Synthesis and spectroscopic investigations of 1,4-benzothiazepine derivatives[1]

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This paper is dedicated to Dr. O. E. (Ted) Edwards

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The reaction of sodium 3,4-dimethoxythiophenolate (**1**) with 2-bromoethylamine (**2**) gave 2′-aminoethyl-3,4-dimethoxyphenyl sulfide hydrochloride (**3**). Ring closure of the acyl derivatives **4***a–c* with phosphoryl chloride furnished the 2,3-dihydro-1,4-benzothiazepines **5***a–c*. In a reaction competing with the cyclization, the acid amides **4** decomposed to 2′-chloroethyl-3,4-dimethoxyphenyl sulfide (**7**) and the corresponding nitrile. A few derivatives (**8–10**) of **5***c* were prepared. Sodium borohydride reduction of **5***b*, *c* yielded the 2,3,4,5-tetrahydro-1,3-benzothiazepines **11***a*, *b*. With substituted acetyl chlorides, compounds **5***c* and **10** were converted to the β-lactam derivatives **12***a–f* and **13**, the configurations and conformations of which were determined by nmr spectroscopy; under similar reaction conditions the analogous compounds **5***a*, *b* gave the enamides **14**, **15**, and **16**.

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La réaction du diméthoxy-3,4 thiphénolate de sodium (**1**) avec la bromo-2 éthylamine (**2**) conduit au chlorhydrate du sulfure d'amino-2 éthyle et de diméthoxy-3,4 phényle (**3**). La cyclisation des dérivés acyles **4***a–c* avec le chlorure de phosphoryle conduit aux dihydro-2,3 benzothiazépines-1,4 **5***a–c*. Les amides acides **4** subissent en même temps une réaction de décomposition qui conduit au sulfure de chloro-2 éthyle et de diméthoxy-3,4 phényle (**7**) et au nitrile correspondant. On a préparé quelques dérivés (**8–10**) de **5***c*. La réduction des composés **5***b*, *c* par le borohydrure de sodium conduit aux tétrahydro-2,3,4,5 benzothiazépines-1,3 **11***a*, *b*. À l'aide de chlorures d'acétyles substitués, on a pu transformer les composés **5***c* et **10** en dérivés β-lactames **12***a–f* et **13** dont on a déterminé les configurations et les conformations en faisant appel à la rmn; dans des conditions semblables, les composés analogues **5***a*, *b* conduisent aux énamides **14**, **15** et **16**.

[Traduit par la revue]

Introduction

Many researchers have dealt with the syntheses of 3-oxo, 5-oxo, and 3,5-dioxo derivatives of 1,4-benzothiazepines, but there are only a few publications (2–9) relating to the preparation of 2,3- and 3,4-dihydro- or 2,3,4,5-tetrahydro-1,4-benzothiazepines containing no carbonyl group. Only a single procedure, following a different pathway, was found in the literature for the synthesis of a β-lactam derivative of 1,4-benzothiazepine (10).

We earlier reported the syntheses of 4,5-dihydro-1,4-benzothiazepine and 4,5-dihydro-1,4-benzothiazepin-3(2*H*)-one derivatives (8, 9, 11). In the present work, convenient preparations of suitably substituted 2,3-dihydro- and 2,3,4,5-tetrahydro-1,4-benzothiazepines and the syntheses of their β-lactam and other derivatives are described.

Syntheses

The reaction of sodium 3,4-dimethoxythiophenolate (**1**) with 2-bromoethylamine (**2**) gave 2′-aminoethyl-3,4-dimethoxyphenyl sulfide, which was isolated as the hydrochloride **3**. With acid anhydrides or acid chlorides, compound **3** was converted to the acid amides **4***a–c*. Heating of the latter with $POCl_3$ furnished the benzothiazepine derivatives **5***a–c* (Scheme 1) in poor yields, since a competitive reaction, probably via disintegration of the intermediary imide chloride **6**, gave rise mainly to the decomposition products 2′-chloroethyl-3,4-dimethoxyphenyl sulfide (**7**) and the corresponding nitrile. Compound **7** and benzonitrile, formed simultaneously with the cyclization of the acid amide **4***c*, were isolated from the reaction mixture. A definitive synthesis of compound **7** was its preparation from sodium 3,4-dimethoxythiophenolate and 1,2-dichloroethane (Scheme 1).

A few characteristic derivatives were prepared from **5***c*, such as the methiodide **8** with methyl iodide, the sulfoxide **9** with $NaIO_4$, and the sulfone **10** with $KMnO_4$. Reduction of **5***b* and **5***c* with $NaBH_4$ furnished the corresponding tetrahydro-1,4-benzothiazepines **11***a*, *b* (Scheme 2).

Analogously to the cycloaddition reactions of imines with acid chlorides, **5***c* gave the β-lactams **12***a–f*. It was found that, except for one case, only one of the diastereomers was formed; thus, the reactions were regio- and stereospecific. However, when **5***c* and 2-chloro-2-phenylacetyl chloride were reacted in the presence of TEA (triethylamine), both stereoisomers **12***e* and **12***f* were isolable (Scheme 3).

The β-lactam **13** obtained from the benzothiazepine dioxide **10** by treatment with phenylacetyl chloride was identical with the compound formed from the β-lactam **12***a* by oxidation with peracetic acid (Scheme 4).

Compound **5***a* with benzoyl chloride and, analogously, **5***b* with dichloroacetyl chloride or benzoyl chloride in the presence of TEA gave the enamides **14**, **15**, and **16**, respectively (Scheme 5), similar to the reactions of 1-alkyl-3,4-dihydroisoquinolines and 4-alkyl-2*H*-1,3-benzothiazines (12, 13). Further investigations relating to these compounds are in progress.

