Synthesis, Stereochemistry and Pharmacological Activity of rac.-*cis*-Tetrahydro-6-hydroxy-7-(4-methoxyphenyl)-1,4-thiazepin-5(2*H*)-ones

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Reaction of 2-aminoethanethiol (**3**) with *trans*-3-(*p*-methoxyphenyl)glycidate (**4**) gave the rac.-*cis*-1,4-thiazepinone **5** and a by-product **6**. The structure of **5** was proven by X-ray crystallography. The X-ray data revealed that this compound adopts the chair conformation in the solid state and the heterocyclic ring is seven-membered. The structure of the by-product **6** was elucidated on the basis of spectral data. Compounds **9** and **10** were inactive as calcium channel blocking agents.

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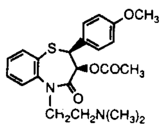
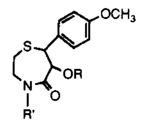
Since the discovery of the calcium channel blocking activity of diltiazem (**1**) [1], a *cis*-1,5-benzothiazepin a great deal of work has been carried out on the structural modification of this compound in order to improve its overall pharmacological profile. The common structural feature of these compounds is the skeletal thiazepinone ring fused to the benzene ring. As part of our studies [2] the synthesis of diltiazem analogues as potential calcium regulating agents, we were interested to determine whether the aromatic ring in **1** is required for substrate activity. Thus, in the hope that the "monocyclic" analogs of **1** would lead to products of biological interest, we have carried out the synthesis of the title compounds **2** by the sequence of reactions outlined in Scheme 1.



1



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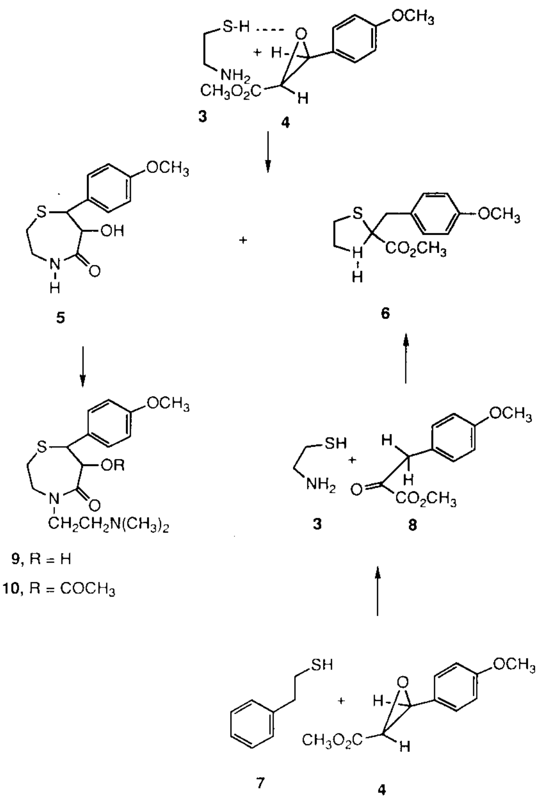
Scheme 1



Reaction of 1-aminoethanethiol (**3**) with *trans*-3-(*p*-methoxyphenyl)glycidate (**4**) [3] in refluxing xylene, followed by removal of the solvent and separation of the products by fractional crystallization yielded the rac.-*cis*-1,4-thiazepinone **5** and a by-product **6** in 41% overall yield. Structural elucidation of these compounds was accomplished on the basis of spectral data and the structure of **5** was confirmed by single crystal X-ray analysis.

