for 1 h and then added to a solution of sodium iodide (39.8 g, 265 mmol) and 2-methyl-2-butene (16.9 mL, 160 mmol) in 500 mL of acetonitrile in a 2-L 3-neck flask under nitrogen. Chlorotrimethylsilane (13.5 mL, 106 mmol) was added slowly by syringe. The mixture was stirred at 23 °C until the reaction was complete as determined by working up 20-μL aliquots and by TLC examination. The reaction was quenched by adding a solution of 13.4 g (106 mmol) of sodium sulfite and 12.5 g (42 mmol) of sodium citrate in 840 mL of water to the flask. The mixture was washed with 4:1 hexane–dichloromethane (3 × 250 mL), and the combined extracts were washed with water (5 × 250 mL) and brine (250 mL) and evaporated. The crude product was taken up in 640 mL of hexane, and the solution was extracted with 320 mL of 0.5 M potassium carbonate in 1:1 methanol–water. The alkaline solution was washed with 1:1 hexane–ether (2 × 160 mL) and then acidified under nitrogen with 90 mL of 4.5 M hydrobromic acid. The oily product was extracted with 2:1 hexane–ether (3 × 100 mL). The extracts were washed with water (2 × 75 mL) and brine (75 mL), dried, and evaporated to give 13.55 g (78%) of pure DHA (**2**): IR (NaCl) 1710 (C=O), 1645 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.38 (m, 12 H, olefinic H), 2.85 (m, 10 H, 6-, 9-, 12-, 15-, and 18-CH_2), 2.42 (m, 4 H, 2- and 3-CH_2), 2.08 (m, 2 H, 21-CH_2), 0.97 (t, 3 H, 22-CH_3); FAB MS, *m/z* (relative intensity) 329, MH^+ (1.9), 133 (12), 131 (18), 119 (27), 117 (33), 107 (24), 105 (47), 95 (31), 93 (56), 91 (98), 81 (38), 79 (97), 67 (100).

Methyl Docosahexaenoate. A 66-mg (200-μmol) sample of **2** was dissolved in 5 mL of distilled ether and the resultant mixture cooled to 0 °C. A slow stream of diazomethane in nitrogen (prepared by bubbling nitrogen through ethereal diazomethane) was passed into the sample in the dark until the esterification was complete. Evaporation gave 68 mg (100%) of methyl docosahexenoate: IR (NaCl) 1745 (C=O), 1645 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.38 (m, 12 H, olefinic H), 3.68 (s, 3 H, OCH_3), 2.85 (m, 10 H, 6-, 9-, 12-, 15-, and 18-CH_2), 2.38 (m, 4 H, 2- and 3-CH_2), 2.10 (m, 2 H, 21-CH_2), 0.97 (t, 3 H, 22-CH_3; MS (70 eV), *m/z* (relative intensity) 342 M^+ (80), 310 (27), 268 (12), 79 (100); high-resolution MS (70 eV) for $C_{23}H_{34}O_2$, calcd 342.25586, found 342.25566; GC (oven 190 °C) R_t 21.35 min, 95%. A sample of the methyl ester was hydrogenated with platinum in methanol; it was found to be identical with authentic methyl docosanoate by GC analysis.[8]

(8) This research was assisted financially by a grant from the National Institutes of Health.

A Novel and Stereospecific Synthesis of (5*R*,6*S*)-6-(Aminomethyl)-2-(ethylthio)penemcarboxylic Acid[1]

Willard M. Welch* and Karen J. C. Guarino

Department of Medicinal Chemistry, Central Research Division, Pfizer Inc., Groton, Connecticut 06340

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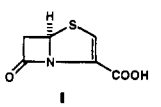
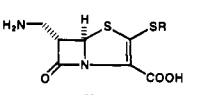
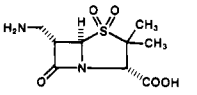
Penem-3-carboxylic acid (I) and its derivatives represent the first major series of totally synthetic β-lactam antibiotics. Structurally, these compounds occupy a position between penicillins and cephalosporins, being, in a sense, nor analogues of the latter.[2] Several penem derivatives bearing a 6(*R*),8(*R*)-hydroxyethyl substituent similar to that found in thienamycin[3] have demonstrated potent, broad-spectrum antibacterial activity.[4] In an effort to prepare structurally novel compounds that might combine the potent antibacterial activity of the 6(*R*)-hydroxyethyl derivatives with enhanced pharmacokinetics, we became interested in derivatives of the 6α-(aminomethyl)penemcarboxylic acid (II) in hopes that the zwitterionic character of these compounds might enhance their stability. While some (aminoalkyl)penems had been previously synthesized by displacement of activated hydroxyl groups from penems,[5] we sought a more direct entry into the system. Also, since only those penem derivatives with the 5*R* absolute configuration demonstrate antibacterial activity,[6] we wanted our synthesis to start with optically pure material and to proceed in such a way as to retain stereochemical integrity.



