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(11) We were unable to effect the separation of the 15-epimeric racemates of **12** and **16**, consistent with previous findings from these laboratories.[1]
(12) Only the 15-natural[7] congeners **15** and **19** were prepared and tested, although the conjugate addition did afford the esters of both epimeric racemates.
(13) Compound **7** was prepared by a direct extension of the cyclopentenone synthesis of Caton and co-workers.[14] Triethylamine-catalyzed Michael addition of ethyl 2-mercaptoacetate to acrolein, followed by condensation of the resulting aldehyde with 1-morpholinocyclopentene (Aldrich) and isomerization-transesterification (HCl–1-butanol, 100 °C, 2 h), provided **7**: IR (neat) 1745, 1705, and 1645 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.43 (m, 1 H, C=CH), 4.17 (t, 2 H, $-OCH_2CH_2-$, $J$ = 7 Hz), 3.23 (s, 2 H, $-SCH_2COO-$), and 0.95 (t, 3 H, $-CH_2CH_3$, $J$ = 7 Hz); UV (EtOH) 223 nm. Anal. ($C_{14}H_{22}O_2S$) C, H; S: calcd, 11.86; found, 11.31.
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(16) A long-acting bronchial spasm is induced by an injection of 400 $\mu$g/kg, followed by perfusion of 4 $\mu$g/kg/min of pilocarpine. The increase of the airway's resistance must be at least 200–300% of the resting value. After a 15-min control period the compound is administered by means of an ultrasonic aerosol device (Monaghan 650). All the parameters are then followed for at least 1 h. The activity of the compound is expressed as percentage of inhibition of the induced spasm. Further details of this method are described by Lulling and co-workers.[17]
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# 3-(3-Substituted prop-1-enyl)cephalosporins[1]

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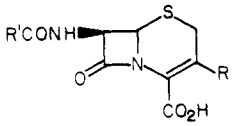
The synthesis of cephalosporin derivatives possessing a 3-substituted prop-1-enyl group at the 3 position is described. This was achieved using the reaction of vinylmagnesium chloride with the 3-formyl derivative 1 to give a vinylcarbinol which readily underwent allylic rearrangements to give the desired side chains. The new derivatives exhibited potent in vitro and in vivo antibacterial activity.

Due to the important role played by cephalosporin antibiotics in current medical practice, considerable effort has been invested in the search for cephalosporin derivatives with improved therapeutic properties. While, as with penicillins, much of the effort involved attaching new acyl groups to the amino group at the 7 position, improvements in activity have also been achieved by varying the substituent at the 3 position.

Early work involved simply replacing the acetoxy group by other groups (A → B), where typically X can be H, alkoxy, acyloxyl, alkyl and arylthio, azido, pyridinium, and many others.[2] Recent work has involved more radical modification at this position (A → C), with Y being H,[3a] $CO_2Me$,[3b] CN,[3c] $CH{=}CHCO_2Me$,[3d] OMe,[3e] Cl,[3e] or NHCOMe[3f] to mention just a few.




A, R = $CH_2OAc$
B, R = $CH_2X$
C, R = Y
D, R = $CH{=}CHCH_2Z$

Our finding that the aldehyde group in the 3-formyl-2-cephem system readily undergoes Grignard reaction with vinylmagnesium chloride to give the 3-[(1-hydroxy)-prop-2-enyl] derivative provided us with an entry into the as yet undescribed 3-(3-substituted prop-1-enyl)cephalosporin system (D) with Z being acetoxy or arylthio, for example. Such a modification involves insertion of a trans olefinic unit (CH=CH) at the 3 position of the conventional cephalosporin (A or B).