The mass spectrum of **5** showed the molecular ion peak as required at m/e 253 and the ir spectrum (chloroform) had an amide carbonyl bond absorption at 1665 cm^{-1} and the expected NH absorption at 3320 cm^{-1}. The ^1H nmr spectrum (deuteriochloroform) of **5** showed a two-proton multiplet at δ 2.74 due to the CH_2S protons, a two-proton multiplet at 3.53 due to the NCH_2 protons, and a three-proton singlet at 3.76 due to the aromatic methoxy protons. The other signals are a one-proton doublet at δ 4.10 (J = 2.5 Hz) due to the SCH proton, a one-proton doublet of doublets at 4.74 (J = 2.5 and 5.5 Hz) due to the HOC*H* proton, a one-proton doublet at 5.04 (J = 5.5 Hz) due to the *H*OCH proton, a AA'BB' pattern at 6.82, 7.33 (J = 8.5 Hz) for the four aromatic protons and a one-proton broad multiplet at 8.15 which can be assigned to the NH proton. Assignment of the relative stereochemistry for **5** was initially based on an analysis of the ^1H nmr coupling constant for the C6 and C7 protons which was 2.5 Hz. By analogy for the diltiazem series [4] the *cis* stereochemistry was thus assigned to **5** [5]. This stereochemical assignment was confirmed by single-crystal X-ray analysis for **5** [6]. The X-ray crystallographic structure of **5** (Figure 1) revealed that in the solid state, the thiazepinone ring has the slightly twisted-chair conformation with the C6 hydroxyl and the C7 aryl groups in a *cis* orientation [5]. On the basis of the results described above the most likely stereochemical course of the reaction is outlined in Scheme 2. It is well documented that the stereochemistry of 3-(*p*-methoxyphenyl)glycidate (**4**) prepared by the Darzens reaction is *trans* [7]. Under the thermal conditions used, the reaction mechanism for the formation of **5** appears to be a two-stage one and is rationalized in terms of the intermediates **11** and **12**. Opening of the glycidate **4** initially protonated by the thiol **3** would be assisted by the *p*-anisyl group leading to a tight ion-pair **11**, which collapses to **12** with retention of configuration. Finally, **12** then cyclizes *in situ* to the *cis*-amide **5**.

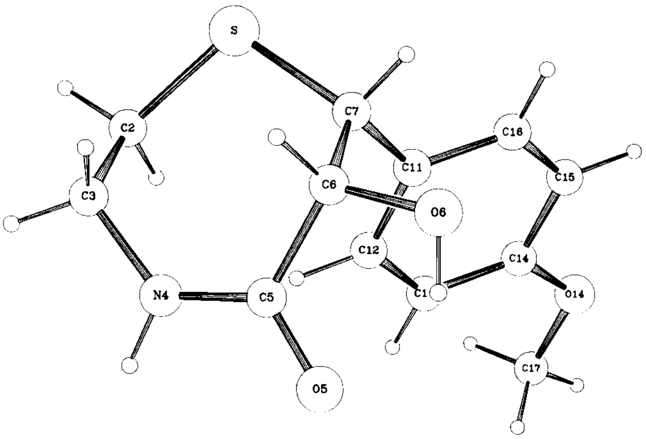
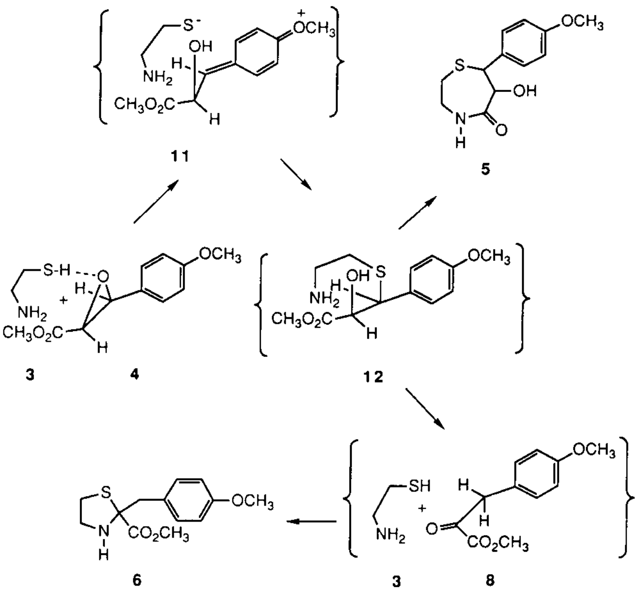


Figure 1. Structure of **5** as determined by X-ray analysis.

Scheme 2



The structure of the by-product **6** was determined on the basis of its spectroscopic data. Its mass spectrum exhibts the molecular ion peaks as required at m/e 267 and the ir spectrum (chloroform) showed to NH absorption at 3325 cm^{-1} and an ester carbonyl absorption at 1735 cm^{-1}. The ^1H nmr spectrum (deuteriochloroform) was in complete agreement with structure **6** and features a one-proton broad absorption at δ 2.55 due to the NH proton, a four-proton multiplet at 2.65-3.84 due to the SCH_2CH_2N protons a two-proton AB pattern at 3.19, 3.28 (J_{gem} 14 Hz), for the CH_2Ar protons, a three proton singlet at 3.73 for the OCH_2 protons, a three proton singlet at 3.76 due to the OCH_3 protons and a four proton AA'BB' pattern at 6.79, 7.20 (J_{ortho} = 8.5 Hz) assigned to the aromatic protons. Furthermore, the most diagnostic features were the signals of the methylene protons adjacent to the aromatic ring which appeared at δ 3.19, 3.28 as the AB pattern. In a decoupling experiment, irradiation of the aromatic doublet at δ 7.20 caused narrowing of the line widths and increased intensity of the AB pattern (δ 3.19, 3.28), thus confirming that the methylene group is benzylic.

