5-Methylcyclohexane-1,3-dione and 5-ethylcyclohexane-1,3-dione were made by condensing diethyl malonate with 3-penten-2-one and with 3-hexen-2-one, respectively.[20] Cycloheptane-1,3-dione, cyclooctane-1,3-dione, and cyclononane-1,3-dione were prepared by a procedure adumbrated by Y. Ito et al.[21] [3]Ferrocenophane-1,3-dione was prepared according to M. Sališová et al.[22]

Syntheses. General Procedure for Preparing Retinylidene Diketones. Retinal (1.0 g, 3.5 mmol) and the diketone (ca. 3.8 mmol) were dissolved in 30 mL of benzene or toluene, catalyst was added, and the mixture was stirred overnight under argon at room temperature in the dark. After the solvent was removed on a rotary evaporator, the residue was passed through silica gel (150 g), eluting with 3:1 hexane ether. A heart cut of the major colored band was collected, stripped, and recrystallized from an ether–petroleum ether (30–60 °C) mixture.

2-Retinylidene-5,5-dimethyl-1,3-cyclohexanedione (6). *all-trans*-Retinal (10 g, 35 mmol) was dissolved in 200 mL of toluene. Dimedone (5.5 g, 39 mmol) was added, followed by 8 drops of piperidine. After stirring at room temperature under argon for 18 h, the dark red solution was stripped, passed through silica gel (350 g) eluting with 3:1 hexane–ether, and recrystallized from ether–petroleum ether to yield 10.8 g (75%) of product: mp 119–121 °C; ^{1}H NMR δ 1.05 and 1.07 [s, 12 H, 1′,1′-$(CH_3)_2$ and 5,5-$(CH_3)_2$], 1.50 (m, 2.27 H, H-2′), 1.63 (m, 1.96 H, H-3′), 1.74 (s, 3.14 H, 5′-CH_3), 2.05 (s superimposed on m, 4.93 H, 9′-CH_3 and H-4′), 2.24 (s, 2.97 H, 13′-CH_3), 2.52 (s, 3.91 H, H-4 and H-6), 6.25 (d, J = 16 Hz, 0.98 H, H-8′), 6.27 (d, J = 12 Hz, 0.98 H, H-10′), 6.40 (d, J = 16 Hz, 1.09 H, H-7′), 6.62 (d, J = 15 Hz, 0.94 H, H-12′), 7.18 (d of d, J = 15 Hz, J' = 12 Hz, 1.02 H, H-11′), 7.84 (d, J = 13 Hz, 0.94 H, H-14′), 8.21 (d, J = 13 Hz, 0.94 H, H-15′); IR (CCl_4) 2950 (m), 2920 (w), 2862 (w), 2820 (w), 1688 (w), 1647 (m), 1510 (s), 1443 (w), 1388 (w), 1372 (m), 1335 (w), 1292 (w), 1227 (w), 1268 (w), 1240 (m), 1175 (m), 1157 (w), 1136 (w), 1110 (w), 965 cm^{-1} (m); EIMS (70 eV) M$^+$ 406 (44%); ^{13}C NMR ($CDCl_3$)[23] δ 12.92, 13.04 (9′- and 13′-CH_3), 19.07 (C-3′), 21.68 (5′-CH_3), 28.39 and 28.86 [1′,1′-$(CH_3)_2$ and 5,5-$(CH_3)_2$], 29.88 (C-5), 33.05 (C-4′), 34.07 (C-1′), 39.46 (C-2′), 52.06 and 53.88 (C-4 and C-6), 126.36, 128.17, 129.49, 130.04, 130.25, 132.74, 136.29, 136.81, 137.23, 141.30, 144.61, and 157.76 (olefinic carbons), 197.19 and 198.24 (carbonyl carbons). Anal. ($C_{28}H_{38}O_2$) C, H.