**Chemistry.** When the aldehyde 1[4] was allowed to react with an excess of vinylmagnesium chloride at low temperature, the desired vinylcarbinol **2** was obtained in good yield as an approximately equal mixture of isomers. Attempts at inducing **2** to undergo an allylic substitution reaction were rewarded when treatment of **2** in 1:1 THF–acetic acid and a catalytic amount of *p*-TsOH at 40 °C led to the acetoxy derivative **4**. Similarly, treatment of **2** with 1.1 equiv of 5-mercapto-1-methyltetrazole and a catalytic amount of *p*-TsOH in THF at 40 °C led to the thioether **5**. Although *p*-TsOH was preferred as catalyst, other acids such as perchloric and hydrochloric acid were found to be similarly effective. The solvent was found to be an important variable, with THF giving superior results to nonbasic solvents such as $CH_2Cl_2$. The isomeric mixture

Table I. Antibacterial Activity

| Compd | In vitro MIC, μmol/mL[a,g] | | | | | In vivo $PD_{50}$,[h] μmol/kg, S.a.[h] |
|---|---|---|---|---|---|---|
| | S.a.[b] | S.a.[c] | S.p.[d] | E.c.[e] | K.p.[f] | |
| 11 | 1.80 | 0.56 | <0.002 | 28.00 | 1.80 | 1.85 |
| 13 | 1.90 | 0.48 | 0.074 | 60.00 | 1.90 | 3.54 |
| 12 | 0.05 | 0.20 | 0.0016 | 50.00 | 0.80 | 0.30 |
| 14 | 0.20 | 0.10 | 0.013 | 6.58 | 0.05 | 1.69 |

[a] The in vitro antibacterial activities are reported as minimum inhibitory concentrations (MIC's) in mmol/mL. The MIC's were determined in twofold dilutions in a brain heart infusion medium at pH 7.4 by the agar inclusion method. [b] *Staphylococcus aureus*, ATCC 6538P. [c] *Staphylococcus aureus*, ATCC 14154 (penicillin G resistant). [d] *Streptococcus pyogenes*, ATCC 8668. [e] *Escherichia coli*, ATCC 25922-1. [f] *Klebsiella pneumoniae*, ATCC 10031-2. [g] The MIC values of 11–14 against *Proteus vulgaris* ATCC 9484 and *Pseudomonas aeruginosa* ATCC 10145 were >400 mmol/mL. [h] The $PD_{50}$ values are expressed as the total dose of compound in milligrams per killogram which afforded protection to 50% of the mice challenged intraperitoneally with approximately $2 \times 10^3$ organisms per mouse of a *Staphylococcus aureus* Smith culture diluted in 4% hog gastric mucin to produce uniformly lethal infections. Twofold dilutions of each compound were injected subcutaneously in equally divided portions at 1 and 5 h postinfection to four groups of ten mice each. Survivors were observed for 72 h postchallenge and the mean protection dose ($PD_{50}$) was calculated by probit analysis.

of acetates **3**, obtained by treating **2** with 1:1 pyridine–acetic anhydride at 0 °C, served equally well as starting material in the above reactions.

Isomerization of **2** to the primary alcohol **6** was effected in a similar way using 10% aqueous THF with *p*-TsOH as catalyst. Treatment of **6** with 1:1 pyridine–acetic anhydride then yielded the acetate **4**, identical with that obtained via the direct route.

The trans configuration was assigned to the new double bond in **4**, **5**, and **6** on account of a 16-Hz vicinal coupling constant for the olefinic protons in their NMR spectra.

Conversion of **4** and **5** to the corresponding $\Delta^3$ isomers **9** and **10** was effected either by direct equilibration (trace of triethylamine in pyridine) or the two step oxidation–reduction sequence via the sulfoxides **7** and **8**. The esters **9** and **10** were then deprotected using trifluoroacetic acid–anisole to yield the corresponding crude acids which were immediately converted to the sodium salts **11** and **12** using sodium 2-ethylhexanoate. The acetate group of **11** could be displaced by nucleophiles, the reaction proceeding with retention and slightly more readily than the corresponding reaction with sodium cephalothin (**13**). Thus, treatment of **11** in aqueous solution with 5-mercapto-1-methyltetrazole and sodium bicarbonate led to the thioether **12**, identical with that obtained above (see Scheme I).

To serve as models in the biological evaluation of **11** and **12** sodium cephalothin **13** was converted in the usual way to the known tetrazole derivative **14**.