The formation of **6** (Scheme 2) presumably resulted from mercaptan catalyzed conversion of the glycidate **4** to the α-ketoester **8**, an intermediate that undergoes reaction with 2-aminoethanethiol (**3**) to yield the by-product **6**. In order to account for such a mechanism, a sample of **8** [8] was independently prepared by reaction of the glycidate **4** with phenylethylmercaptan (**7**) in refluxing xylene (Scheme 1). The α-ketoester **8** on treatment with 2-aminoethanethiol (**3**) in refluxing xylene gave **6**, whose physical and chemical properties (mp, ir uv and ^1H nmr) were identical with those of **6** isolated from the original reaction. This experiment also supports the correctness of our previous structural assignment of **6** based on ^1H nmr data.

Table I

Crystal Data for Compound **5**

Formula	$C_{12}H_{15}NO_3S$
Formula weight	253.32
Crystal system	orthorhombic
Space group	$P2_12_12_1$
Cell constants	
a	6.396(3) Å
b	10.321(2) Å
c	17.513(4) Å
V	1156Å^3
Z	4
d_{calcd}	1.455 g cm^{-3}
μ(CuKα)	24.2 cm^{-1}
Crystal size	0.07 x 0.08 x 0.73 mm
Temperature	110 K
Maximum θ	60°
No. of unique reflections	1005
No. of observed reflections [I>3.0σ(I)]	906
No. of variables	74
R	0.067
R_w	0.082
Largest peak of final difference map	0.6 e Å^{-3}

Table II

Final Atomic Parameters for **5**

Atom	x	y	z	Beqv
S	0.6466(3)	0.4681(2)	0.12265(9)	1.09(3)
O5	0.7379(9)	0.7639(4)	0.3228(3)	1.41(8)*
O6	0.3741(8)	0.6762(4)	0.2885(2)	1.27(8)*
O14	0.5661(9)	1.0918(4)	0.0225(3)	1.63(9)*
N4	0.925(1)	0.6008(5)	0.2738(3)	1.1(1)*
C2	0.921(1)	0.4833(6)	0.1486(4)	1.4(1)*
C3	0.956(1)	0.4759(7)	0.2348(4)	1.5(1)*
C5	0.744(1)	0.6606(6)	0.2872(4)	1.0(1)*
C6	0.539(1)	0.6032(7)	0.2575(4)	1.2(1)*
C7	0.514(1)	0.6020(6)	0.1700(4)	1.0(1)*
C11	0.538(1)	0.7326(6)	0.1316(4)	0.8(1)*
C12	0.727(1)	0.8001(6)	0.1289(4)	1.2(1)*
C13	0.742(1)	0.9204(6)	0.0933(4)	1.0(1)*
C14	0.570(1)	0.9732(6)	0.0588(3)	1.0(1)*
C15	0.380(1)	0.9063(7)	0.0588(4)	1.5(1)*
C16	0.368(1)	0.7876(6)	0.0948(4)	1.4(1)*
C17	0.760(1)	1.1621(7)	0.0186(4)	1.6(1)*
HO6	0.444	0.739	0.314	1.6
HN4	1.047	0.642	0.292	1.4
H2A	0.972	0.569	0.130	1.5
H2B	1.000	0.412	0.124	1.5
H3A	0.860	0.411	0.257	1.6
H3B	1.105	0.448	0.243	1.6
H6	0.535	0.510	0.247	1.4
H7	0.363	0.582	0.163	1.1
H12	0.854	0.763	0.154	1.4
H13	0.879	0.967	0.092	1.2
H15	0.254	0.944	0.033	2.0
H16	0.232	0.740	0.094	1.8
H17A	0.735	1.246	-0.009	2.0
H17B	0.810	1.180	0.072	2.0
H17C	0.865	1.110	-0.009	2.0