9-*cis*-Retinylidenedimedone. A benzene solution (30 mL) of 9-*cis*-retinal (521 mg, 1.84 mmol), dimedone (260 mg, 1.85 mmol), and piperidine (3 drops) was stirred at room temperature for 22 h. After chromatography (150 g of silica gel, 1:1 ether–hexane) and crystallization from cold petroleum ether, 190 mg (25%) of product was obtained, mp 99–104 °C; ^{1}H NMR δ 1.07 and 1.09 [2s, 11.20 H, 1′,1′- and 5,5-$(CH_3)_2$], 1.50 (m, 2.16 H, H-2′), 1.64 (m, 2.07 H, H-3′), 1.77 (s, 3.06 H, 5′-CH_3), 2.06 (s superimposed on m, 5.32 H, 9′-CH_3 and 4′-CH_2), 2.24 (s, 2.89 H, 13′-CH_3), 2.53 (s, 3.88 H, H-4 and H-6), 6.15 (d, J = 11.5 Hz, 0.90 H, H-10′), 6.36 (d, J = 15.5 Hz, 1.08 H, H-7′), 6.52 (d, J = 15.0 Hz, 0.90 H, H-12′), 6.70 (d, J = 15.5 Hz, 0.99 H, H-8′), 7.23 (d of d, J = 15.0 Hz, J' = 11.5 Hz, 0.99 H, H-11′), 7.80 (d, J = 13 Hz, 0.90 H, H-14′), 8.20 (d, J = 13 Hz, 0.99 H, H-15′); IR (CCl_4) 2960 (m), 2940 (m), 2890 (w), 2880 (w), 2835 (w), 1693 (w), 1652 (s), 1512 (s), 1468 (w), 1448 (w), 1388 (m), 1375 (m), 1335 (m), 1295 (w), 1278 (w), 1260 (w), 1240 (m), 1200 (w), 1172 (m), 1145 (m), 1115 (w), 1027 (w), 964 cm^{-1} (m); UV λ_{max} (EtOH) 483 nm (ϵ 41 500), 255 (12 400); MS (CI, NH_3) M$^+$ 407.[24]

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(23) Measured on a JEOL JNM-FX 100 Fourier transform NMR spectrometer in parts per million from Me_4Si and accumulated in 17 min. Long accumulation times led to the appearance of spurious peaks in the olefinic region. Upfield peaks are assigned by comparison with those reported for other retinoids: Jautelat, M.; Grutzner, J. B.; Roberts, J. D. *Proc. Natl. Acad. Sci. U.S.A.* **1970**, *65*, 288. Englert, G. *Helv. Chim. Acta* **1975**, *58*, 2367.
(24) **Note Added in Proof:** TOC assay shows the 9-cis derivative to be inactive in six out of eight cultures at 10^{-9} M.

Notes

Simple β-Lactam Compounds Derived from 6-Aminopenicillanic Acid

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As part of a general program of structural modification in β-lactam antibiotics, we have synthesized several simple penicillins from 6-aminopenicillanic acid where the C-3 carboxyl group has been replaced by a hydroxy or an acetoxy group and the C-6 side chain has been substituted by bromine or hydrogen. Some of the compounds exhibit mild activity against the Gram-positive strain *Bacillus subtilis*.

Structural modifications at the C-3 position of penicillin and C-4 position of cephalosporin seem to indicate that the acid group at these positions is necessary for biological activity. Variations at the C-3 carboxyl group resulting in penicillin compounds with improved or diminished biological activity have been discussed in recent reviews.[1,2] We have synthesized several simple penicillins where the C-3 carboxyl group has been replaced by a hydroxy or an acetoxy group and the C-6 side chain has been substituted by bromine or hydrogen. Interest in bromine and hydrogen as the C-6 substituents arises from recent reports[3,4]

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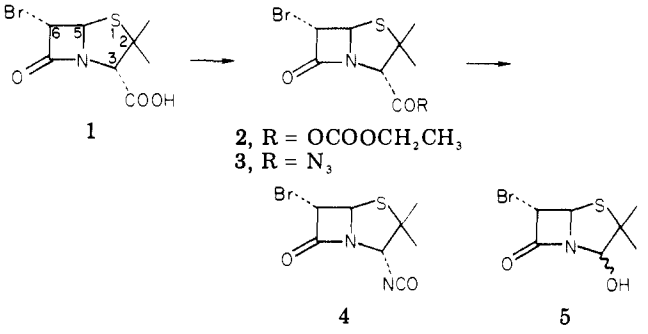
0022-2623/80/1823-0809$01.00/0