Spectroscopic evidence of structures

The ir and ^1H and ^{13}C nmr data supporting the structures of

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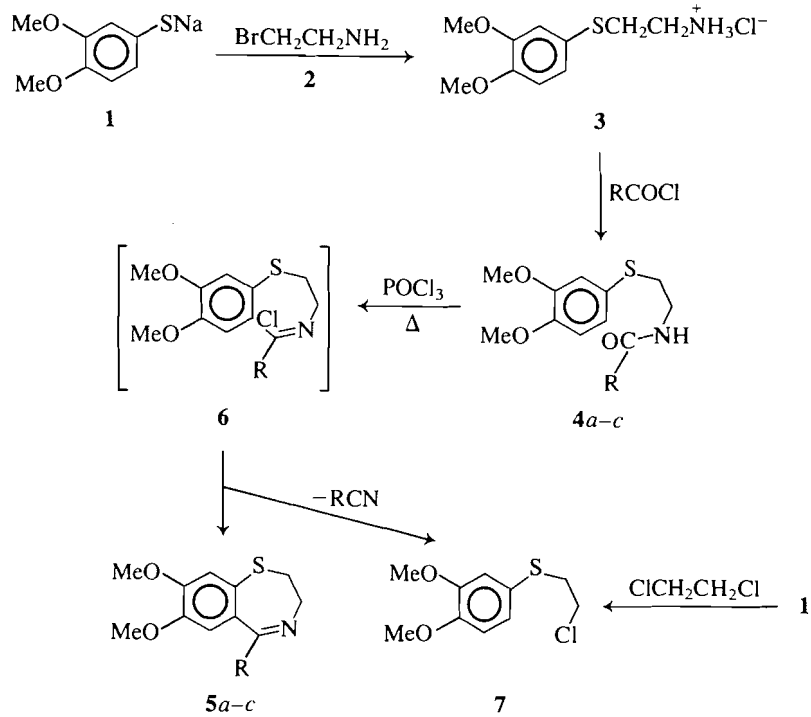
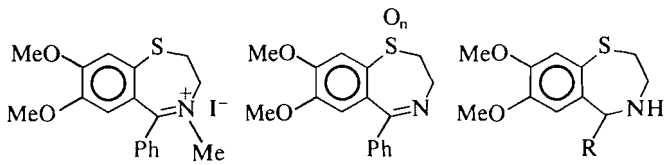


a: R = Me *b*: R = CH_2Ph *c*: R = Ph

SCHEME 1



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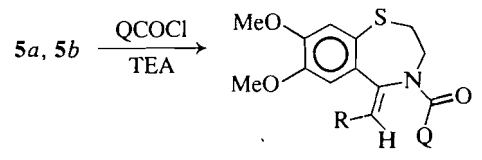
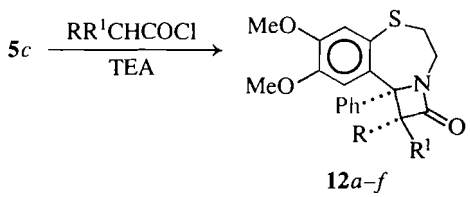
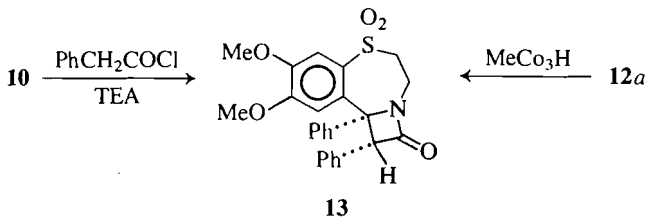


SCHEME 5



a: R = Ph; R^1 = H *d*: R = R^1 = Cl
b: R = OPh; R^1 = H *e*: R = Ph; R^1 = Cl
c: R = Cl; R^1 = H *f*: R = Cl; R^1 = Ph

SCHEME 3



SCHEME 4

the new compounds are given in the Experimental; those of the β-lactams are listed in Tables 1–3.

In the ^1H nmr spectrum of the sulfone analog **10**, the two methylene groups give a singlet of 4H intensity. Thus, the two methylene groups appear to be isochronous in $CDCl_3$ solution, owing to the practically identical substituent effects of the sp^2 nitrogen and the sulfone group. The chemical equivalence of both pairs of methylene protons indicates a rapid interconversion of the thiazepine ring.

The ArH-9 signal of **11***b* shows a very marked upfield shift (−0.5 ppm) as compared with the value for the starting compound **5***c*. This shift is a consequence of the anisotropic shielding of the phenyl substituent (14*a*) attached to the saturated hetero ring, confirming the preference for a conformation in which the ArH-9 atom is situated "above" the plane of the phenyl ring and near to it. This conformation is also indicated by the upfield shift of the C-8 methoxy signal.

The configurations of the C-1 and C-10 atoms in the β-lactams **12***a–f* and **13** remain to be elucidated; this is hampered by the fact that the thiazepine ring may assume several conformations, differing according to the substitution.

In determining the steric structures of the diastereomeric pair **12***e–f*, it is helpful to start with the ^1H nmr data, since there are

TABLE 1. Infrared data (KBr, cm^{-1}) and ^1H nmr chemical shifts[a] ($CDCl_3$, δ_{TMS} = 0 ppm) for compounds **12***a–f* and **13**

Compound	ν C=O band	CH_2 (3, 4) 4dd (4 × 1H)[b]	OCH_3 (7, 8) 2s (2 × 3H)	H-10 s(1H)	ArH-6 s(1H)	ArH-9 s(1H)	ArH (1Ph, 10Ph) 2m/4m (5H/10H)
12*a*	1745	2.77, 2.88 3.46, 4.58	3.92, 4.00	5.35	7.05	7.12	6.73,[c] 7.0–7.3
12*b*	1760	2.76, 2.84 3.41, 4.45	3.48, 3.88	5.76	7.03[e]	6.43	6.68,[c] ≈7.02,[d,e] 7.19,[c] ≈7.38
12*c*	1771	2.74, 2.85 3.43, 4.46	3.92, 3.95	5.53	6.82	7.10	≈6.95,[c] ≈7.35[d]
12*d*	1784	2.67, 2.89 3.38, 4.19	3.92[e]	—	6.86	6.94	≈7.25,[c] ≈7.40[d]
12*e*	1774	2.70, 2.96 3.30, 4.36	3.94, 4.00	—	7.04	7.33	6.87,[c] 7.10,[f] 7.15,[g] 7.45[c]
12*f*	1778	2.70, 2.91 3.53, 4.36	3.43, 3.77	—	6.73	6.03	7.15,[d] 7.3–7.5[h]
13	1770 1753	3.32, 3.46 3.71, 4.50	4.01, 4.07	5.30	7.74	7.32	6.80,[c] 7.05–7.2

[a]For coupling constants, see Table 2.
[b]Assignments, in order of increasing downfield shifts, are: δ H-4*e*, δ 4′*a*, δ H-3′*a*, δ H-3*e* (**12***a–c*), δ H-4′*a*, δ H-4*e*, δ H-3*e*, δ H-3′*a* (**12***d–f*), δ H-4*e*, δ H-3′*a*, δ H-4′*a*, δ H-3*e* (**13**).
[c]H-2′,6′ (2H).
[d]H-3′,4′,5′ (3H).
[e]Two coalesced signals.
[f]H-3′,5′ (2H).
[g]4H.
[h]7H.