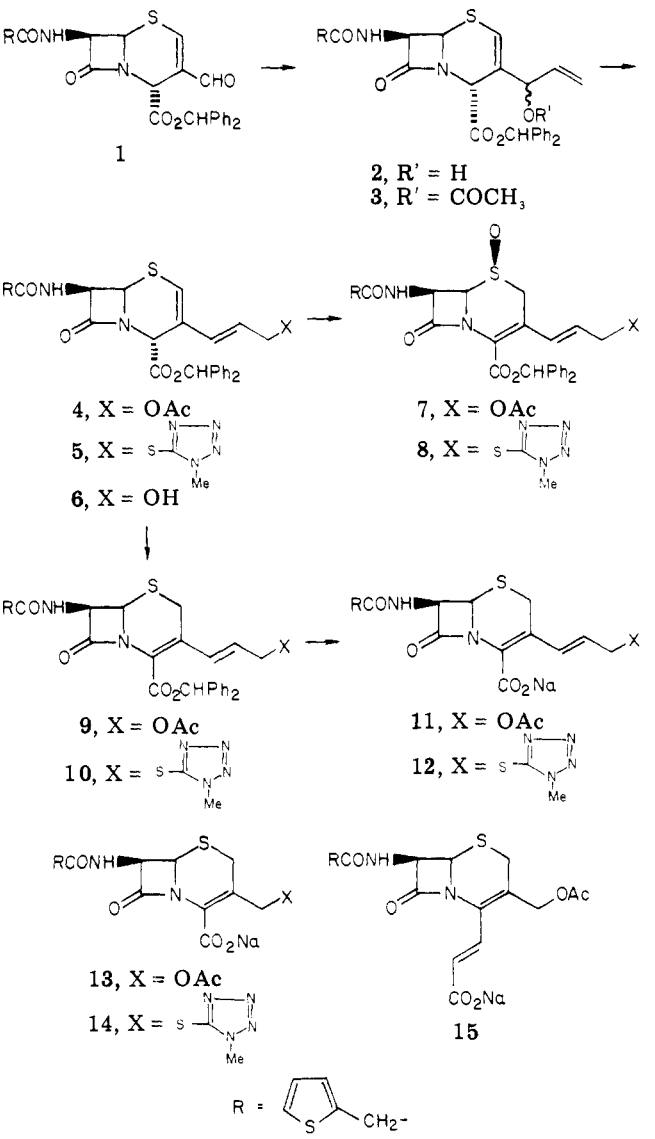
**Biology**. The new derivative (**11**) differs from the important cephalosporin antibiotic cephalothin only by the insertion of a double bond between the 3 position of the dihydrothiazine ring and the acetoxymethyl group, and, hence, a close similarity between the antibacterial activities of these compounds might be expected. The results, presented in Table I, show this to be the case. For the other pair of compounds, the vinylogue **12** performed significantly better than the parent cephem **14** against *Staphylococcus aureus* and *Streptococcus pyogenes* in vitro and against *S. aureus* Smith in vivo. Interestingly, the vinylogue **12** was less effective than **14** against *Escherichia coli* and *Klebsiella pneumoniae* in vitro.

We previously reported[5] the synthesis of the cephalothin vinylogue **15**, which, in contrast with **11**, was essentially inactive. It is noteworthy that the same modification which has little effect on activity when carried out at the 3 position totally destroys it when carried out at the 4 position.

## Experimental Section

Melting points are uncorrected. Infrared spectra were recorded with a Perkin-Elmer 237B spectrometer, and ultraviolet spectra

Scheme I




were determined with a Cary 14 instrument. NMR spectra were obtained with Varian A-60 and HA-100 instruments, and chemical shifts are given in parts per million from $Me_4Si$. Elemental analyses were performed by the Analytical Department at Syntex Research, Institute of Organic Chemistry, and are within ±0.4% of calculated values.