I



II

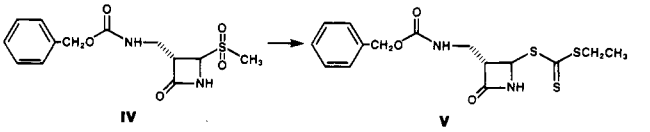


III

A series of 6α-(aminomethyl)penicillanic acid sulfones, including the 6α-aminomethyl derivative III, which display potent β-lactamase-inhibiting activity, has been recently reported from our laboratories.[7,8] This readily available starting material had the proper chirality at C-5 and appeared to provide an excellent entry into the 6α-(aminomethyl)penem series, provided that the penem ring could be constructed upon the β-lactam ring while maintaining stereochemical integrity.

The *p*-NO_2-CBZ-protected methyl ester of compound III (compound **1**, Scheme I) was subjected to DBN (or DBU) in CH_2Cl_2 for 3 h, essentially under the conditions of Stoodley et al.[9] The resulting sulfinic acid **2** could be isolated by extraction into aqueous sodium bicarbonate and purified by column chromatography, after which it could be alkylated in essentially quantitative yield to give the sulfone **3** by treatment of its tetra-*n*-butylammonium salt with methyl iodide. Although the DBN salt of **2** arising from the ring-opening reaction could be alkylated directly with methyl iodide to give the sulfone **3**, the two step procedure resulted in a higher, cleaner yield.[10] Dealkylation on nitrogen was achieved with $KMnO_4$ with $NaIO_4$ as reoxidant by the method of Yoshida et al.[11] to give the desired crystalline azetidinone **4** $[\alpha]^{22}_D$ −8.3° (*c* 1.0, acetone).

The azetidinone reacted readily with potassium ethyltrithiocarbonate under phase-transfer conditions to give the desired crystalline trithiocarbonate **5** in 31% yield. A similar reaction with the carbobenzyloxy analogue IV gave the corresponding crystalline trithiocarbonate V in 72% yield, supporting the fact that displacement of the sulfone moiety from the α-aminomethyl-substituted azetidinone can be a facile, high-yield process.



IV V

(1) This material was presented in part at the 15th IUPAC Symposium on Organic Synthesis, The Hague, Netherlands, August 17–22, 1986.
(2) Ernest, I.; Gosteli, J.; Greengrass, C. W.; Holick, W.; Jackman, D. E.; Pfaendler, H. R.; Woodward, R. B. *J. Am. Chem. Soc.* **1978**, *100*, 8214.
(3) Ganguly, A. K.; Girijavallabhan, V. M.; McCombie, S. W.; Pinto, P.; Rizvi, R.; Jeffrey, P. D. *J. Antimicrob. Chemother.* **1982**, *9*(Suppl. C), 1.
(4) Neu, H. C. *Am. J. Med.* **1986**, *80*(6B), 195 and references therein.
(5) Kirkup, M. P.; McCombie, S. W.; Lin, S.-L. Presented at the 18th Middle Atlantic Regional Meeting of the American Chemical Society, May 21–23, 1984.
(6) Pfaendler, H. R.; Gosteli, J.; Woodward, R. B. *J. Am. Chem. Soc.* **1979**, *101*, 6306.
(7) Barth, W. E. for Pfizer, Inc. U.S. Patent 4 452 796, 1984.
(8) Pirie, D. K.; Welch, W. M.; Weeks, P. D.; Volkman, R. A. *Tetrahedron Lett.* **1986**, *27*, 1549.
(9) Pant, C. M.; Steele, J.; Stoodley, R. J. *J. Chem. Soc., Perkin Trans. 1* **1981**, 595.
(10) Vennstra, G. E.; Zwaneburg, B. *Synthesis* **1975**, 519.
(11) Yoshida, A.; Hayashi, T.; Takeda, N.; Oida, S.; Ohki, E. *Chem. Pharm. Bull.* **1981**, *29*, 2899.