TABLE 2. Geminal and vicinal proton–proton coupling constants for compounds **12***a–b* and **13** (Hz)

Compound	^2J(4,4′)	^2J(3,3′)	^3J(3′,4′)	^3J(3′,4)	^3J(3,4′)	^3J(3,4)
12*a*	14.2	10.9	11.6	2.9	2.9	2.9
12*b*	14.4	13.8	7.8	3.6	3.4	3.6
12*c*	14.5	13.7	11.0	3.2	3.1	3.3
12*d*	15.0	13.3	9.0	4.2	4.0	5.4
12*e*	14.6	13.4	8.0	4.0	3.5	6.9
12*f*	15.0	13.4	9.5	4.5	4.0	4.9
13	14.5	14.5	11.8	3.2	2.9	3.2

no significant differences either in the ir frequencies or in the chemical shifts of the carbon resonance signals. On the other hand, in the ^1H nmr spectrum of **12***f* both methoxy signals and also the H-6 and H-9 singlets, mainly one of each, reveal very considerable upfield shifts. The two larger shifts amount to about −0.5 and −1.0 ppm. This is indicative of a configuration and conformation in which the C-10 phenyl ring, occupying different positions in the diastereomers, has come near to the methoxy groups. This steric structure is possible only when the C-1 and C-10 phenyl rings are in the *trans* position, i.e. if the relative configuration is 1*R*,10*S* (1*S*,10*R*). Further evidence for this is given in the spectrum of **12***e* by the higher shielding of some of the aromatic hydrogens, indicating that the two rings in this compound are nearer to each other, i.e. in the *cis* position relative to the β-lactam ring. In view of the data listed in Table 1, **12***b* and **12***f* have analogous structures (the C-1 phenyl and C-10 phenoxy groups are in the *trans* position), whereas the structures of the β-lactams **12***a,c,d* and **13** are identical with that of isomer **12***e*.

Information about the conformations is obtained primarily from the vicinal proton–proton coupling constants of the methylene groups (Table 2). As shown by molecular models,

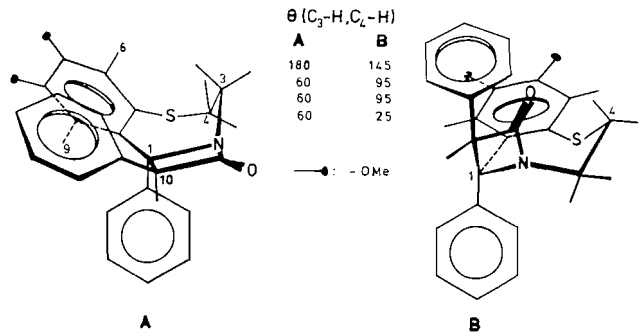


FIG. 1. The possible conformations of compounds **12***a–c* (A) and **12***d–f* (B), respectively.

two sterically favored, relatively stable conformations are possible (Fig. 1). In one of these (**A**), the thiazepine ring is in a boat-like form; the β-lactam ring is attached *quasi-equatorially*, and the dihedral angles of the methylene hydrogens are about 180, 60, 60, and 60°. In the other conformation (**B**), there is a chair-like seven-membered heterocycle (in which C-1 and C-4 are situated out of the plane of the other five atoms constituting the ring), and a *quasi-axially* annelated β-lactam ring is coupled

TABLE 3. The ^{13}C nmr chemical shifts ($\delta_{TMS} = 0$ ppm) for compounds **12***a–f* and **13** in $CDCl_3$ solution at 20.14 MHz

Compound	C-1	C-3	C-4	C-5a	C-6,9	C-7	C-8	C-9a	C-10	OCH_3(7,8)	C-1′	C-2′,3′,5′,6′	C-4′	C=O
12*a*	74.4	42.3	33.0	126.8	115.3 118.6	148.3[a]	148.6[a]	138.3[b]	66.8	56.2 56.6	137.6[b]	127.8[c] 128.0 128.5[d]	127.3 128.5[d]	167.3
12*b*[e]	76.5[f]	42.2	32.4	126.8	114.1 117.4	148.0[a]	148.3[a]	136.4[b]	91.6	55.8 56.0	135.6[b] 157.6[g]	118.8[g] 128.7 128.1[c] 129.5	123.5[g] 128.1[c]	165.7
12*c*[e]	74.8	43.2	32.7	127.1	114.0 118.2	148.8[c]	136.2[d]	67.6	56.3 56.7	136.2[d]		128.3 128.5	128.6	163.4
12*d*	81.4	43.7	31.6	126.9	115.1 116.4	146.9	148.7	136.7	91.4	55.9 56.3	129.3[b]	128.4[c]	129.2[b]	162.1
12*e*[e]	80.0	43.0	32.4	127.8	116.1 118.4	147.0[a]	148.5[a]	137.8[b]	84.1	56.1 56.7	130.6[g] 136.3[b]	128.2 128.4[h] 128.9[c]	128.4[h] 128.9[c]	165.8
12*f*[e]	86.1	43.8	32.0	127.5	114.8 117.3	146.5	148.0	138.2	84.3	56.0[c]	129.0[g] 135.7	128.0[d] 128.1 129.7	128.7 128.9	166.2
13[e]	75.1	34.1[i]	55.1[i]	133.2[a]	112.4 115.2	148.7	152.2	133.1[a]	70.1	56.6 56.8	128.5[c,g] 136.7	127.3[b] 127.4[b] 128.0[b] 128.4[b]	127.9[b] 128.5[c,b]	166.7

[a,b]Assignments may be reversed.
[c,d]Two overlapping lines.
[e]Assignments were proved by DEPT measurements.
[f]Measured in DMSO-d_6 solution (in $CDCl_3$ this line is hidden by the triplet of the solvent).
[g]Phenyl in position 10.
[h]Three overlapping lines.
[i]These assignments are due to α and β effects of the SO_2 substituent.

