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The Penems, a New Class of β-Lactam Antibiotics. 2.[1] Total Synthesis of Racemic 6-Unsubstituted Representatives

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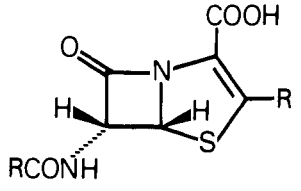
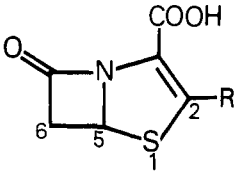
Abstract: Synthetic methods are described for the preparation of racemic compounds **1b**. The new substances differ from the previously described, penicillin-derived penems in their lack of an acylamino side chain. In striking contrast to penicillanic acid (**2**) and cephalosporanic acid (**3**), the new substances show antibiotic activity.

Recently we disclosed the preparation of compounds **1a** representing a new category of biologically active β-lactams. Structurally related to both the penicillins and the cephalosporins, these long-sought substances were obtained in optically active form by partial synthesis from penicillin V.[1] The antibiotic properties of these first members **1a** of the penem family justified the undertaking of a more extensive effort directed at elaborating synthetic routes to the penems. Besides widening the range of accessible structures and thereby giving insight into structure-activity relationships, such an endeavor was likely to produce synthetic methods applicable in related areas.

In this paper we present a first group of totally synthetic penems. At the outset we chose as the general target compounds represented by structure **1b**.

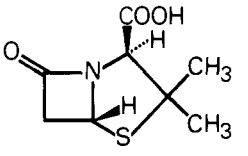


1a



1b

These differ from the substances described earlier in their lack of an acylamino side chain at position 6. Compounds containing a condensed β-lactam system unsubstituted in the 6 (or equivalent) position had been prepared by total and partial synthesis before.[2a,b] Our decision to construct the 6-unsubstituted members of the penem class rested on chemical rather than biological grounds; we felt that the fundamental chemistry of the new system could be best explored with these simple representatives. Further, we discerned the possibility, which in the event was realized, of preparing such substances relatively simply by total synthesis. Had we been guided by the biological activity of compounds such as **2** and **3** in our synthetic endeavors, the venture might have seemed fatuous, since both **2** and **3** are devoid of anitbiotic activity.[2b,3]



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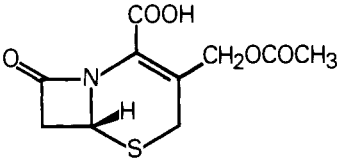

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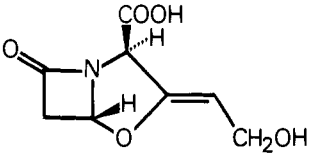

4

Clavulanic acid (**4**), a substance in some ways related to **1b**, which was isolated from natural sources by the Beecham group,[4] likewise carries no side chain at carbon 6. While this

† Deceased July 8, 1979.

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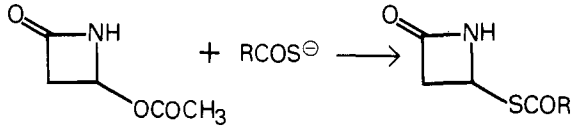
Table I. Minimum Inhibitory Concentrations (MIC) (μg/mL)

	Gram-positive strains				Gram-negative strains					
12	*Staphylococcus aureus* (Smith) 14	*Staphylococcus aureus* 2999 (resistant)	*Streptococcus pyogenes* Aronson/K 1129	*Streptococcus pneumoniae*/III/84	*Neisseria meningitidis*/ K 1316	*Haemophilus influenzae* NCTC 4560	*E. coli* 205	*Salmonella typhimurium* 277	*Proteus rettgeri*/ K 856	*Pseudomonas aeruginosa*/ K 1118
R = CH_3	1	1	0.5	0.5	0.1	4	8	4	8	8
R = phenyl	1	4	0.05	0.1	0.1	4	8	8	4	*b*
R = *n*-pentyl	0.2	2	0.05	0.05	0.05	2	32	16	32	64
cephalexin	1	8	1	1	0.5	32	8	4	128	*a*
penicillin V	0.05	64	0.05	0.05	0.5	4	128	64	*a*	*a*

[a] No inhibition at 128 μg/mL. [b] Not measured.

compound displays only weak antibacterial activity, it is highly distinctive in its potent β-lactamase inhibiting property.