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Compound **5** was treated with 4-nitrobenzyl chloro oxalate and the intermediate oxalamide was then directly reacted with triethyl phosphite in refluxing, ethanol-free chloroform under the conditions of Alfonso[12] to give the crystalline, doubly blocked penem compound **7**. The trans geometry of this compound was fully demonstrated by its 300-MHz proton NMR spectrum, the 1.5-Hz coupling constant between H-5 and H-6 being clearly observed.

The protecting groups of **7** were removed by catalytic hydrogenation over 10% Pd on Celite to give, after filtration of catalyst and extraction of organic byproduct, the desired zwitterionic penem **8** as an amorphous white foam.[13] This compound was relatively stable in its zwitterionic form but displayed only weak activity vs. Gram-positive bacteria in vitro.

Experimental Section

Melting points (uncorrected) were taken with a Thomas-Hoover capillary apparatus. NMR spectra were recorded on Varian T-60, EM-390, and XL-300 spectrometers and are reported as ppm downfield from TMS. IR spectra were determined on a Perkin-Elmer Model 283B infrared spectrophotometer. Mass spectra were obtained with a Finnigan Model 4510 mass spectrometer. Microanalyses were performed by the Pfizer Analytical Department. Column chromatography was performed by the flash method on 32–63 μm silica gel.

6α-[[(4-Nitrobenzyloxycarbonyl)amino]methyl]-penicillanic Acid 1,1-Dioxide. A rapidly stirred solution of 6.06 g (23.16 mmol) of 6α-(aminomethyl)penicillanic acid 1,1-dioxide[7] in 165 mL of 2:1 CH_3OH/H_2O was treated with 5.99 g (35.1 mmol) of 4-nitrobenzyl chloroformate at room temperature. The pH was held between 6 and 7 by dropwise addition of dilute NaOH. After 15 min, the pH remained steady. The reaction mixture was washed twice with isopropyl ether and was then layered with CH_2Cl_2. The pH was adjusted to 1.9 with concentrated HCl. The organic layer was separated and combined with one CH_2Cl_2 wash of the aqueous layer. This solution was dried with brine and $MgSO_4$, filtered, and treated with 3 equiv of DBU at room temperature (a slight exotherm was noted), and the mixture was then stirred for 15 min. The epimerized reaction mixture was quenched by pouring it into ice-cold dilute HCl. The product was extracted from the CH_2Cl_2 extracts with excess dilute $NaHCO_3$, and then this solution was cooled in ice while the pH was adjusted to 2.0. The title compound was extracted into CH_2Cl_2 and dried with brine and $MgSO_4$, and the solvent was evaporated to give the product as an amorphous white foam. An analytical sample was obtained by column chromatography: IR (KBr) 5.58, 5.81 μm; NMR ($CDCl_3$) δ 1.43 (3 H, s), 1.58 (3 H, s), 3.50–4.00 (3 H, m), 4.23 (1 H, s), 4.77 (1 H, s), 5.18 (2 H, s), 5.30 (1 H, s), 7.22 (1 H, br s), 7.78 (4 H, q); $[\alpha]^{23}_D$ +93.0° (*c* 1.0, CH_3OH).

Methyl 6α-[[(4-Nitrobenzyloxycarbonyl)amino]-methyl]-1,1-dioxopenicillanate (1). A solution of the starting acid in 250 mL of CH_2Cl_2 was layered with a solution of 6.49 g (19.1 mmol) of tetra-*n*-butylammonium hydrogen sulfate in 200 mL of water. Then 2.30 g (21.7 mmol) of Na_2CO_3 was added. The reaction mixture was stirred for 30 min, and then the CH_2Cl_2 layer was separated and combined with one CH_2Cl_2 wash of the aqueous layer. The combined extracts were dried with $MgSO_4$, filtered, and treated at room temperature with stirring with 2.72 g (1.20 mL, 19.1 mmol) of CH_3I. This reaction mixture was then stirred overnight at room temperature.