to it. (The C-H,C-H dihedral angles of the C-3 and C-4 methylene groups are approximately 145, 95, 95, and 25°.) In this more strained skeletal structure, the substituent in the position *trans* to the C-1 phenyl group is sterically favored. The distance between H-9 and the C-1 phenyl group is increased. It is therefore obvious that compounds **12***d–f* have the **B** conformation, whereas for the analogs **12***a*,*c* and **13**, which have no C-10 substituent in the position *trans* to the C-1 phenyl group, the preferred conformation is the boat-like form **A**. In **12***b*, with *trans* C-1 and C-10 substituents in the postulated configuration, the phenoxy group can avoid steric hindrance through rotation about the C_{10}—O—C_{aryl} chain. Consequently, the predominant conformer is **A**. This is indicated by the higher value of the ^3J(H-3′,H-4′) coupling constant and the lower value of its ^3J(H-3,H-4) counterpart in compounds **12***a–c* and **13**.

Evidence of the conformational difference is furnished by the switchover of the relative chemical shifts of the methylene proton pairs. In **12***a–c* and **13** the usual relations δ H-3*e* > δ H-3′*a* and δ H-4*e* < δ H-4′*a* were observed (it is characteristic of sulfur-containing saturated heterocycles (14*b*) that the sequence of shifts of the C-4 methylene hydrogens is opposite in direction to that for the cyclohexane derivatives, i.e. the *equatorial* proton is more shielded than its *axial* counterpart); in the C-10 disubstituted analogs, just the opposite sequence is found. This is probably due to the anisotropic effect of the β-lactam ring, which increases the shielding around H-4′*a* and decreases it around H-3*e*, the chair-like conformation of the thiazepine ring. The assignments given in Table 1 are based partly on a consideration of the expected substituent effects, and partly on the magnitudes of the coupling constants.

The preferred conformations of compounds **14–16** are supported by the broadening and downfield shifts of some of the ^1H nmr signals. In the spectrum of **14**, the C-8 methoxy signal is found at 3.63 ppm, upfield by about 0.25 ppm in comparison with the average shifts in the other compounds. The ArH-9 singlet is at 6.22 ppm, i.e. in the same direction, but with a very markedly larger shift and broadened. This strongly suggests a predominant conformation in which the benzoyl group is near to the C-8 methoxy group and the ArH-9 atom. In one of the rotamers, the aromatic ring exerts an anisotropic shielding effect on this group and atom; this is the reason why the upfield shifts appear, while the broadening of the signal is caused by the slow interconversion of the rotational isomers. In this conformation, the ethylidene group is *quasi-axial* relative to the hetero ring; in the *N*-benzoyl substituent, the phenyl ring and the amide group are not coplanar. This is evidenced by the observation that the signals of the phenyl *ortho* hydrogens are not separated in the downfield direction from the signals of the *meta* and *para* protons, as generally occurs in benzoyl compounds, due to the anisotropic effect of a coplanar carbonyl group (14*c*).

The conformation of **15** is analogous to that of **14**; the relative positions of the benzylidene ring to the C-8 methoxy group and to the ArH-9 atom are also quite similar; accordingly, similar upfield shifts of these signals are found, and there is a broadening of the latter, due to the hindered amide rotation.

The combined anisotropic effect of the two phenyl groups in compound **16** results in anomalous upfield shifts of the corresponding signals; that of the 8-methoxy group is found at 3.13 ppm, i.e. shifted by about −0.8 ppm as compared with the usual value for these compounds; the very broad ArH-9 signal is at 5.50 ppm, the chemical shift being about 1.5 ppm smaller

than the average. This is evidence of the analogous conformation; at the same time the *E*-configuration about the olefin bond in compounds **15** and **16** is shown, in which the phenyl ring of the benzylidene group is situated in the direction of the fused veratryl ring, and the olefin hydrogen toward the benzoyl group.

Experimental

The ir spectra were run in KBr discs on a Perkin–Elmer 125 (**3**, **4***a–c*, **5***c*, **8–10**, **11***b*, and **15**) or an Aspect 2000 computer-controlled Bruker IFS-113v-FT spectrometer (all other compounds).

The nmr spectra were recorded in 5- or 10-mm tubes at room temperature on a Varian EM-60 (**3**, **4***a–c*, **5***a–c*, **8**, **11***b*, and **15**) or a Bruker WM-250 (all others) instrument (^{1}H) at 60 and 250 MHz, respectively, and on a WP-80-SY FT spectrometer controlled by an Aspect 2000 computer at 20.14 MHz (^{13}C) in $CDCl_3$ or DMSO-d_6 solution, using the deuterium signal to the solvent as the lock and TMS as internal reference. The most important measuring parameters for the FT mode were as follows: sweep width: 5 kHz; pulse width: 1 (^{1}H) or 3.5 (^{13}C) μs (ca. 20° or 30° flip angle); acquisition time 1.64 s; number of scans: 16 or 2^{10}–2^{16}; computer memory: 16K; Lorentzian exponential multiplication for signal-to-noise enhancement (LB 0.7 or 1.0 Hz) and complete proton noise decoupling (ca. 1.5 W) for ^{13}C measurements were applied.

DEPT experiments (16) were performed (for compounds **12***b*, *c*, *e*, *f* and **13**) in a standard way (17), using only the θ = 135° pulse to separate the CH/CH_3 and CH_2 lines phase "up" and "down", respectively. Typical acquisition data were number of scans: 128–2048 K; relaxation delay for proton 3 s; 90° pulse width: 10.8 and 22.8 μs for ^{13}C and ^{1}H, respectively. The estimated value for J(C,H) resulted in a 3.7 ms delay for polarization.

Spectral data on the β-lactams **12***a–f* and **13** are given in Tables 1–3; parameters on the other structures are listed separately below.

Melting points are uncorrected.