Scheme I



1

2, R = $OCOOCH_2CH_3$
3, R = N_3

4 5

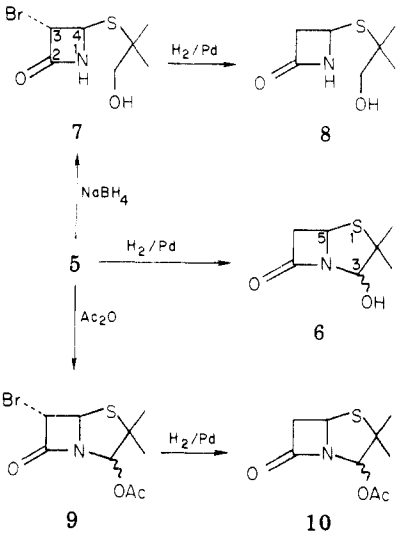
which indicate that sulfones of penicillanic acid and its 6-halogeno derivative have properties of β-lactmase inhibitors. We report here the synthesis and biological data of these new compounds.

Results and Discussions

6-Bromopenicillanic acid (1), obtained by deaminative bromination[5] of 6-aminopenicillanic acid (6-APA), was subjected to penam 3,4 bond cleavage.[6] The bromide was treated with ethyl chloroformate in the presence of triethylamine to give the mixed anhydride **2** (Scheme I). Treatment of **2** with sodium azide in aqueous THF gave the acid azide **3**, which underwent smooth rearrangement to the isocyanate **4** during storage in vacuo at room temperature for 30 h. IR spectroscopy was used to monitor the reaction. Both the azide (2100 cm^{-1}) and carbonyl bands (1700 cm^{-1}) of **3** disappeared, and the isocyanate band (2260 cm^{-1}) of **4** emerged as the reaction proceeded. The isocyanate was hydrolyzed with an equimolar amount of hydrochloric acid in aqueous THF to give 6-bromo-3-hydroxypenam (**5**). The NMR spectrum of **5** contained signals of H-3 [δ 5.30 (s)] and OH [δ 3.09 (br s)] but had no signal attributable to NH or aldehyde proton, indicating that compound **5** exists mostly in the cyclized penam structure. This is, in fact, what is expected of compound **5**, since the C-6β substituent is hydrogen. Larger substituents at C-6β are known[7] to give open-chain aldehydes as a result of interaction between C-2β and C-6β substituents.

The bromopenam **5** was hydrogenolyzed over Pd/C in the presence of sodium acetate to produce compound **6** (Scheme II), which showed 3-H [δ 5.60 (s)] and OH (δ 6.10) in the NMR spectrum, indicating the bicyclic β-lactam structure. Penam **5** was reduced with sodium borohydride[8] in aqueous THF at 0 °C for 3 min to give the single β-lactam compound **7**. This compound showed a cross β-lactam ring coupling[9] (J = 2.50 Hz) between NH [δ 7.48 (br)] and 3β-H [δ 4.90 (m)] but no coupling between NH and 4-H [δ 5.25 (d)]. In a similar manner, penam **6** gave compound **8** having the long-range coupling of NH [δ 7.50 (br)] with both 3β-H [δ 2.65 (m, J = 1.5 Hz)] and 3α-H [δ 3.40 (m, J = 1.8 Hz)]. The *O*-acetate **9** was prepared by acetylation of **5** with acetic anhydride and pyridine.

Scheme II



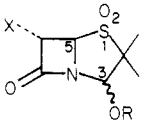
7 8

5 6

9 10

The IR spectrum of **9** showed the β-lactam band at 1795 cm^{-1}, while the carbinolamide penams **5** and **6** absorbed at 1760 cm^{-1}. Hydrogenolysis of compound **9** with Pd/C gave penam **10**.

Sufones **11** and **12** were prepared by permanganate oxidation[10] of **5** and **9**, respectively. Compounds **11** and **12** on hydrogenolysis with Pd/C afforded the corresponding debromo derivatives **13** and **14**.



11, X = Br; R = H
12, X = Br; R = $COCH_3$
13, X = H; R = H
14, X = H; R = $COCH_3$

Biological activity of the compounds, in general, decreased in the order carbinolamides (**5** and **6**) > monocyclic β-lactams (**7** and **8**) > *O*-acetates (**9** and **10**). Compounds **5**, **6**, and **8** were the most active against *Bacillus subtilis* ATCC 6051, the MIC (minimum inhibitory concentration) values being 6.25, 25, and 100, respectively. Against other strains, MIC values were >100 for all compounds. Sulfones **11**–**13** showed poor activity as penicillanase inhibitors.