Th starred atoms were refined isotropically. The parameters of the hydrogen atoms were not refined. Standard deviations are in parenthesis. Anisotropically refined atoms are given in the form of the isotropic equivalent displacement parameter defined as: (4/3) * [a2*B(1,1) + b2*B(2,2) + c2*B(3,3) + ab(cos gamma)*B(1,2) + ac(cos beta)*B(1,3) + bc(cos alpha)*B(2,3)]

Table III

Bond Lengths (Å) for **5**

Bond		Length	Bond		Length
S	C2	1.820(8)	C5	C6	1.53(1)
S	C7	1.822(7)	C6	C7	1.541(9)
O5	C5	1.235(8)	C7	C11	1.515(9)
O6	C6	1.405(9)	C11	C12	1.40(1)
C14	C14	1.380(8)	C11	C16	1.38(1)
O14	C17	1.437(9)	C12	C13	1.392(9)
N4	C3	1.473(9)	C13	C14	1.37(1)
N4	C5	1.330(9)	C14	C15	1.40(1)
C2	C3	1.528(9)	C15	C16	1.380(9)

Table IV

Bond Angles (°) for **5**

Bond			Angle	Bond			Angle
C2	S	C7	105.7(3)	S	C7	C11	115.2(5)
C14	O14	C17	116.9(5)	C6	C7	C11	115.0(5)
C3	N4	C5	127.3(6)	C7	C11	C12	123.1(6)
S	C2	C3	112.6(5)	C7	C11	C16	119.5(6)
N4	C3	C2	113.2(6)	O14	C14	C15	114.9(6)
O5	C5	N4	121.2(7)	C13	C14	C15	120.1(6)
O5	C5	C6	118.5(6)	C14	C15	C16	119.1(7)
N4	C5	C6	120.3(6)	C11	C16	C15	122.2(7)
O6	C6	C5	107.7(5)	C12	C11	C16	117.4(6)
O6	C6	C7	108.1(6)	C11	C12	C13	121.2(6)
C5	C6	C7	115.6(6)	C12	C13	C14	119.9(7)
S	C7	C6	114.2(5)	O14	C14	C13	125.0(6)

Standard deviations are in parentheses.

Finally, alkylation of **5** with 2-dimethylaminoethyl chloride in dimethyl sulfoxide in the presence of potassium carbonate gave **9**, which on treatment with acetic anhydride afforded the racemic *cis*-ester **10**.

Compounds **9** and **10** were tested for potential calcium blocking activity [9] and found to be inactive.

In conclusion, based on these results, the aromatic group in 1,5-benzothiazepinons is required for calcium regulating activity.

EXPERIMENTAL

Melting points were taken in capillary tubes with a Thomas Hoover melting point apparatus and are uncorrected. Ultraviolet spectra were measured in 95% ethanol with a Carey Model 14 spectrophotometer. Infrared spectra were determined with a Beckman Model IR-9 spectrophotometer. Nuclear magnetic resonance spectra were measured with a Varian A-60 or HA-100 spectrometer and recorded in δ values with deuteriochloroform or dimethyl sulfoxide-d_6 as the solvent and tetramethylsilane as an internal reference. The proton signals are designated as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Mass spectra (70 ev, direct inlet system) were determined with a CEC type 21-110 spectrometer. Crystallographic data were measured on a Hilger-Watts diffractometer (Ni-filtered CuKα radiation, 0-20 scans, pulse-height discrimination).

rac.-*cis*-Tetrahydro-6-hydroxy-7-(4-methoxyphenyl)-1,4-thiazepin-5(2*H*)-one (**5**) and 2-[(4-Methoxyphenyl)methyl]-2-thiazolidinecarboxylic Acid Methyl Ester (**6**).

A mixture of 5.9 g (0.076 mole) of 2-aminoethanethiol (**3**), and 15.3 g (0.073 mole) of *trans*-3-(*p*-methoxyphenyl)glycidate (**4**) in 250 ml of xylene was heated at reflux for 17 hours. The solvent was removed under reduced pressure and the residue was partitioned between methylene chloride and 1*N* hydrochloric acid.

