ml round-bottom flask at 120° (0.3 mm). The distillate was pure **4i** (17.5 g, 57.4%): ν_{max} 1742 cm^{-1} (ester C=O); nmr ($CDCl_3$) τ 1.97 (d, 1 H, J = 2 Hz, 2-H), 4.83 (m, 1 H, $J_{1,4}$ = 2 Hz, $J_{4,5}$ = 7 Hz, 4-H), 5.7 (q, 2 H, J = 7 Hz, OCH_2), 6.38 and 6.53 (2 s, 2 H, 5-2H), 8.67 (t, 3 H, J = 7 Hz, CH_3).

Preparation of Penams and Cephams. 6-Methoxy-5-phenylpenam (6a). In a 1-l. flask equipped with a condenser, a pressure-equalized dropping funnel, and a nitrogen-inlet tube were placed 2-phenyl-2-thiazoline (6.52 g, 0.025 mol), methoxyacetyl chloride (4.34 g, 0.025 mol), and 750 ml of methylene chloride. This solution was maintained at reflux while a solution of triethylamine (4.04 g, 0.025 mol) in 125 ml of methylene chloride was slowly added dropwise over a period of 7–9 hr. After the addition was completed the reaction mixture was refluxed for an additional 17 hr. Evaporation of the solvent gave a yellowish solid which was extracted with 2 × 500 ml of diethyl ether. The ethereal extract was washed with water and dried ($MgSO_4$). Removal of ether left a light red, viscous oil, 9.3 g (99.3%), which showed a strong band at 1773 cm^{-1} (β-lactam C=O) in the ir spectrum. This crude product was dissolved in methylene chloride and filtered through Florisil (80 g, 60–100 mesh); the first 200 ml of the eluent gave the desired bicyclic β-lactam (8.5 g, 90.7%). Crystallization of the β-lactam from benzene–hexane gave pure **6a.**

The penams (**6b–g** and **7a,b**) were also prepared by this general method using the appropriate acid chloride and the thiazoline.

The reaction of the dihydrothiazine **5** with methoxyacetyl chloride and phenoxyacetyl chloride in the presence of NEt_3 afforded the cephams **8a** and **8c,** respectively.

Preparation of Penam and Cepham Sulfoxides. 6-Phenoxy-5-phenylpenam 1-Oxide (6h). A solution of **6b** (0.9 g, 0.003 mol) and *m*-chloroperoxybenzoic acid (0.52 g, 0.003 mol) in 150 ml of anhydrous ether was stirred at room temperature for 15 hr. Ether was evaporated and the product dissolved in 100 ml of methylene chloride. *m*-Chlorobenzoic acid formed during the reaction was neutralized with 20 ml of 10% $NaHCO_3$ solution. The organic layer was washed with 2 × 50 ml of water, dried ($MgSO_4$), and filtered. Evaporation of the solvent gave a white crystalline solid which on recrystallization from methylene chloride–petroleum ether afforded 0.75 g of **6h.**

Using the same general procedure the penam sulfoxide **6j** was obtained from the corresponding penam. In a similar manner the cephams **8a** and **8b** gave the sulfoxides **8c** and **8d,** respectively.

Preparation of Penam Sulfones. 5-(*p*-Carbobenzyloxyphenyl)-6-methoxypenam 1,1-Dioxide (6k). A mixture of **6i** (0.38 g, 0.001 mol) and *m*-chloroperoxybenzoic acid (0.17 g, 0.001 mol) in 100 mol of CH_2Cl_2 was stirred at room temperature for 48 hr. The reaction mixture was washed with $NaHCO_3$ solution followed by water and dried ($MgSO_4$). Removal of the solvent and recrystallization of the residue from methylene chloride–hexane gave 0.36 g of **6k.**

The penam **6a** could be converted directly to the sulfone **6j** by using 2 *M* proportions of *m*-chloroperoxybenzoic acid.

The spectral data on the penams, their sulfoxides, and sulfones are reported in Table I. The data on cephams are recorded in Table II.

***trans*-1-(*p*-Tolyl)-3-benzylthio-4-(*p*-anisyl)azetidin-2-one (9).** To a solution of *S*-benzylthioglycolyl chloride (6.88 g, 0.02 mol) in 300 ml of CH_2Cl_2 was added under stirring a mixture of *p*-anisylidene-*p*-toluidine (4.50 g, 0.02 mol) and Et_3N (2.50 g, 0.025 mol) in 100 ml of CH_2Cl_2 over a period of 2 hr and contents were further stirred for 10 hr. CH_2Cl_2 solution was washed with $NaHCO_3$ solution followed by water and dried ($MgSO_4$), and solvent was removed. The residue was crystallized from methylene chloride–hexane to give 4.35 g.

Using similar reaction conditions the Schiff bases **12a–c** on treatment with appropriate acid chlorides afforded the β-lactams **13a–f.**

***trans*-1-(*p*-Tolyl)-3-deuterio-4-(*p*-anisyl)azetidin-2-one (10).** To a solution of **9,** (1.90 g, 0.005 mol) in 100 ml of MeOD containing 50 ml of D_2O was added Raney nickel (15 g) previously washed thrice with D_2O. The reaction mixture was refluxed for 10 hr and worked up as described for **9** to give 0.88 g (65%) of **10:** mp 70–71°; ir (Nujol) 1742 cm^{-1} (β-lactam CO); nmr ($CDCl_3$) τ 2.70–3.26 (m, 8 H), 5.12 (d, 1 H, J = 2 Hz), 6.27 (s, 3 H), 7.15 (d, 1 H, J = 2 Hz), 7.79 (s, 3 H); mass spectrum M^+ at m/e 268.