**Diphenylmethyl 3-(1-Hydroxyprop-2-enyl)-7β-[2-(2-thienyl)acetamido]-2-cephem-4-carboxylate (2).** A solution of the aldehyde **1** (2.5 g, 4.8 mmol) in dry THF (50 mL) was stirred under $N_2$ at −70 °C and vinylmagnesium chloride solution (2.5

M in THF, 10 mL, 25 mmol) was added dropwise over 5 min. After 15 min, the cooling bath was removed, pH 7 phosphate buffer solution (50 mL) was added to the vigorously stirred solution, and the mixture was warmed to room temperature. The pH of the mixture was adjusted to 3 using 2 N HCl, and it was then extracted twice with EtOAc. The combined extracts were washed twice with brine, dried ($Na_2SO_4$), and evaporated, giving the alcohol **2** as a pale yellow oil (2.7 g). TLC (silica gel, 95:5 $CH_2Cl_2$–acetone) of the product showed two spots of roughly equal intensities. Separation of a portion of the mixture using thick-layer chromatography provided samples of the diastereoisomers as colorless oils: for isomer 1 (higher $R_f$) NMR ($CDCl_3$) 3.78 (s, 2 H, thiophene methylene), 4.59 (br d, $J$ = 14 Hz, 1 H, *H*-OH), 4.9–5.7 (m, 6 H), 6.36 (br s, 1 H, 2-H), 6.7–7.5 (m, 14 H); for isomer 2 (lower $R_f$) NMR ($CDCl_3$) 3.79 (s, 2 H, thiophene methylene), 4.63 (m, 1 H, C*H*OH), 5.0–5.8 (m, 6 H), 6.25 (s, 1 H, 2-H), 6.8–7.5 (m, 14 H).

**Diphenylmethyl 3-(3-Acetoxyprop-1-*trans*-enyl)-7β-[2-(2-thienyl)acetamido]-2-cephem-4-carboxylate (4).** A solution of the alcohol **2** (3.2 g, 5.9 mmol) in THF (10 mL) and acetic acid (10 mL) was stirred at 40 °C and *p*-toluenesulfonic acid (50 mg, 0.25 mmol) was added. After stirring for 6 h at 40 °C, the mixture was poured into water and extracted three times with EtOAc. The combined extracts were washed (water, sodium bicarbonate solution, and brine), dried ($Na_2SO_4$), and evaporated to give a yellow oil (3.1 g). This was chromatographed on silica gel eluting with $CH_2Cl_2$–acetone (95:5). Fractions homogeneous by TLC were combined to give the acetate **4** as a pale yellow oil (1.5 g, 44%): NMR ($CDCl_3$) 1.98 (s, 3 H, OAc), 3.82 (s, 2 H, thiophene methylene), 4.43 (d, $J$ = 5.5 Hz, 2 H, 3′-$CH_2$), 5.22 (d, $J$ = 4.0 Hz, 1 H, 6-H), 5.25 (s, 1 H, 4-H), 5.52 (dd, $J$ = 4, 8 Hz, 1 H, 7-H), 5.68 (dt, $J$ = 15, 5.5 Hz, 1 H, 2′-H), 6.18 (d, $J$ = 15 Hz, 1 H, 1′-H), 6.30 (s, 1 H, 2-H), 6.65 (d, $J$ = 8 Hz, 1 H, NH), 6.8–7.5 (m, 14 H).

**Diphenylmethyl 3-[3-(1-Methyltetrazol-5-ylthio)prop-1-*trans*-enyl]-7β-[2-(2-thienyl)acetamido]-2-cephem-4-carboxylate (5).** A solution of the alcohol **2** (2.7 g, 4.9 mmol) in THF (30 mL) was stirred at 40 °C and 5-mercapto-1-methyltetrazole (0.6 g, 5.7 mmol) and *p*-toluenesulfonic acid (50 mg, 0.26 mmol) were added. After stirring at 40 °C for 5 h, the mixture was cooled, diluted with water, and extracted twice with EtOAc. The combined extracts were washed (sodium bicarbonate solution and brine), dried ($Na_2SO_4$), and evaporated to give 2.8 g of an orange oil. This was chromatographed on silica gel eluting with $CH_2Cl_2$–acetone (95:5), and fractions homogeneous by TLC were combined to afford the tetrazole **5** as a pale yellow glass (2.1 g, 66%): $[\alpha]_D$ +321° (c 1, $CHCl_3$); UV (EtOH) 248 nm (ε 21 600); IR (KBr) 1780, 1740, 1675 $cm^{-1}$; NMR ($CDCl_3$) 3.80 (s, 3 H, NMe), 3.82 (s, 2 H, thiophene methylene), ~3.8 (2 H, 3′-$CH_2$), 5.2 (m, 2 H, 4-H and 6-H), 5.56 (dd, $J$ = 4, 8 Hz, 1 H, 7-H), 5.7 (dt, $J$ = 16, 7 Hz, 1 H, 2′-H), 6.2 (d, $J$ = 16 Hz, 1 H, 1′-H), 6.27 (s, 1 H, 2-H), 6.51 (d, $J$ = 8 Hz, 1 H, NH), 6.8–7.4 (m, 14 H).