The solvents were then removed from the reaction mixture, and the residues were taken up in ethyl acetate. Crystalline solids (TBA salts) that separated were filtered, and the concentrated filtrate was flash chromatographed with 3:2 and 1:1 hexane/ethyl acetate as eluents. Product-containing fractions were combined, and the solvents were removed to give the title compound as a colorless foam: IR(KBr) 5.56, 5.68, 5.78 μm; NMR($CDCl_3$) δ 1.35 (3 H, s), 1.57 (3 H, s), 3.8 (5H, s + m), 4.35 (1 H, s), 4.65 (1 H, s), 5.18 (2 H, s), 5.90 (1 H, br t), 7.75 (4 H, q); $[\alpha]^{23}_D$ +98.1° (*c* 1.0, CH_3OH). Anal. Calcd for $C_{18}H_{21}O_9N_3S$: C, 47.47; H, 4.65; N, 9.23. Found: C, 47.55; H, 4.74; N, 8.94.

1-[1-(Methoxycarbonyl)-2-methyl-1-propenyl]-3-[[(4-nitrobenzyloxycarbonyl)amino]methyl]-4-oxoazetidine-2-sulfinic Acid (2). A stirred solution of the starting ester (2.83 g, 6.21 mmol) in 50 mL of CH_2Cl_2 was treated with 1.42 g (1.39 mL, 9.32 mmol) of DBU. After 3 h, no more starting material could be detected. The reaction mixture was diluted with ethyl acetate and was washed thoroughly with dilute HCl. The product was extracted into dilute $NaHCO_3$ solution (four times), and then the combined extracts were cooled in ice while the pH was adjusted to 2.0 with concentrated HCl. The product was extracted into CH_2Cl_2, and the solution was dried ($MgSO_4$) and evaporated to give the title compound in 67% yield as a colorless foam: IR (KBr) 5.64, 5.80 μm; NMR ($CDCl_3$) δ 2.00 (3 H, s), 2.23 (3 H, s), 3.78 (5 H, m), 4.78 (1 H, s), 5.23 (2 H, s), 6.10 (1 H, br s), 7.80 (4 H, q); $[\alpha]^{23}_D$ +29.9° (*c* 1.0, CH_3OH). Anal. Calcd for $C_{18}H_{21}O_9N_3S$: C, 46.68; H, 4.65; N, 9.23. Found: C, 47.25; H, 4.79; N, 8.90.

Methyl 1-[1-(Methoxycarbonyl)-2-methyl-1-propenyl]-3-[[(4-nitrobenzyloxycarbonyl)amino]methyl]-2-oxoazetidin-4-yl Sulfone (3). A stirred solution of the starting sulfinic acid (1.50 g, 3.30 mmol) in 50 mL of CH_2Cl_2 was layered with a solution of tetra-*n*-butylammonium hydrogen sulfate (1.12 g, 3.30 mmol) in 50 mL of water. Then 0.55 g (6.60 mmol) of $NaHCO_3$ was added. After 30 min, the CH_2Cl_2 layer was separated and combined with one CH_2Cl_2 wash of the aqueous phase, and the mixture was dried over $MgSO_4$. The solution was then treated with 0.94 g (0.41 mL, 6.60 mmol) of CH_3I and stirred overnight at room temperature. The solvent was evaporated, and the product was purified by chromatography to give the title compound as a colorless foam: IR(KBr) 5.62, 5.81 μm; NMR ($CDCl_3$) δ 2.07 (3 H, s), 2.23 (3 H, s), 2.80 (3 H, s), 3.60–3.83 (2 H, m), 3.58 (3 H, s), 5.18 (2 H, s), 5.55 (1 H, br s), 7.45 (4 H, q); $[\alpha]^{22}_D$ −40.7° (c 1.0, MeOH). Anal. Calcd for $C_{19}H_{23}O_9N_3S$: C, 48.60; H, 4.94; N, 8.95. Found: C, 48.52; H, 5.05; N, 8.72.