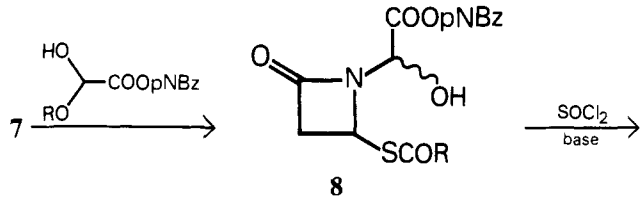
One of the bases for the synthesis of the unsubstituted series was laid by Clauss, Grimm, and Prossel,[5] who prepared 4-acetoxy-2-azetidinone (**5**) and showed that the acetoxy group could be displaced readily with nucleophiles. By allowing **5** to react with various thiocarboxylates **6** we obtained the thioanalogues **7**.



5 **6** **7**

Thio acids **6**, if not commercially available, were prepared by variants of three standard methods:[6] (A) reaction of the corresponding carboxylic acid chloride with potassium hydrosulfide, prepared in situ; (B) treatment of the acid chloride in pyridine and a chlorinated solvent with hydrogen sulfide; (C) treatment of a mixed carboxylic carbonic anhydride in methylene chloride with hydrogen sulfide in the presence of triethylamine.

For the following three steps the elaboration of the thiazoline ring followed precisely the path worked out in our laboratory some years ago[7] and used since for the synthesis of the first members of the penem class.[1] Thus, the acylmercapto β-lactams **7** reacted with glyoxylic esters, their hydrate, or hemiacetals to give the adducts **8** as a mixture of diastereomers. In the light of prior work[1] with these glyoxylates, especially in relation to liberation of the carboxylic acid function in the final product, we chose the *p*-nitrobenzyl group as a protector of the acid function. Thionyl chloride and base transformed the carbinolamines **8** into the corresponding chlorides **9** which were, as diastereomeric mixtures and without further purification, warmed with triphenylphosphine in dioxane solution.



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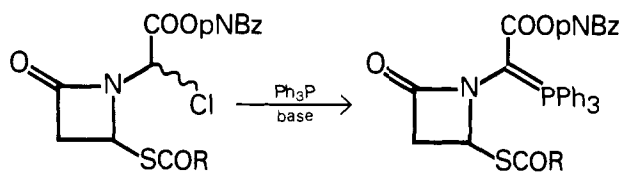
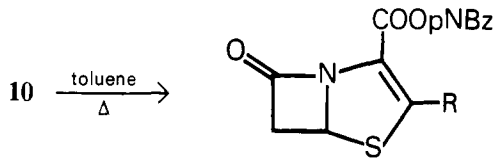


9 **10**

The resulting phosphonium salts were deprotonated in situ to the phosphoranes **10** through the presence of a base (usually polymeric Hünig base[1]) in the reaction solution.

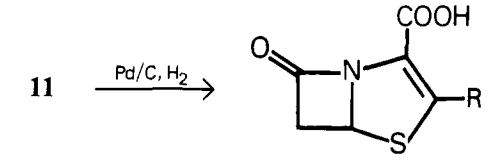
When the phosphorane esters **10** were warmed in toluene, usually at 90 °C, and in the presence of a small amount of hydroquinone, ring closure occurred, and the penem esters **11** were produced along with triphenylphosphine oxide. In some cases it proved advisable not to carry the reaction to completion but rather to isolate the product after partial cyclization of **10**.



11

Spectroscopic data of **11** agreed with the penem esters carrying an acylamino side chain;[1] the UV spectra (EtOH) exhibited a maximum at ca. 308 nm (R = alkyl), the IR spectra (CH_2Cl_2) showed the typical short-wavelength band for the β-lactam carbonyl between 5.55 and 5.60 μ. Moreover, an X-ray diffraction structure determination of **11** (R = CH_3)[8] clearly corroborated the structure and revealed, among other things, the pyramidal nature of the β-lactam nitrogen, with the height of the pyramid formed by C_3, C_5, C_7, and apical N_4 being 0.43 Å. This value is higher than those found with penicillins (0.38–0.40 Å), and lower than those observed for carbapenems (0.49–0.50 Å).

Finally, hydrogenolytic cleavage of the *p*-nitrobenzyl group in compounds **11** with palladium on carbon as catalyst, using the system ethyl acetate–aqueous sodium bicarbonate as reaction medium, yielded the penem acids **12**.



12

Astonishingly, and unlike **2** and **3**,[2b,3] the compounds **12**, though unsubstituted in the 6 position, were found to be powerful antibiotic substances. In the light of this surprising observation, it appears that the limits of structural variation in relation to biological activity in this area are virtually undefined.