**Diphenylmethyl 3-(3-Hydroxyprop-1-*trans*-enyl)-7β-[2-(2-thienyl)acetamido]-2-cephem-4-carboxylate (6).** A solution of the alcohol **2** (0.5 g, 0.92 mmol) in THF–water (10:1) (10 mL) was stirred at room temperature and *p*-toluenesulfonic acid (50 mg, 0.26 mmol) was added. After stirring for 12 h at room temperature, TLC analysis [silica gel, $CH_2Cl_2$–acetone (9:1)] indicated that a 2:1 mixture of unrearranged alcohol **2** and rearranged alcohol **6** had resulted. The mixture was diluted with water and extracted twice with EtOAc. The combined extracts were washed (sodium bicarbonate solution and brine), dried ($Na_2SO_4$), and evaporated to give 0.45 g of a yellow oil. Chromatography on silica gel eluting with $CH_2Cl_2$–acetone (9:1) gave the alcohol **2** (0.22 g, 44%) and the rearranged alcohol **6** (0.11 g, 22%) as a colorless oil: NMR ($CDCl_3$) 3.79 (s, 2 H, thiophene methylene), 3.96 (br d, $J$ = 5 Hz, 2 H, 3′-$CH_2$), 5.16 (d, $J$ = 4 Hz, 1 H, 6-H), 5.24 (br s, 1 H, 4-H), 5.52 (dd, $J$ = 4, 8.5 Hz, 1 H, 7-H), 5.71 (dt, $J$ = 16, 5 Hz, 1 H, 2′-H), 6.11 (d, $J$ = 16 Hz, 1 H, 1′-H), 6.22 (s, 1 H, 2-H), 6.7–7.5 (m, 15 H).

**Diphenylmethyl 3-(3-Acetoxyprop-1-*trans*-enyl)-7β-[2-(2-thienyl)acetamido]-3-cephem-4-carboxylate 1-Oxide (7).** A solution of the acetate **4** (1.5 g, 2.5 mmol) in $CH_2Cl_2$ (50 mL) was stirred at 0 °C and *m*-chloroperbenzoic acid was added in small portions until optimal conversion to the sulfoxide had occurred as judged by TLC [silica gel, $CH_2Cl_2$–acetone (9:1)] (about 0.5 g, 2.9 mmol, was required). The mixture was evaporated and the residue dissolved in EtOAc and washed (sodium bicarbonate and brine), dried ($Na_2SO_4$), and evaporated. On adding ether to the residue, a white crystalline solid deposited. This was collected by filtration and dried under vacuum to give the sulfoxide **7** as white crystals (0.9 g, 58%): mp 209–211 °C; $[\alpha]_D$ −133° (c 1, $CHCl_3$); UV (EtOH) 302 nm (ε 16 000); IR (KBr) 1780, 1735, 1715, 1650 $cm^{-1}$; NMR ($CDCl_3$) 1.98 (s, 3 H, OAc), 3.07 (d, $J$ = 18 Hz, 1 H, 2-H), 3.81 (s, 2 H, thiophene methylene), 3.92 (d, $J$ = 18 Hz, 1 H, 2-H), 4.45 (d, $J$ = 5 Hz, 1 H, 6-H), 4.52 (d, $J$ = 6 Hz, 2 H, 3′-$CH_2$), 5.88 (dt, $J$ = 16, 6 Hz, 1 H, 2′-H), 6.01 (dd, $J$ = 5, 10 Hz, 1 H, 7-H), 6.8–7.5 (m, 15 H). Anal. ($C_{31}H_{28}N_2O_7S_2$) C, H, N.