Methyl 3-[[(4-Nitrobenzyloxycarbonyl)amino]methyl]-2-oxoazetidin-4-yl Sulfone (4). A 9.11-g (42.6-mmol) portion of $NaIO_4$ was added to a solution of 0.50 g (3.16 mmol) of $KMnO_4$ in 150 mL of 0.1 M pH 7.0 buffer. Then 10.0 g (21.3 mmol) of methyl 1-[1-(methoxycarbonyl)-2-methyl-1-propenyl]-3-[[(4-nitrobenzyloxycarbonyl)amino]methyl-2-oxoazetidin-4-yl sulfone in 150 mL of acetone was added. The resulting reaction was mildly exothermic. After 3 h, the reaction appeared to be complete. The acetone solvent was removed by evaporation, and the aqueous residue was extracted thoroughly with ethyl acetate. The combined extracts were dried and evaporated to give an oil that was purified by flash-column chromatography, eluting with ethyl acetate to give the desired product: 1.4 g (18%); mp 168.5–169.5 °C; IR(KBr) 5.65, 5.88 μm; NMR (DMSO-d_6) δ 3.03 (3 H, s), 3.43 (2 H, t, *J* = 7 Hz), 3.58 (3 H, t, *J* = 7 Hz), 4.74 (1 H, d, *J* = 1.5 Hz), 5.19 (2 H, s), 7.70 (1 H, t, *J* = 7 Hz), 7.94 (4 H, d of d, *J* = 8, 158 Hz), 9.14 (1 H, s); $[\alpha]^{22}_D$ +1.5° (*c* 1.0, CH_3OH). Anal. Calcd for $C_{13}H_{15}N_3O_7S$: C, 43.69; H, 4.23; N, 11.76. Found: C, 43.55; H, 4.40; N, 11.98.

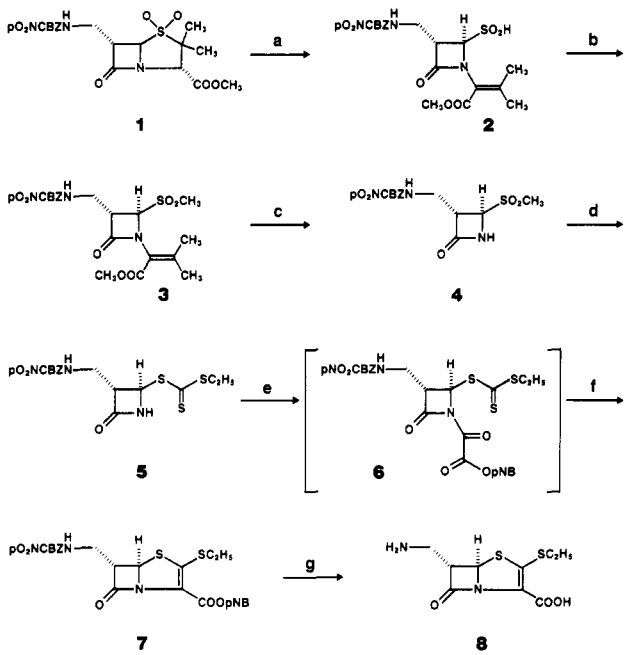
Methyl 3-[[(4-Nitrobenzyloxycarbonyl)amino]methyl]-2-oxoazetidin-4-yl Trithiocarbonate (5). Ethanethiol (0.95 g, 15.97 mmol) was added to a rapidly stirred mixture of 15.80 mL of a 1.0 M NaOH solution, a catalytic amount of tetrabutylammonium bromide, 100 mL of CS_2, and 100 mL of water. This bright yellow mixture was stirred for 90 min at room temperature, and then 1.90 g (5.32 mmol) of methyl 3-[[(4-nitrobenzyloxycarbonyl)amino]methyl]-2-oxoazetidin-4-yl sulfone was added. After 6 h, the CS_2 layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were dried, concentrated, and then chromatographed, eluting with 1:1 ethyl acetate/hexane to give 680 mg (31%) of the desired product as yellow crystals: mp 101–103 °C from ether; IR(KBr) 5.62, 5.70, 5.93 μm; NMR ($CDCl_3$) δ 1.32 (3 H, t, *J* = 7 Hz), 3.28 (2 H, q, *J* = 7 Hz), 3.28–3.90 (3 H, m), 5.17 (2 H, s), 5.38 (1 H, d, *J* = 1.5 Hz), 5.77 (1 H, t, *J* = 7 Hz), 7.12 (1 H, s), 7.73 (4 H, d of d, *J* = 9, 42 Hz); $[\alpha]^{22}_D$ +88.5° (*c* 0.5, CH_3OH). Anal. Calcd for $C_{15}H_{17}O_5N_3S_3$: C, 43.36; H, 4.13; N, 10.11. Found: C, 43.31; H, 3.95; N, 10.02.