Experimental Section

Melting points were obtained on a Fisher–Jones apparatus and are reported uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded with Hitachi Perkin-Elmer R-20B spectrometer and are reported in parts per million (δ) relative to Me_4Si as an internal standard. Infrared spectra (IR) were recorded on a Perkin-Elmer 237 spectrophotometer. Mass spectra were recorded on MAT-44 (70 eV). Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Biological Tests. (a) Minimum Inhibitory Concentration (MIC). A set of trypticase soy plates was prepared containing concentrations of sample or standard ranging from 0 to 200 μg/mL agar. All solutions were prepared and diluted in either Me_2SO or water. Each plate was inoculated twice with all organisms using a Steers replicator. The organisms used were the following. Gram-positive bacteria: *Staphylococcus aureus* ATCC 25923, *Staphylococcus epidermidis* ATCC 14990, *Streptococcus pyogenes* ATCC 10389, *Bacillus subtilis* ATCC 6051, *Sarcina lutea* ATCC 9341. Gram-negative bacteria: *Escherichia coli* ATCC 25922, *Enterobacter cloacae* ATCC 13047, *Salmonella typhi-*

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murium ATCC 13311, *Proteus mirabilis* MIT B-52, *Proteus vulgaris* ATCC 6380, *Serratia marcescens* MIT B-43, *Klebsiella pneumoniae* ATCC 27736, *Shigella sonnei* ATCC 11060, *Pseudomonas aeruginosa* ATCC 9721. The plates were incubated for 18 h at 37 °C. The minimum inhibitory concentration (MIC) was the lowest level which inhibited growth.

(b) Synergy Test. Trypticase soy agar was prepared containing no antibiotic, ampicillin (5 μg/mL), or penicillin G (10 μg/mL). All of the above were seeded with *Klebsiella aerogenes* ATCC 15380, a penicillinase producer. Sample compounds were tested at 5 mg/mL; two known synergistic standards, BRL 1437 and clavulanic acid, were run at 1 mg/mL and 10 μg/mL, respectively. Filter paper disks (6.35 mm) were dipped into the test solutions and placed on the agar plates. Each plate also had disks with the standard solutions. Plates were incubated for 18 h at 37 °C. A compound with synergistic activity produces a larger zone of growth on one or both of the antibiotic-containing plates than on the unsupplemented plate where it may produce no zone.

6-Bromo-2,2-dimethyl-3-hydroxypenam (5). To a solution of 6-bromopenicillanic acid (1; 15.5 g, 55.3 mmol) in THF (150 mL) was added triethylamine (9.5 mL) and ethyl chlorformate (6 mL) at −20 °C. The mixture was stirred for 30 min at −20 to −10 °C, following which sodium azide (4.06 g) in H_2O (30 mL) was added drop by drop over 40 min. The resulting mixture was stirred for an additional 30 min at 0–5 °C, diluted with methylene chloride (300 mL), and then washed with saturated NaCl (300 mL × 2). The organic layer was separated, dried (Na_2SO_4) and evaporated to give brown oily acid azide **3**: IR (KBr) 2150 (N_3), 1790 (β-lactam), 1700 (C=O of acid azide) cm^{-1}. Upon drying **3** in vacuo for 32 h, brown oily isocyanate **4** was obtained: IR 2260 (N=C=O), 1790 (β-lactam) cm^{-1}. The crude product, which dissolved in THF (200 mL), was added drop by drop over 4 h to 50% aqueous THF (1000 mL) containing 26 mL of 1 N HCl at 0–5 °C. The solution was stirred for an additional hour and saturated with NaCl to separate THF and water. The organic layer was washed with saturated NaCl (500 mL) and concentrated to one-third volume. The resulting mixture was diluted with chloroform (500 mL) and washed with saturated NaCl (500 mL × 2). The organic layer was dried (Na_2SO_4) and evaporated to give 8 g of **5** which was purified employing a column of silicic acid (250 g) and using 10:1 carbon tetrachloride–ethyl acetate as the eluent to give 3.5 g (25%) of crystalline compound **5**: mp 89–92 °C; IR 3350, 1760 cm^{-1}; NMR (acetone-d_6) δ 5.30 (s, 1 H, H-3), 5.20 (d, J = 1.7 Hz, 1 H, H-5), 4.75 (d, J = 1.7 Hz, 1 H, H-6), 3.09 (br s, 1 H, OH, exchange with D_2O), 1.50 and 1.55 (2 s, 6 H, Me_2). Anal. ($C_7H_{10}BrNO_2S$) C, H, Br, S.