2′-Aminoethyl-3,4-dimethoxyphenyl sulfide hydrochloride **3**

Sodium 3,4-dimethoxythiophenolate (19.22 g; 100 mmol) was added to a solution of 2-bromoethylamine (12.4 g; 100 mmol) in dry benzene (100 mL). The mixture was stirred and refluxed for 1 h, then extracted with 5% NaOH solution (50 mL), and the benzene phase was dried (Na_2SO_4) and evaporated to dryness. The residue was dissolved in ethanol (15 mL) and ethanol (20 mL) saturated with HCl was added. Compound **3** precipitated as colorless crystals (18.48 g; 74%), mp 175–176°C (EtOH); ir: ν N^+H: 3200–2300, ≈1990 cm^{-1}; ^{1}H nmr (D_2O): CH_2: 3.30 s (4H); OCH_3: 3.90 s (6H); ArH-5: 6.90 d (8 Hz, 1H); ArH-2,6: ≈7.1 m (2H). *Anal.* calcd. for $C_{10}H_{16}NO_2S$: C 48.09, H 6.46, N 5.61; found: C 48.11, H 6.85, N 5.22%.

2′-Acetaminoethyl-3,4-dimethoxyphenyl sulfide **4**a

Compound **3** (2.5 g; 10 mmol) was refluxed in acetic anhydride for 2 h. The mixture was poured into water and extracted with benzene. The extract was washed with dilute Na_2CO_3 solution and then with dilute H_2SO_4 and water, dried (Na_2SO_4), and evaporated. The residue was crystallized from CCl_4 to give colorless needles (1.66 g; 65%), mp 82–83°C. *Anal.* calcd. for $C_{12}H_{17}NO_3S$: C 56.44, H 5.53, N 5.49; found: C 56.59, H 5.72, N 5.60%.

3,4-Dimethoxyphenyl-2′-phenylacetaminoethyl sulfide **4**b

Compound **3** (2.5 g; 10 mmol) was dissolved in ice-water (20 g) and, with continuous stirring, phenylacetyl chloride (2 mL) and then a solution of NaOH (1.1 g NaOH in 5 mL of water) were added dropwise. The mixture was extracted with benzene, and the extract was dried (Na_2SO_4) and evaporated. The residue crystallized. Recrystallization from methanol gave colorless needles (2.92 g; 88%), mp 99–100°C. *Anal.* calcd. for $C_{18}H_{21}NO_3S$: C 65.23, H 6.39, N 4.23; found: C 65.62, H 6.73, N 4.29%.

2′-Benzoylaminoethyl-3,4-dimethoxyphenyl sulfide **4**c

Compound **3** (2.5 g; 10 mmol) was dissolved in pyridine (10 mL). Benzoyl chloride (1.7 mL) was added with stirring, and the mixture was allowed to stand for 30 min. It was then poured into ice-cold dilute H_2SO_4 and the crystals that separated were collected by filtration (2.85 g; 90%); colorless prisms, mp 108–109°C (MeOH); ir: ν NH: 3310 (**4***a*), 3270 (**4***b*), 3380 (**4***c*); amide-I: 1635, 1640, 1650 cm^{-1}; ^{1}H nmr: $COCH_3$ (**4***a*): 1.93 s (3H); SCH_2: 2.95 t (2H, **4***a*), 2.90 t (2H, **4***b*), 3.03 t (2H, **4***c*); NCH_2: 3.45, 3.35, 3.60 q (2H); $PhCH_2$ (**4***b*): 3.50 s (2H); OCH_3: 3.83, 3.86 2s (2 × 3H, **4***a*), 3.80 s (6H, **4***b*), 3.78 s (6H, **4***c*); NH: ≈6.2 br s (1H, **4***a*), ≈6.1 br s (1H, **4***b*), ≈7.0 m (overlapped with the ArH, **4***c*); ArH-5: 6.78, 6.75, 6.75 d (8 Hz, 1H); ArH-2: 6.90, 6.85, 6.93 d (2 Hz, 1H); ArH-6: 6.95, 6.90, 6.98 dd (1H); Ar (Ph): 7.20 ≈s (5H, **4***b*); ArH-3′,5′ (Ph): ≈7.4 m (3H); ArH-2′,6′ (Ph): ≈7.7 m (2H, **4***c*). *Anal.* calcd. for $C_{17}H_{19}NO_3S$: C 64.33, H 6.03, N 4.41; found: C 64.01, H 6.17, N 4.70%.

2,3-Dihydro-7,8-dimethoxy-5-methyl-1,4-benzothiazepine **5**a

A mixture of compound **4***a* (10.2 g; 40 mmol) and $POCl_3$ (15 mL) was heated on a steam bath for 1 h. The reaction mixture was decomposed in ice-water, made alkaline with Na_2CO_3, and extracted with benzene. The extract was reextracted with 10% HCl (100 mL). The acid phase was neutralized with Na_2CO_3 and extracted with benzene. After drying (Na_2SO_4), the benzene solution was evaporated. The pale-yellow oily residue was dissolved in ethanol, and **5***a* was precipitated from the solution as yellow crystals of the picrate (1.55 g; 8.3%), mp 195–197°C (dec.). The base liberated from the picrate was a pale-yellow, slowly crystallizing oil. Recrystallization from petroleum ether yielded a product melting at 100–102°C, in all respects identical with the compound synthesized in a different way (2).

5-Benzyl-2,3-dihydro-7,8-dimethoxy-1,4-benzothiazepine **5**b

A mixture of **4***b* (2.31 g; 10 mmol) and $POCl_3$ (3 mL) was heated on a steam bath for 1 h. The mixture was treated with ice-water, made alkaline with Na_2CO_3, and extracted with benzene. The organic phase was dried (Na_2SO_4) and concentrated. The residue was dissolved in ethanol (2 mL) and **5***b*·HCl was precipitated, by the addition of ethanol saturated with HCl, as pale-yellow crystals (0.32 g; 14.7%), mp 195–196°C. *Anal.* calcd. for $C_{18}H_{20}ClNO_2S$: C 61.79, H 5.76, Cl 10.14; found: C 62.18, H 6.09, Cl 10.66%.

The *picrate* was prepared as yellow crystals (EtOH), mp 197–199°C (dec.).

The base liberated from **5***b*·HCl was a viscous oil. *Anal.* calcd. for $C_{18}H_{19}NO_2S$: C 68.98, H 6.11, N 4.47; found: C 69.10, H 6.35, N 4.60%.