(5*R*,6*S*)-4-Nitrobenzyl 2-(Ethylthio)-6-[[(4-nitrobenzyl-

(12) Alfonso, A.; Hon, F.; Weinstein, J.; Ganguly, A. K.; McPhail, A. T. *J. Am. Chem. Soc.* **1982**, *104*, 6138.

(13) The impurities present were mainly inorganic salts. Attempts at purification by ion-exchange techniques led to a loss of β-lactam.

Scheme I[a]



[a] (a) DBU, CH_2Cl_2; (b) n-Bu_4NHSO_4, CH_3I; (c) $KMnO_4$, $NaIO_4$, pH 7; (d) $C_2H_5SC(S)S^-$, n-Bu_4NBr, CS_2; (e) ClC(O)C(O)O-p-NB, DIPEA, CH_2Cl_2; (f) $(C_2H_5O)_3P$, $CHCl_3$, Δ ; (g) H_2, 10% Pd on Celite; p-NO_2Cbz=$O_2NC_6H_4CH_2OC(O)$—; p-NB=$CH_2C_6H_4NO_2$; DIPEA=$C_2H_5N(i\text{-}C_3H_7)_2$.

oxycarbonyl)amino]methyl]penemcarboxylate (7). A solution of 0.680 g (1.64 mmol) of methyl 3-[[(4-nitrobenzyloxycarbonyl)amino]methyl]-2-oxoazetidin-4-yl trithiocarbonate and 0.797 g (3.27 mmol) of chloro 4-nitrobenzyl oxalate in 30 mL of ethanol-free $CHCl_3$ was treated with 0.327 g (3.27 mmol) of $CaCO_3$ and cooled to 3 °C. Then a solution of 0.422 g (3.27 mmol) of diisopropylethylamine in a few milliliters of ethanol-free $CHCl_3$ was added dropwise such that the temperature of the reaction mixture remained below 5 °C. This mixture was stirred for 30 min in an ice bath and then poured into ice water. The $CHCl_3$ layer was separated and combined with one $CHCl_3$ wash of the aqueous layer, and the mixture was dried over Na_2SO_4 and filtered.

The resulting solution containing the intermediate oxalamide was heated to reflux, and a solution of 0.815 g (4.91 mmol) of distilled $P(OEt)_3$ in 25 mL of $CHCl_3$ was added dropwise over a period of 4 h. Then the reaction mixture was heated 6 h more and was stirred at room temperature for 12 h. The solution was evaporated, and the residues were taken up in EtOAc from which the product crystallized, giving 215 mg (23%) of crystals: mp 205–207 °C; IR(KBr) 5.59, 5.92 μm; NMR (DMSO-d_6) δ 1.32 (3 H, t, J = 7 Hz) 3.03 (2 H, d of q, J = 7 Hz), 3.52 (2 H, br t), 4.01 (1 H, t, J = 7 Hz), 5.20 (2 H, s), 5.37 (2 H, AB q, J = 8, 25.4 Hz), 5.69 (1 H, d, J = 1.5 Hz), 7.81 (1 H, t, J = 7 Hz), 7.90 (4 H, d of d, J = 8, 158 Hz), 7.95 (4 H, d of d, J = 8, 130 Hz); $[\alpha]^{22}_D$ +92.7° (c 1.0, DMSO). Anal. Calcd for $C_{24}H_{22}N_4O_9S_2$: C, 50.17; H, 3.86; N, 9.75. Found: C, 50.16; H, 3.93; N, 9.47.

(5*R*,6*S*)-6-(Aminomethyl)-2-(ethylthio)penemcarboxylic Acid Sodium Salt. A solution of 235 mg of (5*R*,6*S*)-4-(nitrobenzyl) 2-(ethylthio)-6-[[(4-nitrobenzyloxycarbonyl)amino]methyl]penemcarboxylate in 25 mL of THF was diluted with 25 mL of water, and then 35 mg of 10% Pd on Celite was added. This mixture was hydrogenated at 50 psi for 1 h, and then a second portion of catalyst was added followed by hydrogenation for 30 min. The mixture was filtered through Celite, and the THF was evaporated. The aqueous residue was extracted two times with EtOAc and with ether, and the solution was then filtered through a Millipore filter and freeze-dried to afford 45 mg of a tan solid. This material was not pure[13], but the presence of the desired product was indicated by spectral data: IR(KBr) 5.65, 6.19 μm; NMR (D_2O) δ 1.37 (3 H, t, J = 7 Hz), 3.00 (2 H, d of q, J = 7 Hz), 3.36 (2 H, d of d, J = 1.5, 7 Hz), 4.10 (1 H, t, J = 6 Hz), 5.70 (1 H, d, J = 1.5 Hz); $[\alpha]^{22}_D$ +15.6° (c 1.0, H_2O).