The methylene chloride solution was dried (sodium sulfate) and the solvent removed to give 16.2 g of crude product, which after crystallization from ethanol afforded 3.9 g (21%) of **5** as a white solid, mp 164-165°; ir (chloroform): 3320 (NH), 1665 (lactam CO) cm^{-1}; uv: λ max (ethanol): 229 mμ (ϵ 12250), 276 (1330), 283 (1178); ^{1}H nmr (deuteriochloroform): δ 2.74 (m, 2H, SCH_2), 3.53 (m, 2H, $NC\mathit{H}_2$), 3.76 (s, 3H, OCH_3), 4.10 (d, 1H, J = 2.5 Hz, SCH), 4.74 (dd, 1H, J = 2.5 and 5.5 Hz, HOC*H*), 5.04 (d, 1H, J = 5.5 Hz, OH), 6.82, 7.33 (AA'BB', 4H, J_{ortho} = 8.5 Hz, ArH), 8.15 (brm, 1H, NH); ms: (70 ev) 253 (M^+).

Anal. Calcd. for $C_{12}H_{15}NO_3S$: C, 56.91; H, 5.97; N, 5.53. Found: C, 56.55; H, 6.14; N, 5.47.

Evaporation of the filtrate after removal of **5**, gave a yellow solid which was crystallized from ethyl ether to yield 4.0 g (20%) of **6**, mp 88-90°; ir (chloroform): 3325 (NH), 1735 (ester CO) cm^{-1}; uv: λ max (ethanol): 227 mμ (ϵ 11900), 275 (1470), 281 (1230); ^{1}H nmr (deuteriochloroform): δ 2.55 (br, 1H, NH), 2.65-3.84 (m, 4H, SCH_2CH_2N), 3.19, 3.28 (AB, 2H, J_{gem} = 14 Hz, $ArCH_2$) [11], 3.73 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 6.79, 7.20 (AA'BB', 4H, J_{ortho} = 8.5 Hz, ArH); ms: (70 ev) 267 (M^+).

Anal. Calcd. for $C_{13}H_{17}NO_3S$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.39; H, 6.27; N, 5.34.

4-Methoxyphenylpyruvic Acid Methyl Ester (8).

A mixture of 2.7 g (0.019 mole) of phenylethyl mercaptan (**7**) and 4.1 g (0.019 mole) of *trans*-3-(*p*-methoxyphenyl)glycidate (**4**) in 50 ml of xylene was heated at reflux for 18 hours and the solvent was removed under reduced pressure. The residue was dissolved in ethyl ether (60 ml) and the solution was washed with saturated aqueous sodium bicarbonate solution (2 x 40 ml), water (40 ml), and dried (magnesium sulfate). Removal of the solvent and recrystallization of the residue from methanol gave 3.2 g (78%) of **8** as colorless, unstable crystals, mp 91-93° (reported mp 90-93° [8]); ir (chloroform): 1692 (ester CO) cm^{-1}; uv: λ max (ethanol): 225 mμ (ϵ 8600), 305 (3099); ms: (70 ev) 208 (M^+).

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.46; H, 5.77. Found: C, 63.42; H, 5.81.

Reaction of 4-Methoxyphenylpyruvic Acid Methyl Ester 8 with 2-Aminoethanethiol (3).

Under nitrogen, a mixture of 0.2 g (0.0025 mole) of 2-aminoethanethiol (**3**), 0.314 g (0.0015 mole) of 4-methoxyphenylpyruvic acid methyl ester (**8**) and 8 ml of xylene was heated at reflux for 5 hours. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (60 g) using methylene chloride and ethyl acetate (4:2 v/v) elutants. Removal of the solvents and crystallization of the residue from ethyl ether afforded 0.12 g (30%) of **6**, mp 88-90°. The mixed melting point of the product with a sample of **6** isolated from the original reaction was undepressed. In addition, the ir, uv, and ^{1}H nmr spectra were identical.

rac.-*cis*-Tetrahydro-6-hydroxy-4-[2-(dimethylamino)ethyl]-7-(4-methoxyphenyl)-1,4-thiazepin-5(2*H*)-one (9) Hydrochloride.