2,3-Dihydro-7,8-dimethoxy-1,4-benzothiazepine **5**c *and 2′-chloroethyl-3,4-dimethoxyphenyl sulfide* **7**

Compound **4***c* (9.51 g; 30 mmol) and $POCl_3$ (11 mL) were heated in a steam bath for 3 h. The mixture was poured into ice-water (150 mL) and extracted with benzene. The extract was dried (Na_2SO_4) and the solvent was evaporated. Fractional distillation of the oily residue in a water-pump vacuum gave benzonitrile (1.55 g), and 2′-chloroethyl-3,4-dimethoxyphenyl sulfide (3 g); $n_\alpha^{20°}$ 1.5816. *Anal.* calcd. for $C_{10}H_{13}ClO_2S$: C 51.60, H 5.63, Cl 15.24; found: C 51.76, H 5.53, Cl 15.45%.

The acidic aqueous solution was made alkaline and extracted with benzene. After drying (Na_2SO_4), the solvent was evaporated and the residue was crystallized from ethanol to give colorless prisms of **5***c* (3.3 g; 36.7%), mp 167–168°C. *Anal.* calcd. for $C_{17}H_{17}NO_2S$: C 68.20, H 5.73, N 4.68; found: C 69.09, H 6.03, N 4.89%.

The *picrate* crystallized from ethanol as a yellow product, mp 238–240°C (dec.); ^{1}H nmr: $COCH_3$ (**5***a*): 2.36 s (3H); CH_2: 3.50 s (4H, **5***a*), 3.47, and 3.56 2m (2 × 2H, **5***b*), ≈3.65 AA′BB′-type m (4H) with close A and B parts (**5***c*); OCH_3: 3.90 s (6H, **5***a*), 3.73 and 3.84 2s (2 × 3H, **5***b*), 3.73 and 3.82 2s (2 × 3H, **5***c*); $PhCH_2$ (**5***b*): 4.01 s (2H); ArH-6: 6.80, 6.95, 7.08 s (1H); ArH-9: 7.00, 6.63, 6.60 s (1H); ArH(Ph): 7.1–7.3 m (5H, **6***b*), 7.2–7.7 m (5H, **5***c*). *Anal.* calcd. for $C_{23}H_{20}N_4O_9S$: C 52.27, H 3.82, N 10.60; found: C 52.02, H 3.88, N 10.66%.

2′-Chloroethyl-3,4-dimethoxyphenyl sulfide **7**

3,4-Dimethoxythiophenol (1.7 g; 10 mmol) was dissolved in 1,2-dichloroethane (10 mL). The solution was refluxed under a nitrogen protecting atmosphere while a solution of $NaOCH_3$ (10 mmol)

in methanol (10 mL) was added dropwise. The mixture was refluxed for 3 h. It was then diluted with water and extracted with $CHCl_3$. The extract was washed with $NaHCO_3$ solution, dried (Na_2SO_4), and evaporated. The oily residue was distilled, in the vacuum of a water pump, on an air bath at 125°C. The product was a colorless oil (1.6 g; 70%), $n_\alpha^{20°}$ 1.5808, in all properties identical with compound **7** isolated from the reaction mixture in the preparation of **5***c*; ^{1}H nmr: CH_2: 3.11, 3.58 AA'BB'-type m (4H); OCH_3: 3.87, 3.88 2s (2 × 3H); ArH-5: 6.81 d (8.5 Hz, 1H); ArH-2: 6.97 d (2.0 Hz, 1H); ArH-6: 7.03 dd (1H); ^{13}C nmr: SCH_2: 38.0; $ClCH_2$: 42.4; OCH_3: 56.01, 56.05; C(Ar)-2: 112.3; C(Ar)-5: 116.4; C(Ar)-1: 125.1; C(Ar)-6: 125.4; C(Ar)-3,4: 149.5, 149.6.

2,3-Dihydro-7,8-dimethoxy-4-methyl-5-phenyl-1,4-benzothiazepinium iodide ***8***

Compound **5***c* (0.75 g; 2.5 mmol) was dissolved in CH_3CN (5 mL). CH_3I (0.4 mL) was added and the mixture was refluxed for 1 h. On cooling, crystals of **8** separated (0.72 g; 65.5%). Recrystallization from CH_3CN gave a product with mp 204–205°C (dec.); ^{1}H nmr: N^+CH_3: 3.67 s (3H); OCH_3: 4.00, 4.05 2s (2 × 3H); CH_2: ≈4.05 (overlapped by the OCH_3 singlets), 4.45, AA'BB'-type m (4H); ArH-9: 6.60 s (1H); ArH-6: 7.20 s (1H); ArH(Ph): ≈7.65 m (5H). *Anal.* calcd. for $C_{18}H_{20}INO_2S$: C 48.99, H 4.57, N 3.17; found: C 48.80, H 4.82, N 3.16%.

2,3-Dihydro-7,8-dimethoxy-5-phenyl-1,4-benzothiazepine 1-oxide ***9***

A solution of **5***c* (1 g; 3.3 mmol) in methanol (40 mL) was stirred at room temperature for 3 days with a solution of $NaIO_4$ (0.7 g) in water (10 mL). After dilution with water, the precipitate was filtered off. Recrystallization from methanol (3 mL) gave colorless prisms (0.67 g; 63.8%), mp 157–158°C; ir: ν SO: 1065 cm^{-1} (the strongest band of the ir spectrum); ^{1}H nmr: CH_2: 3.10 dd (1H), 3.44 dt (1H), ≈4.1 (1H, overlapped by one of the OCH_3 singlets), 4.63 dt (1H); OCH_3: 3.83, 4.07 2s (2 × 3H); ArH-9: 6.75 s (1H); ArH-3',5' (Ph): 7.4 m (3H); ArH-6: 7.53 s (1H); ArH-2',6' (Ph): 7.60 ≈d (2H). *Anal.* calcd. for $C_{17}H_{17}NO_3S$: C 64.74, H 5.44, N 4.44; found: C 64.56, H 5.67, N 4.19%.

The *picrate*, yellow crystals from ethanol, had mp 210–211°C (dec.). *Anal.* calcd. for $C_{23}H_{20}N_4O_{10}S$: C 50.73, H 3.70, N 10.29; found: C 50.89, H 3.98, N 10.58%.