Synthesis of a New Heterocycle: *cis*-4b,5,6,10b,11,12-Hexahydro-5,12-diazachrysene

Christos Papageorgiou* and Xaver Borer

Preclinical Research, SANDOZ Ltd., CH-4002 Basel, Switzerland

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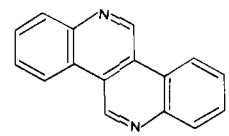
The 6,12-diazachrysene chromophore is a structural moiety found in degradation products such as calycanine (**6**).[1] The reported syntheses[2] of calycanine being rather



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lengthy and low yielding, we investigated a straightforward approach to diazachrysenes. Retrosynthetic analysis indicated that they could be obtained via Beckmann rearrangement of bis oxime **3a**. The required intermediates were prepared by methanesulfonic acid (MSA) cyclization of diphenylsuccinic acid (**1**).[3] Complete stereoconversion was observed during the ring-closure procedure. Once one ring is formed, only the cis-oriented carboxy and phenyl groups can further cyclize to give the diketo derivative **2**. The latter was converted into a mixture of isomeric oximes **3a** upon treatment with $HONH_2$·HCl/Na_2CO_3 (Scheme I).

The Beckmann rearrangement of **3a** to bis lactam **4** was then attempted. Treatment of the bis oxime under various Beckmann rearrangement conditions (PPA,[4] HMPT,[5] PPSE,[6] $POCl_3$/pyridine[7]) resulted either in extensive decomposition or fragmentation. Additionally a two-stage procedure[8] involving formation of a bromonitroso derivative followed by its reaction with triphenylphosphine did not lead to formation of any isolable product. The corresponding tosylate **3b** was also unreactive possibly because of its poor solubility in the acidic reaction media.

These disappointing results prompted us to examine the reductive Beckmann rearrangement.[9] When the bis oxime **3a** was allowed to react with a large excess of diisobutyl aluminium hydride (DIBAH) a basic compound was obtained in 23% yield. Surprisingly the ^1H NMR spectrum was consistent with a nonsymmetric structure. An ABX and a benzylic AB systems were present. Furthermore the angular protons appeared as a doublet and a doublet of triplet (X part of the ABX). Their small coupling constant (4.8 Hz) indicated that the ring junction was cis. Confirmation of the structure **5** was obtained by ^{13}C NMR. The chemical shift of C-1a occured approximately 10 ppm downfield from that of C-6a.

(1) Saxton, J. E. *Alkaloids (N.Y.)* 1960, *7*, 147.
(2) Clark, V. M.; Cox, A. *Tetrahedron* **1966**, *22*, 3421. Kobayashi, T.; Kikumoto, R. *Ibid.* **1962**, *18*, 813. Gopinath, K. W.; Govindachari, T. R.; Rajappa, S. *Ibid.* **1960**, *8*, 291.
(3) Davis, R. B.; Ward, J. A. *Organic Syntheses*; Wiley: New York, 1962; Collect. Vol. 4, p 392. Wawzonek, S. *J. Am. Chem. Soc.* **1940**, *62*, 745.
(4) Guy, A.; Guetté, J.-P. *Synthesis* **1980**, 322.
(5) Monson, R.; Broline, B. *Can. J. Chem.* **1973**, *51*, 942.
(6) Imamoto, T.; Yokoyama, H.; Yokoyama, M. *Tetrahedron Lett.* **1981**, 1803.
(7) Schmidt-Thomé, J. *Chem. Ber.* **1955**, *88*, 895.
(8) Ohno, M.; Sakai, I. *Tetrahedron Lett.* **1965**, 4541.
(9) Sasatani, S.; Miyasaki, T.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1983**, 4711.

0022-3263/87/1952-4403$01.50/0