Table I portrays antibacterial data obtained for three representative crystalline, analytically pure 6-unsubstituted penem

Table II

6	RCOSH	method
a	$CH_2CH_2COOCH_3$	A
b	CH_2OCOCH_3	B
c	$CH_2NHCOCH_2OPh$	C
d	$CH_2CH_2NHCOOCH_2Ph$-*p*-NO_2	C
e	$CH_2CH_2CH_2NHCOOCH_2Ph$-*p*-NO_2	C
f	CH_2Ph	A
g	*m*-dimethylaminophenyl	C

carboxylic acids. It should be emphasized that these compounds are *racemic*. Values for cephalexin and penicillin V are appended for comparison.

Experimental Section

Melting points were determined on a Reichert micro hot stage and are uncorrected. Infrared (CH_2Cl_2) and ultraviolet spectra (EtOH 96%) were recorded on Perkin-Elmer 137 and Beckman DB-GT spectrophotometers, respectively. ^1H NMR spectra were measured in deuteriochloroform (unless stated otherwise), containing tetramethylsilane as internal standard (δ 0 ppm) on a Varian HA-100 D spectrometer; shifts are given in δ values. Mass spectra were recorded with a Varian CH 7 spectrometer. Merck silica gel 60 F_{254} was used for thin layer chromatography.

Thiocarboxylic Acids 6. Thioacetic and thiobenzoic acids (**6**, R = CH_3, C_6H_5, respectively) were purchased from Fluka AG, CH-9470 Buchs, Switzerland, and used without purification. **6**, R = *n*-pentyl,[10] R = α-furyl,[11] and thionicotinic[12] acid were prepared according to literature procedures. The remaining thio acids were prepared by methods based upon one of three known procedures;[6] each of the methods is exemplified below for a particular case and in Table II the procedure used for each thio acid is designated. All thio acids prepared were processed without purification.

Method A. 6f. Potassium hydroxide (10 g) was dissolved in 5 mL of water and 90 mL of ethanol. The solution was saturated with hydrogen sulfide (1 h, 0 °C). Phenylacetyl chloride (6.71 g, 43.4 mmol) was slowly added at 0 °C. This was followed by stirring the mixture for 2 h at room temperature, whereupon the solution was diluted with water and made alkaline by addition of 1 N sodium hydroxide. The solution was extracted once with ether and the extract discarded. The aqueous phase was acidified with 1 N hydrochloric acid and extracted several times with ether. The combined extracts were dried over sodium sulfate and evaporated in vacuo to afford 5 g of the crude thio acid **6f**: yield 75%; IR 3.30, 3.90, 5.85, 9.70 μ.

Method B. 6b. A steady stream of hydrogen sulfide was passed for 1 h into an ice-cooled solution of 161 mL of pyridine in 100 mL of methylene chloride. A solution of 68.25 g of acetoxyacetyl chloride[13] in 100 mL of methylene chloride was added dropwise and the combined mixture stirred for 2 h at 5 °C. Upon acidification with 4 N sulfuric acid the organic layer was separated and combined with three portions of 250 mL of methylene chloride which had been used to extract the aqueous layer. When the organic solution was dried over sodium sulfate and evaporated in vacuo, 63.5 g of crude acetoxythioacetic acid was obtained as a yellow oil, yield 95%.

Method C. 6c. A solution of 5.63 g of *N*-phenoxyacetylglycine[14] and 7.4 mL (2 equiv) of triethylamine in 50 mL of dry methylene chloride was cooled to −10 °C. A solution of 3.7 mL of isobutyl chloroformate in 10 mL of the same solvent was added dropwise. The reaction mixture was stirred at −10 °C for 90 min, after which dry hydrogen sulfide was bubbled through the solution for 2 h. The mixture was allowed to warm to room temperature and then acidified with 2 N sulfuric acid. The organic phase was separated, dried over sodium sulfate, and evaporated at water-pump vacuum. There resulted 6.00 g of crude **6c**, yield 99%.

4-Acylthio-2-azetidinones 7. 4-Acetylthio-2-azetidinone (**7**, R = CH_3) was prepared according to Clauss et al.[5] and obtained in the yield indicated by these workers.

7, R = Phenyl. Acetoxyazetidinone (5.15 g, 40 mmol) was dissolved in 20 mL of water and cooled on ice; a precooled solution of 5.5 g (40mmol) of thiobenzoic acid in 40 mL of 1 N NaOH was then added drop by drop with stirring.