The procedure described below for synthesizing **11a** is typical of the desulfurization carried out on other β-lactams.

cis-**1-Ethyl-3-phenoxy-4-(2-furyl)azetidin-2-one (11a).** To a solution of **6g** (1.44 g, 0.005 mol) in 300 ml of acetone was added 30 g of Raney nickel (W-7) and the contents were refluxed on a steam bath for 10 hr. After filtration, the acetone solution was concentrated under vacuum and the residue obtained was crystallized from methylene chloride–hexane to furnish crude **11a** which was further purified by chromatography over a column of Florisil using benzene as eluent to give 60% yield of the pure title compound.

Using the same reaction conditions **8c** was converted to **11b.** Similarly the cis monocyclic β-lactam **11c** could be prepared *via* the desulfurization of the cepham **8b** or its sulfoxide **8d.**

Similarly the desulfurization of **13a, 13b** or **13c** resulted in the formation of **14a.** Also the cis β-lactams **14b, 14c,** and **14d** were formed by the Raney Ni treatment of the methylthio β-lactams **13d, 13e,** and **13f,** respectively.

The analytical and spectral data for all the monocyclic β-lactams are given in Table III.

S-**Methylthiobenzanilide (12a)** was prepared by the method of May,[30] mp 63–64°.

S-**Benzylthiobenzanilide (12b).**[31] To a solution of thiobenzanilide (4.26 g, 0.02 mol) in 50 ml of 10% KOH was added benzyl chloride (2.52 g, 0.02 mol), the contents were stirred at room temperature for 10 hr and extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with water and dried ($MgSO_4$), and the solvent was removed to give an oil: ν_{max} 1603 cm^{-1} (C=N); nmr ($CDCl_3$) τ 2.71–3.32 (m, 15 H, aromatic H), 5.79 (s, 2 H, SCH_2); mass spectrum M^+ at *m/e* 303.

S-(*p*-**Nitrobenzyl)thiobenzanilide (12c).** A suspension of thiobenzanilide (8.52 g, 0.04 mol) and *p*-nitrobenzyl bromide (8.64 g, 0.04 mol) in 100 ml of 10% KOH was stirred for 12 hr at 85°. The contents were cooled and extracted with CH_2Cl_2 (3 × 75 ml), washed with water, and dried ($MgSO_4$), and the solvent was removed under vacuum. Recrystallization of the residue from benzene–hexane gave 12.3 g (88.5%) of **12c:** mp 98–99°; ν_{max} 1613 cm^{-1} (C=N); nmr ($CDCl_3$) τ 1.75–45 (m, 14 H), 5.67 (s, 2 H).

Anal. Calcd for $C_{20}H_{16}N_2O_2S$: C, 68.96; H, 4.60; N, 8.05. Found: C, 68.71; H, 4.75; N, 8.25.

Registry No.—**4a,** 2722-34-1; **4b,** 19983-15-4; **4d,** 51932-22-0; **4e,** 37950-61-1; **4f,** 51932-23-1; **4g,** 14117-27-2; **4h,** 51932-24-2; **4i,** 51932-25-3; **5,** 6638-35-3; **6a,** 51932-26-4; **6b,** 37958-31-9; **6c,** 52019-83-7; **6d,** 52019-84-8; **6e,** 51932-27-5; **6f,** 51932-28-6; **6g,** 51932-29-7; **6h,** 51932-30-0; **6i,** 52022-26-1; **6j,** 51932-31-1; **6k,** 51932-32-2; **7a,** 51932-33-3; **7b,** 51932-34-4; **8a,** 37958-33-1; **8b,** 37958-32-0; **8c,** 51932-35-5; **8d,** 51932-36-6; **9,** 38395-81-2; **10,** 51932-37-7; **11a,** 38395-85-6; **11b,** 37958-36-4; **11c,** 37958-35-3; **12a,** 52019-85-9; **12b,** 52019-86-0; **12c,** 51932-38-8; **13a,** 52019-87-1; **13b,** 38395-82-3; **13c,** 38395-83-4; **13d,** 51932-39-9; **13e,** 51932-40-2; **13f,** 52019-88-2; **14a,** 33812-92-9; **14b,** 33812-89-4; **14c,** 16141-50-7; **14d,** 29834-35-3; benzyl 4-cyanobenzoate, 18693-97-5; 4-cyanobenzoic acid, 619-65-8; cysteamine, 60-23-1; diphenyldiazomethane, 883-40-9; L-cysteine ethyl ester hydrochloride, 868-59-7; *N*-formylcysteine ethyl ester, 52022-27-2; methoxyacetyl chloride, 38870-89-2; *S*-benzylthioglycolyl chloride, 7031-28-9; *p*-anisylidene-*p*-toluidine, 3246-78-4; thiobenzanilide, 636-04-4; benzyl chloride, 100-44-7; *p*-nitrobenzyl bromide, 100-11-8; phenoxyacetyl chloride, 701-99-5; azidoacetyl chloride, 30426-58-5; phenylacetyl chloride, 103-80-0; phthalimidoacetyl chloride, 6780-38-7.

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References and Notes

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