2,3-Dihydro-7,8-dimethoxy-5-phenyl-1,4-benzothiazepine 1,1-dioxide ***10***

Compound **5***c* (1 g; 3.3 mmol) was dissolved in a mixture of dioxan (5 mL) and acetic acid (5 mL). A solution $KMnO_4$ (3 g) in water (20 mL) was added, in portions, to the stirred mixture and stirring was continued for 1 h. H_2O_2 was added dropwise until dissolution of the MnO_2 was complete. The solution was diluted with water (100 mL), made alkaline with Na_2CO_3, and stirred for 1 h more. It was then extracted with benzene, and the extract was dried (Na_2SO_4) and evaporated to dryness. The residue was crystallized from a small amount of ethanol as colorless prisms (0.6 g, 54.5%), mp 162–164°C; ir: ν_{as} SO_2: 1315; ν_s SO_2: 1125 cm^{-1}; ^{1}H nmr: OCH_3: 3.79, 4.01 2s (2 × 3H); CH_2: 3.88 s (4H); ArH-9: 6.68 s (1H); ArH-3',5' (Ph): 7.40 m (3H); ArH-6: 7.58 s (1H); ArH-2',6' (Ph): 7.62 d (2H). *Anal.* calcd. for $C_{17}H_{17}NO_4S$: C 61.61, H 5.17, N 4.23; found: C 61.20, H 5.24, N 4.48%.

Picrate: yellow crystals from ethanol, mp 245–246°C (dec.). *Anal.* calcd. for $C_{23}H_{20}N_4O_{11}S$: C 49.28, H 3.60, N 10.00; found: C 49.08, H 3.85, N 9.91%.

5-Benzyl-7,8-dimethoxy-2,3,4,5-tetrahydro-1,4-benzothiazepine ***11***a

Compound **5***b*·HCl (0.35 g; 1 mmol) was dissolved in methanol (25 mL). $NaBH_4$ (0.5 g) was added in portions, and the mixture was allowed to stand overnight. After the addition of water (0.5 mL), the mixture was evaporated to dryness and extracted with ether. The ethereal extract was concentrated and a solution of HCl in ether was added to precipitate **11***a*·HCl as colorless crystals (0.29 g; 82.6%), mp 110–112°C. *Anal.* calcd. for $C_{18}H_{22}ClNO_2S$: C 61.44, H 6.30, Cl 10.08, N 3.98; found: C 61.11, H 6.60, Cl 10.38, N 3.68%.

The base **11***a* liberated from the hydrochloride was a viscous oil; ^{1}H nmr: NH: 1.80 s (1H); SCH_2: 2.68 m (2H); CH_2(Ph): 3.0–3.2 m (2H); NCH_2: 3.3–3.4 m (2H); NCH: 4.59 dd (9.6 and 5.6 Hz, 1H); ArH-9: 6.77 s (1H); ArH-6: 7.08 s (1H); ArH(Ph): ≈7.25 ≈s (5H); ^{13}C nmr: C-4: 35.4; C-3: 40.0; CH_2Ph: 49.9; OCH_3: 55.9 (two overlapping lines); C-1: 61.4; C-6: 111.2; C-9: 117.0; C-4': 126.0; C-5a: 126.9; C-3',5': 128.2; C-2',6': 128.9; C-9a: 139.2; C-1': 140.3; C-7: 147.1; C-8: 148.5. *Anal.* calcd. for $C_{18}H_{21}NO_2S$: C 68.54, H 6.71, N 4.44; found: C 68.70, H 6.95, N 4.20%.

7,8-Dimethoxy-5-phenyl-2,3,4,5-tetrahydro-1,4-benzothiazepine ***11***b

Compound **5***c* (1.5 g; 5 mmol) was dissolved in methanol (50 mL). $NaBH_4$ (1 g) was added in small portions, and the mixture was left to stand overnight. Water (1 mL) was then added, and the mixture was evaporated to dryness and extracted with benzene. The extract was concentrated, whereupon the residue crystallized to give colorless prisms (1.45 g; 96%), mp 145–146°C (from methanol); ir: ν NH: 3340 cm^{-1} (weak); ^{1}H nmr: NH: 1.70 s (1H); CH_2: ≈2.7 m (2H), ≈3.4 m (2H, overlapped by one of the OCH_3 singlets); OCH_3: 3.50, 3.82 2s (2 × 3H); NCH: 5.60 s (1H); ArH-9: 6.10 s (1H); ArH-6: 7.05 s (1H); ArH(Ph): 7.30 ≈s (5H). *Anal.* calcd. for $C_{17}H_{19}NO_2S$: C 67.74, H 6.35, N 4.65; found: C 67.41, H 6.57, N 4.79%.

The **11***b*·HCl was precipitated from benzene with ether containing HCl; mp 102–105°C. *Anal.* calcd. for $C_{17}H_{20}ClNO_2S$: C 60.43, H 5.97, Cl 10.49, N 4.15; found: C 60.27, H 6.27, Cl 10.52, N 4.16%.

General procedure for preparation of β-lactams ***12***a–f *and* ***13***

The appropriate acid chloride (5 mmol) was added to a solution of **5***c* (1.5 g; 5 mmol) in benzene (30 mL). The mixture was refluxed and, with continuous stirring, TEA (0.5 g; 5 mmol) in benzene (30 mL) was added dropwise during 1 h. The crystalline TEA·HCl was removed by filtration, the filtrate was evaporated, and the residue was crystallized from ethanol to yield colorless crystals (cf. Table 4).

Separation of diastereomers ***12***e *and* ***12***f

The reaction was effected according to the general procedure. The residue was dissolved in ethanol and, after the mixture had stood for 3 h, the precipitated crystals of **12***e* were collected by filtration. The mother liquor was stored in a refrigerator at 5°C overnight, whereupon compound **12***f* crystallized.

Synthesis of compounds ***13*** *by oxidation of* ***12***a

Compound **12***a* (1.40 g; 3.3 mmol) was dissolved in acetic acid (20 mL); peracetic acid (15 mL) was added, and the solution was left to stand overnight. The crystals (1.07 g; 71.3%) that separated on dilution with water were filtered off and recrystallized from ethanol; the colorless product had mp 239–240°C and was in all respects identical with compound **13** prepared from **10**.