2,2-Dimethyl-3-hydroxypenam (6). 6-Bromopenam **5** (200 mg, 0.79 mmol) and sodium acetate (65 mg) were dissolved in methanol (20 mL) and H_2O (5 mL). To the solution was added 150 mg of Pd/C (10%), and the suspension was hydrogenated at 25 °C (1 atm) for 16 h, after which time it was adjusted to pH 4 with acetic acid and filtered and the catalyst was washed with methanol (5 mL). The combined filtrate was diluted with chloroform (100 mL) and the solution was washed with H_2O (50 mL × 2). The organic layer was separated, dried (Na_2SO_4) and evaporated to give crystalline compound **6** (85 mg, 62%), which was then recrystallized from carbon tetrachloride and petroleum ether: mp 60–63 °C; IR 1760 (β-lactam) cm^{-1}; NMR (acetone-d_6) δ 6.10 (br d, 1 H, OH, exchange with D_2O), 5.60 (d, J = 9 Hz, 1 H, sharpened with D_2O, H-3), 5.00 (m, J = 4 and 1.9 Hz, 1 H, H-5), 3.45 (m, J = 12 and 4 Hz, 1 H, 6α-H), 2.85 (m, J = 12 and 1.9 Hz, 1 H, 6β-H), 1.45 and 1.40 (2 s, 6 H, Me_2). Anal. ($C_7H_{11}NO_2S$) C, H, N, S.

3-Bromo-4-[(2′-hydroxy-1′,1′-dimethylethyl)thio]azetidin-2-one (7). A solution of **5** (1.7 g, 7.4 mmol) in 30 mL of THF was cooled to 0–5 °C and a solution of sodium borohydride (280 mg) in H_2O (3 mL) was added. The red reaction mixture was stirred at 0 °C for 3 min and quenched with acetic acid, adjusting to pH 3–4. The resulting mixture was diluted with chloroform (80 mL), washed with H_2O (40 mL × 3), dried (Na_2SO_4), and evaporated to a yellow foam. The crude product mixture was passed through a column of silicic acid (40 g) and eluted with 2:1 carbon tetrachloride–ethyl acetate to give 1.28 g (75%) of crystalline compound **7**: mp 78–82 °C; IR 3430 (OH), 3220 (NH), 1760 (β-lactam) cm^{-1}; NMR ($CDCl_3$) δ 7.48 (br, 1 H, NH), 5.25 (d, J = 1.9 Hz, 1 H, H-4), 4.90 (m, J = 2.5 and 1.9 Hz, 1 H, H-3), 3.90 (s, 2 H, CH_2), 3.10 (br, 1 H, OH), 1.75 and 1.65 (2 s, 6 H, Me_2). Anal. ($C_7H_{12}BrNO_2S$) C, H, N.

4-[(2′-Hydroxy-1′,1′-dimethylethyl)thio]azetidin-2-one (8). The bromo compound **7** (400 mg, 1.8 mmol) was dissolved in 90% aqueous methanol (20 mL) and the solution was hydrogenolyzed in the presence of sodium acetate (150 mg) and Pd/C (10%, 250 mg) at 25 °C (1 atm) for 16 h. After filtering and washing with chloroform, the whole filtrate was extracted with chloroform (50 mL) and H_2O (50 mL). The organic layer gave 180 mg (65%) of **7** as an oil after drying (Na_2SO_4) and evaporation. The oil was crystallized from ether–petroleum ether: mp 55–59 °C; IR 1760 cm^{-1}; NMR (acetone-d_6) δ 7.50 (br, 1 H, NH, exchange with D_2O), 5.05 (m, J = 5.5 and 2 Hz, 1 H, H-4), 4.1 (br s, 1 H, OH, exchange with D_2O), 3.55 (s, 2 H, CH_2), 3.25 (m, J = 14, 5.5, and 1.8 Hz, 1 H, 3α-H), 2.65 (m, J = 14, 2, and 1.5 Hz, 1 H, 3β-H), 1.35 and 1.30 (2 s, 6 H, Me_2); MS m/e 175 (M^+), 145, 117, 102, 70. Anal. ($C_7H_{13}NO_2S$) C, H, N.