**Diphenylmethyl 3-[3-(1-Methyltetrazol-5-ylthio)prop-1-*trans*-enyl]-7β-[2-(2-thienyl)acetamido]-3-cephem-4-carboxylate 1-Oxide (8).** The tetrazole derivative **5** (1.0 g, 1.55 mmol) was oxidized as described above for **4** (about 0.35 g, 1.9 mmol, of *m*-chloroperbenzoic acid was required). The crude product was purified by chromatography on silica gel eluting with $CH_2Cl_2$–acetone (85:15), and fractions homogeneous by TLC were combined to give the sulfoxide **8** as a white crystalline solid (0.6 g, 58%): mp 125–127 °C; $[\alpha]_D$ −204° (c 1, $CHCl_3$); UV (EtOH) 307 nm (ε 20 000); IR (KBr) 1790, 1720, 1680 $cm^{-1}$; NMR ($CDCl_3$) 3.06 (d, $J$ = 19 Hz, 1 H, 2-H), 3.95 (d, $J$ = 19 Hz, 1 H, 2-H), 3.82 (s, 2 H, thiophene methylene), 3.85 (s, 3 H, NMe), 3.92 (d, $J$ = 7 Hz, 2 H, 3′-$CH_2$), 4.47 (d, $J$ = 4.5 Hz, 1 H, 6-H), 5.9–6.3 (m, 2 H, 2′-H and 7-H), 6.8–7.6 (m, 16 H). Anal. ($C_{31}H_{28}N_6O_5S_3$) C, H, N.

**Diphenylmethyl 3-(3-Acetoxyprop-1-*trans*-enyl)-7β-[2-(2-thienyl)acetamido]-3-cephem-4-carboxylate (9).** A solution of the sulfoxide **7** (0.5 g, 0.83 mmol) in DMF (10 mL) was stirred at 0 °C under $N_2$ and stannous chloride (0.5 g, 2.6 mmol) and acetyl chloride (1 mL) were added. The mixture was stirred at 0 °C for 15 min and at room temperature for 20 min. It was then diluted with water and extracted twice with EtOAc, and the combined extracts were washed (water and brine), dried ($Na_2SO_4$), and evaporated to give a yellow oil (0.55 g). This was chromatographed on silica gel eluting with $CH_2Cl_2$–acetone (19:1), and fractions homogeneous by TLC were combined to give the acetate **9** (0.4 g, 82%) as a white crystalline solid: mp 162–164 °C; $[\alpha]_D$ −119° (c 1, $CHCl_3$); UV (EtOH) 299 nm (ε 15 500); IR (KBr) 1770, 1745, 1720, 1675 $cm^{-1}$; NMR ($CDCl_3$) 1.98 (s, 3 H, OAc), 3.47 (br s, 2 H, 2-$CH_2$), 3.81 (s, 2 H, thiophene methylene), 4.52 (d, $J$ = 6 Hz, 2 H, 3′-$CH_2$), 4.97 (d, $J$ = 4.5 Hz, 1 H, 6-H), 5.79 (dd, $J$ = 4.5, 9 Hz, 1 H, 7-H), 5.88 (dt, $J$ = 16, 6 Hz, 1 H, 2′-H), 6.49 (d, $J$ = 9 Hz, 1 H, NH), 6.8–7.5 (m, 15 H). Anal. ($C_{31}H_{28}N_2O_6S_2$) C, H, N.

**Diphenylmethyl 3-[3-(1-Methyltetrazol-5-ylthio)prop-1-*trans*-enyl]-7β-[2-(2-thienyl)acetamido]-3-cephem-4-carboxylate (10). Method A.** The sulfoxide **8** (0.5 g) was reduced and the product purified as described above for the sulfoxide **7**. Obtained was 0.4 g (82%) of the sulfide **10** as a white solid: mp 90–95 °C; $[\alpha]_D$ −158° (c 0.9, $CHCl_3$); UV (EtOH) 301 nm (ε 19 400); IR (KBr) 1785, 1720, 1680 $cm^{-1}$; NMR ($CDCl_3$) 3.4 (m, 2 H, 2-$CH_2$), 3.80 (s, 2 H, thiophene methylene), 3.83 (s, 3 H, NMe), 3.91 (d, $J$ = 7.5 Hz, 2 H, 3′-$CH_2$), 4.95 (d, $J$ = 4.5 Hz, 1 H, 6-H), 5.79 (dd, $J$ = 4.5, 9 Hz, 1 H, 7-H), 6.08 (dt, $J$ = 16, 7.5 Hz, 1 H, 2′-H), 6.63 (d, $J$ = 9 Hz, 1 H, NH), 6.8–7.5 (m, 15 H). Anal. ($C_{31}H_{28}N_6O_4S_3$) C, H, N.