A mixture of 2.5 g (0.01 mole) of **5**, 1.3 g (0.01 mole) of powdered potassium carbonate and 1.3 g (0.011 mole) of 2-dimethylaminoethyl chloride in 100 ml of ethyl acetate was stirred at reflux for 2 hours, then twice an additional 0.3 g of dimethylaminoethyl chloride was added at 2 hours intervals. The mixture was heated at reflux for a total of 17 hours, cooled to room temperature and diluted with water. The organic solution was separated, washed with brine, dried (magnesium sulfate) and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and extracted with 1*N* hydrochloric acid (3 x 50 ml). The acidic solution was made basic with 10% aqueous sodium hydroxide and the suspension was extracted with ethyl acetate (3 x 50 ml). The combined organic solutions were washed with water (30 ml), dried (magnesium sulfate) and the solvent was removed under reduced pressure. The residue was dissolved in acetone and passed through a silica gel pad which was washed with acetone (a total of 300 ml). Removal of the solvent gave the crude base **9**, which, after treatment with hydrogen chloride (anhydrous) in ethyl acetate, and recrystallization from acetonitrile afforded 1.50 g (43%) of **9**•HCl as a white solid, mp 97-99°; ir (potassium bromide): 3432 (OH), 2700-2400 (NH^+), 1649 (lactam CO) cm^{-1}; uv (ethanol): λ max 227 mμ (ϵ 11230), 276 (1230), 283 (1040).

Anal. Calcd. for $C_{16}H_{24}N_2O_3S{\cdot}HCl$: C, 53.25; H, 6.98; N, 7.76. Found: C, 52.97; H, 7.09; N, 7.76.

A sample of **9**•HCl in water was treated with dilute sodium hydroxide and the aqueous suspension was extracted with ethyl acetate. The organic solutions were dried (magnesium sulfate) and removal of the solvent gave after distillation the pure base **9**, bp 180-185° (0.025 mm); ir (chloroform): 3415 (OH), 1650 (lactam CO) cm^{-1}; uv (ethanol): λ max 226 mμ (ϵ 12000), 276 (1550), 283 (1080); ms: (70 ev) 324 (M^+).

Anal. Calcd. for $C_{16}H_{24}N_2O_3S$: C, 59.24; H, 7.46; N, 8.64. Found: C, 59.35; H, 7.58; N, 8.32.

rac.-*cis*-5-(Acetyloxy)-7-(4-methoxyphenyl)-4-[2-(dimethylamino)-ethyl]-1,4-thiazepin-5(2*H*)-one 10 Hydrochloride.

A mixture of 1.0 g (0.003 mole) of **9**•HCl and 25 ml of acetic anhydride was heated at 100° for 17 hours and then concentrated to dryness. The residue was dissolved in water and made basic with concentrated ammonium hydroxide. The aqueous suspension was extracted with ethyl ether (3 x 30 ml). The combined organic solutions were washed with brine (30 ml), then dried (magnesium sulfate) and removal of the solvent gave 0.9 g (90%) of **10**, bp 190-195° (0.025 mm); ir (chloroform): 1742 (ester CO) 1668 (lactam CO) cm^{-1}; uv (ethanol): λ max 226 mμ (ϵ 12202), 275 (1320), 282 (1130); ms: (70 ev) 366 (M^+).

Anal. Calcd. for $C_{18}H_{26}N_2O_4S$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.94; H, 7.52; N, 7.64.

A sample of the above base **10**, on treatment with hydrogen chloride (anhydrous) in ethyl acetate afforded after recrystallization from ethanol-ethyl acetate **10**•HCl as a white solid, mp 140-142°; ir (potassium bromide): 1741 (ester CO), 1668 (lactam CO) cm^{-1}; uv (ethanol): λ max 227 mμ (ϵ 11320), 276 (1150), 283 (980).

Anal. Calcd. for $C_{18}H_{26}N_2O_4S{\cdot}HCl$: C, 53.66; H, 6.75; N, 6.95. Found: C, 53.62; H, 6.81; N, 7.01.

Crystal Data and Structure Determination.

Details of the crystal data for compound **5** are summarized in Table I. The intensity data were measured on an Enraf-Nonius CAD4 diffractometer (graphite-monochromated CuKα radiation, ω-2θ scans). The structure was solved by a multiple-solution procedure [10] and was refined by full-matrix least squares. When the nonhydrogen atoms were refined anisotropically, some of their temperature factors became marginally negative; and so, in the final refinement, only the sulfur atom was refined anisotropically, while the other nonhydrogen atoms were refined isotropically. The hydrogen atoms were included in the structure-factor calculations, but their parameters were not refined.

The final atomic coordinates and equivalent isotropic thermal factors are given in Table II. Bond lengths and bond angles are listed in Tables III and IV.

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[11] Confirmation that the AB pattern (δ 3.17, 3.28) is benzylic was obtained by irradiation of the aromatic doublet at δ 7.20. The irradiation resulted in the narrowing of the line widths and increased intensity of the AB pattern.