6-Bromo-3-acetoxy-2,2-dimethylpenam (9). To a solution of **5** (800 mg, 1.37 mmol) in THF (50 mL) was added 1.5 mL of pyridine and 4.4 mL of acetic anhydride at 0–5 °C. The solution was stirred at room temperature for 16 h. The product (**9**; 920 mg) was isolated upon evaporation of the reaction mixture. The pure oil was obtained by column chromatography through silicic acid (30 g) using 50:1 carbon tetrachloride–ethyl acetate: IR 1795 (β-lactam), 1760 (ester) cm^{-1}; NMR ($CDCl_3$) δ 6.40 (s, 1 H, H-3), 5.30 (d, J = 1.7 Hz, 1 H, H-5), 4.85 (d, J = 1.7 Hz, 1 H, H-6), 2.20 (s, 3 H, CH_3CO), 1.65 and 1.55 (2 s, 6 H, Me_2); MS m/e 293 (M^+), 234, 179, 114, 98, 74, 59, 43.

3-Acetoxy-2,2-dimethylpenam (10). Compound **9** (300 mg, 1.02 mmol) was dissolved in 90% aqueous methanol (15 mL) and sodium acetate (67 mg) and Pd/C (10%, 270 mg) were added. The suspension was hydrogenolyzed (25 °C, 1 atm) for 17 h. The catalyst was filtered off, and the filtrate was extracted with chloroform (50 mL) and H_2O (50 mL). After drying (Na_2SO_4), the organic layer was evaporated to give **10** as an oil (132 mg): IR 1795 (β-lactam), 1760 (C=O), 1050 cm^{-1}; NMR ($CDCl_3$) δ 6.30 (s, 1 H, H-3), 5.10 (m, J = 5.5 and 2 Hz, 1 H, H-5), 3.45 (m, J = 14 and 5.5 Hz, 1 H, 6α-H), 2.65 (m, J = 14 and 2 Hz, 1 H, 6β-H), 2.20 (s, 3 H, CH_3CO), 1.60 and 1.55 (2 s, 6 H, Me_2); MS m/e 215 (M^+), 156, 101, 59, 43.

Sulfones 11–14.[6] Compound **5** (100 mg, 3.9 mmol) was dissolved in 80% acetic acid (10 mL). The solution was cooled to 0 °C and a solution of $KMnO_4$ (300 mg in 1 mL of H_2O) was added drop by drop until the color of permanganate persisted. After 30 min, 30% H_2O_2 was added in quantity sufficient to discharge the pink color. This was followed by the addition of 15 mL of H_2O. The mixture was extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$),and evaporated to give 30 mg of sulfone **11** as an oil: IR 3350 (OH), 1805 (β-lactam), 1325, 1200 (S=O) cm^{-1}; NMR ($CDCl_3$) δ 5.40 (s, 1 H, H-3), 5.32 (d, J = 1.7 Hz, 1 H, H-5), 4.86 (d, J = 1.7 Hz, 1 H, H-6), 2.20 (br s, 1 H, OH), 1.50 (s, 6 H, Me_2); MS m/e 284 (M^+).

The same procedure as described above was used to convert compound **9** to **12**: IR 1810 (β-lactam), 1750 (ester), 1325, 1200 (S=O) cm^{-1}; NMR ($CDCl_3$) δ 6.35 (s, 1 H, H-3), 5.30 (d, J = 1.7 Hz, 1 H, H-5), 4.80 (d, J = 1.7 Hz, 1 H, H-6), 2.20 (s, 3 H, CH_3CO), 1.48 and 1.54 (2 s, 6 H, Me_2); MS m/e 325 (M^+).

Sulfones **13** and **14** were obtained by hydrogenolysis of **11** and **12**, respectively, as described for the preparation of compound **6**. **13**: IR 3340 (OH), 1800 (β-lactam), 1330, 1210 (S=O) cm^{-1}. **14**: IR 1810 (β-lactam), 1760 (ester), 1325, 1200 (S=O) cm^{-1}; NMR ($CDCl_3$) δ 6.15 (s, 1 H, H-3), 4.65 (m, J = 5 and 2 Hz, 1 H, H-5), 3.45 (m, 2 H, CH_2), 2.15 (s, 3 H, CH_3CO), 1.42 and 1.50 (2 s, 6 H, Me_2); MS m/e 247 (M^+).

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