**Method B.** A solution of the sulfide **5** (0.9 g, 1.4 mmol) in dry pyridine (5 mL) was treated with 0.1 mL of triethylamine, and the mixture was allowed to stand at room temperature for 24 h. The mixture was then evaporated and the residue chromatographed on silica gel eluting with benzene–EtOAc (85:15). Combining fractions homogeneous by TLC led to the desired isomer **10** (0.25 g) and recovered starting material (0.5 g). Treating the recovered starting material as above led to a further 0.15 g of isomer **10**, giving a combined yield of 0.4 g (44%), identical with material obtained using method A.

**Sodium 3-(3-Acetoxyprop-1-*trans*-enyl)-7β-[2-(2-thienyl)acetamido]-3-cephem-4-carboxylate (11).** A mixture of the ester **9** (0.2 g) and anisole (0.5 mL) was stirred at 0 °C and trifluoroacetic acid (2.5 mL) was added. After stirring vigorously for 2 min at 0 °C, the mixture was evaporated. The residue was mixed with ether, and the crude carboxylic acid which separated as a white solid was collected by filtration. The solid was dissolved in THF and filtered, and to the filtrate was added an excess of

sodium 2-ethylhexanoate (ca. 0.2 g). The mixture was then evaporated and 2-propanol was added to the residue giving a white solid which was collected by filtration, washed twice with 2-propanol, and dried under vacuum to give the sodium salt 11 (0.12 g, 79%) as a white powder which decomposed on attempted melting point determination: UV ($H_2O$) 292 nm ($\epsilon$ 20 100); IR (KBr) 1765, 1740, 1663, 1620 $cm^{-1}$; NMR ($Me_2SO$-$d_6$) 1.97 (s, 3 H, OAc), 3.44 (s, 2 H, 2-$CH_2$), 3.73 (s, 2 H, thiophene methylene), 4.53 (d, $J$ = 6 Hz, 2 H, 3'-$CH_2$), 4.98 (d, $J$ = 4.5 Hz, 1 H, 6-H), 5.48 (dd, $J$ = 4.5, 9 Hz, 1 H, 7-H), 5.65 (dt, $J$ = 16, 6 Hz, 1 H, 2'-H), 6.8–7.0 (m, 2 H, thiophene), 7.06 (d, $J$ = 16 Hz, 1 H, 1'-H), 7.2–7.5 (m, 1 H, thiophene), 9.06 (d, $J$ = 9 Hz, 1 H, NH).

**Sodium 3-[3-(1-Methyltetrazol-5-ylthio)prop-1-*trans*-enyl]-7β-[2-(2-thienyl)acetamido]-3-cephem-4-carboxylate (12). Method A.** The ester 10 (0.2 g) was deprotected, and the sodium salt of the resulting acid was prepared as described above for the ester 9. Obtained was 0.11 g (71%) of the sodium salt 12 as a white powder which decomposed on attempted melting point determination: UV ($H_2O$) 296 nm ($\epsilon$ 20 100); IR (KBr) 1760, 1660, 1600 $cm^{-1}$; NMR ($Me_2SO$-$d_6$) 3.4 (br s, 2 H, 2-$CH_2$), 3.75 (s, 2 H, thiophene methylene), 3.92 (s, 3 H, NMe), 4.00 (d, $J$ = 7.5 Hz, 2 H, 3'-$CH_2$), 4.97 (d, $J$ = 5 Hz, 1 H, 6-H), 5.47 (dd, $J$ = 5, 9 Hz, 1 H, 7-H), 5.71 (dt, $J$ = 15, 7.5 Hz, 1 H, 2'-H), 6.8–7.0 (m, 2 H, thiophene), 7.10 (d, $J$ = 15 Hz, 1 H, 1'-H), 7.25–7.4 (m, 1 H, thiophene), 9.06 (d, $J$ = 9 Hz, 1 H, NH).