4-Benzoyl-2,3-dihydro-7,8-dimethoxy-5-methylene-1,4-benzothiazepine ***14***

A solution of TEA (1.01 g; 10 mmol) in benzene (20 mL) was added to **5***a*·HCl (1.75 g; 5 mmol) and, with constant stirring, a solution of benzoyl chloride (0.70 g; 5 mmol) in benzene (20 mL) was added. Stirring was continued for 1 h more. After removal of the TEA·HCl by filtration, the filtrate was evaporated to dryness. The residue crystallized slowly. It was suspended in petroleum ether and filtered off to yield the product (0.35 g; 20.6%), which was recrystallized from benzene; mp 140–142°C; ir: amide-I: 1647, ν C=C(H_2): 1622, ν (=CH_2): 864, 792 cm^{-1}; ^{1}H nmr: SCH_2: 3.23 ≈t (5.8 Hz, 2H); OCH_3: 3.63, 3.84 2s (2 × 3H); NCH_2: 4.21 ≈t (2H); =CH_2: 5.24, 5.38 2 × ≈s (2 × 1H); ArH-9: 6.22 s (1H, broadened due to hindered rotation of the *N*-benzoyl group); ArH-6: 6.76 s (1H); ArH(Ph) ≈7.3 m (5H); ^{13}C nmr: C-4: 31.8; C-3: 50.4; OCH_3: 55.8 (two overlapping lines); C-6: 112.9; =CH_2: 113.3; C-9: 116.0; C-5a: 125.2; C-2',6' and C-3',5': 127.3, 127.4; C-4': 129.0; C-1': 130.5; C-9a: 136.7; C-1 and C-8: 147.3 (two overlapping lines); C-7: 148.9; C=O: 170.8. *Anal.* calcd. for $C_{19}H_{19}NO_3S$: C 66.84, H 5.61, N 4.10; found: C 66.56, H 5.90, N 4.32%.

5-Benzylidene-7,8-dimethoxy-4-dichloroacetyl-2,3-dihydro-1,4-benzothiazepine ***15***

TEA (1.01 g; 10 mmol) in benzene (20 mL) was added to **5***b*·HCl (1.75 g; 5 mmol). With constant stirring, a solution of dichloroacetyl

TABLE 4. Physical and analytical data for compounds **12***a–f* and **13**

Compound	Yield (%)	Melting point (°C)	Molecular formula Mol. Wt.	Analysis Calculated C	H	N	S	Found C	H	N	S
12*a*	57.6	205–206	$C_{25}H_{23}NO_3S$ 417.50	71.92	5.55	3.36	7.68	72.20	5.81	3.25	7.93
12*b*	89.1	176–177	$C_{25}H_{23}NO_4S$ 433.50	69.26	5.35	3.23	—	69.08	5.32	3.19	—
12*c*	92	220–221	$C_{19}H_{18}ClNO_3S$ 375.86	60.71	4.83	3.73	—	60.79	4.81	3.85	—
12*d*	95	192–193	$C_{19}H_{17}Cl_2NO_3S$ 410.31	55.61	4.18	3.41	—	55.42	44.6	3.54	—
12*e*	87	217–218	$C_{25}H_{22}ClNO_3S$ 451.96	66.43	4.91	3.10	—	66.73	5.04	3.23	—
12*f*	8	209–210	$C_{25}H_{22}ClNO_3S$ 451.96	66.43	4.91	3.10	—	66.56	5.02	3.01	—
13	40.4	239–240	$C_{25}H_{23}NO_5S$ 449.50	66.80	5.16	3.12	7.13	67.08	5.07	3.27	7.49

chloride (0.74 g; 5 mmol) in benzene (20 mL) was added and stirring was continued for 1 h. After removal of the TEA·HCl by filtration, the benzene solution was evaporated to dryness in vacuum. Recrystallization of the residue from ethanol gave pale-yellow crystals (1.2 g; 56.6%), mp 160–161°C (dec.); ir: amide-I: 1685 cm^{-1}; ^1H nmr: SCH_3: 3.25 t (6 Hz, 2H); OCH_3: 3.53, 3.90 2s (2 × 3H); NCH_2: ≈4.3 ≈t (2H, broad due to hindered rotation of the amide group); $CHCl_2$: 6.33 s (1H); ArH-9: 6.60 s (1H, br); =CH(Ph): 6.85 s (1H); ArH-6: 6.90 s (1H); ArH(Ph): 7.27 ≈s (5H). *Anal.* calcd. for $C_{20}H_{19}Cl_2NO_3S$: C 56.61, H 4.51, Cl 16.71, N 3.30; found: C 56.23, H 4.80, Cl 17.00, N 3.57%.

4-Benzoyl-5-benzylidene-2,3-dihydro-7,8-dimethoxy-1,4-benzothiazepine ***16***

Compound **5***b* (0.70 g; 2 mmol) was dissolved in benzene (15 mL). TEA (0.20 g) and then, with constant stirring, a solution of benzoyl chloride (0.28 g; 2 mmol) in benzene (10 mL) were added, and the mixture was stirred for 1 h more. The precipitated TEA·HCl was removed by filtration, the filtrate was evaporated in vacuum, and the residue was crystallized from a mixture of benzene and petroleum ether to give colorless crystals, mp 165–166°C; ir: amide-I: 1655 cm^{-1}; ^1H nmr: SCH_2: 3.19 ≈t (2H); OCH_3: 3.13, 3.84 2s (2 × 3H); NCH_2: br t (2H); ArH-9: 5.50 br s (1H); =CHPh: 6.82 s (1H); ArH-6: 6.89 s (1H); ArH^o(=CHPh): ≈7.02 dd (2H); $ArH^{m,p}$(=CHPh): ≈7.13 m (3H); $ArH^{m,p}$(COPh): ≈7.27 m (3H); ArH^o(COPh): 7.36 m (2H). *Note*: broadening of the NCH_2 and ArH-9 signals due to hindered rotation of the amide group; ^{13}C nmr: C-4: 31.8; C-3: 53.1; OCH_3: 55.3, 55.8; C-6: 113.7; C-9: 114.5; C-5a: 126.1; C-1′(COPh): 127.6 (two overlapping lines), C-2′,3′,4′,5′(=CHPh and COPh): 127.6, 127.9, 128.1, and 128.7; C-4′(=CHPh): 129.3; C-1′(=CHPh): 131.4; C-4′(COPh): 132.0; =CH: 134.9; C-9a: 137.2; C-1: 140.3; C-8: 147.0; C-7: 148.4; C=O: 171.0. *Anal.* calcd. for $C_{25}H_{23}NO_3S$: C 71.92, H 5.55, N 3.36; found: C 72.30, H 5.72, N 3.64%.

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