**Method B.** A solution of the acetate 11 (0.1 g, 0.22 mmol), 5-mercapto-1-methyltetrazole (30 mg, 0.26 mmol), and sodium bicarbonate (25 mg, 0.3 mmol) in water (10 mL) was stirred at 50 °C for 8 h. The pH of the cooled mixture was adjusted to 2 with dilute HCl, and the mixture was extracted twice with EtOAc. The combined extracts were washed with brine, dried ($Na_2SO_4$), and evaporated, giving the crude acid as an amorphous solid. This was dissolved in EtOAc (4 mL) and an excess of sodium 2-ethylhexanoate (ca. 0.1 g) was added. The mixture was stirred for 15 min and the white solid which separated was collected by filtration, washed twice with 2-propanol, and dried under vacuum, giving 75 mg (67%) of the sodium salt 12 as a white powder, identical with the material obtained using method A.

**Acknowledgment.** We are indebted to Ms. Sharon Hitt and Dr. Allan Braemer for the antibacterial assays and to Dr. Lewis Throop and associates for analytical and spectral data.

## References and Notes

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# Analogues of Sparteine. 5. Antiarrhythmic Activity of Selected N,N'-Disubstituted Bispidines

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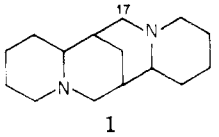
A series of seven N,N'-disubstituted bispidines, structurally analogous to the inner (B and C) rings of sparteine (1) and encompassing a range of lipophilicity in which 1 was centered, has been compared to 1 in regard to antiarrhythmic potency and acute toxicity. Several of the bispidines were of comparable potency, and all but one were somewhat less toxic than 1. The ability of the mononitrate salts of 1 and bispidines 6 and 7 to bind calcium and magnesium cations in $Me_2SO$-$d_6$ solvent has been evaluated by proton magnetic resonance analysis. No binding could be demonstrated under these conditions, which suggested that pharmacologic effects of these compounds may be due to properties other than direct binding of these cations.

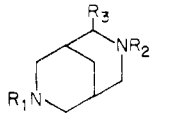
Sparteine (1), one of the more common quinolizidine alkaloids, has been used in the management of cardiac arrhythmias.[1] Its antiarrhythmic activity as well as its



1

effects on uterine and skeletal muscle appears to be due to a "stabilizing" effect on muscle cell membrane function.[2]

The two inner rings of sparteine constitute the 3,7-diazabicyclo[3.3.1]nonane (bispidine[3]) moiety. We have prepared several N,N'-disubstituted bispidines 2–8, whose chemical and physical similarity to 1 warranted their evaluation as antiarrhythmics. Compounds were chosen for this study which appeared to encompass a significant range of lipophilicity in which 1 would be approximately centered. We took this approach since a study of the comparative antiarrhythmic effects of 1 and a series of 17-alkyl analogues had indicated that activity was de-



| | $R_1$ | $R_2$ | $R_3$ |
|---|---|---|---|
| 2 | $CH_3$ | $n$-$C_4H_9$ | H |
| 3 | $CH_3$ | $CH_3$ | $i$-$C_3H_7$ |
| 4 | $CH_3$ | $CH_2Ph$ | H |
| 5 | $n$-$C_4H_9$ | $n$-$C_4H_9$ | H |
| 6 | $n$-$C_4H_9$ | $CH_2Ph$ | H |
| 7 | $CH_2Ph$ | $CH_2Ph$ | H |
| 8 | $CH_3$ | $CHPh_2$ | H |

pendent not only on the presence of a protonated amino group but also on lipophilicity.[4] Other reports have also emphasized the influence of this property in determining potency.[5]

Lipophilicity (hydrophobicity) has been measured in series of compounds such as this by determination or calculation[6] of apparent or intrinsic octanol–water partition coefficients.[7] In this paper, we report the results of an-