After the addition, the pH was adjusted to ca. 7 and the reaction mixture was stirred overnight. The desired compound precipitated from the reaction mixture. The precipitate was filtered, washed free of alkali with cold water, and recrystallized from CH_2Cl_2–hexane as a colorless, crystalline solid: mp 104–105 °C; yield 4.96 g (60%); IR 2.92, 5.57, 5.95, 6.20, 6.27, 8.22, 8.45, 10.85, 11.10 μ; NMR δ 7.4–8.0 (compl 5 H), 6.76 (b, NH), 5.42 (q, 1, J = 2 and 5 Hz), 3.56 (m, 1, J = 2, 5, and 15 Hz), 3.09 (m, 1, J = 2, 2, and 15 Hz). Anal. Calcd for $C_{10}H_9NSO_2$ (207.25): C, 57.95; H, 4.38; N, 6.76; S, 15.47. Found: C, 57.92; H, 4.42; N, 6.83; S, 15.46.

7, R = α-Furyl. α-Thiofuroic acid (6.4 g, 50.7 mmol) was dissolved in 51 mL of 1 N aqueous sodium hydroxide and the solution was added dropwise to 5.15 g (35 mmol) of 4-acetoxyazetidinone suspended in 20 mL of water and stirred under dry nitrogen. When TLC showed clean conversion (4–6 h), the mixture was extracted three times with methylene chloride. Drying over Na_2SO_4, filtration, and evaporation of the solvent gave 7.75 g of crude material. Column chromatography (SiO_2, toluene–ethyl acetate (4:1)) gave 4.6 g of pure **7** (67%). The crystals had mp 94–95 °C: IR 2.97, 5.6, 6.05, 6.37, 6.85 μ; NMR δ 7.60 (m, 1), 7.22 (d, 1, J = 3.5 Hz), 6.85 (m, 1, exchanges with D_2O), 6.55 (dd, 1, J = 2 and 3.5 Hz), 2.95–3.65 (m, 2). Anal. Calcd for $C_8H_7NO_3S$ (197.21): C, 48.73; H, 3.58; N, 7.10; S, 16.26. Found: C, 48.8; H, 3.7; N, 7.1; S, 16.1.

7, R = 3-Pyridyl. 5 (5.16 g) was dissolved in 30 mL of water and treated at room temperature with a solution of 6.95 g of thionicotinic acid in 50 mL of 1 N sodium hydroxide. A slight excess of sodium hydroxide was added in order to keep the pH near 8. After having been stirred for 1 h at room temperature, the mixture was extracted three times with methylene chloride. These extracts gave, after drying over Na_2SO_4, filtration, and evaporation, the crude product. Subsequent column chromatography (250 g of SiO_2, toluene–ethyl acetate (2:3)) gave 3.85 g (46%) of the expected azetidinone **7**: mp 112–113 °C; IR 2.95, 5.6, 5.97, 6.27, 8.15, 8.2, 10.85, 11.12 μ; NMR δ 9.1 (m, 1), 8.8 (m, 1), 8.17 (m, 1), 7.4 (m, 1), 6.75 (m, 1, exchanges with D_2O), 5.45 (dd, 1), 3.0–3.7 (m, 2). Anal. Calcd for $C_9H_8N_2O_2S$ (208.23): C, 51.91; H, 3.87; N, 13.45; S, 15.40. Found: C, 51.85; H, 3.88; N, 13.70; S, 15.26.

7, R = 2-Carbomethoxyethyl. 5 (966 mg, 7.48 mmol) was dissolved in 5 mL of water. Thiosuccinic acid monomethyl ester (1.11 g, 7.48 mmol) dissolved in 7.48 mL of 1 N aqueous sodium hydroxide was slowly added. After addition of the acid, more 1 N sodium hydroxide was added until the pH value of the reaction mixture was adjusted to 8. The mixture was then stirred for 4 h at room temperature and was extracted with methylene chloride several times. The combined extracts were dried over sodium sulfate. After evaporation of the solvent, the residue was chromatographed on silica gel. Elution with toluene–ethyl acetate (9:1, 4:1, and 7:3, successively) afforded 266 mg (16% yield) of the product as a colorless oil: IR 2.95, 3.40, 5.60, 5.73, 5.88, 6.95, 7.10, 7.30, 7.42 μ; NMR δ 6.84 (br, NH), 5.27 (dd, 1, J = 2 Hz), 3.70 (s, 3), 3.48 (dd, 1, J = 5 and 15 Hz), 3.05 (m, 1), 2.90 (m, 2), 2.65 (m, 2).

7, R = *n*-Pentyl. Thiohexanoic acid (2.64 g, 20 mmol) was dissolved in precooled 10 mL of 2 N NaOH and 5 mL of dioxane. 4-Acetoxyazetidinone (2.58 g, 20 mmol) was dissolved in 10 mL of dioxane, cooled in ice; the thio acid solution was then added drop by drop. After the addition the reaction mixture was stirred for 30 min at room temperature. The reaction mixture was extracted with CH_2Cl_2, the organic phase dried and evaporated, and the residue chromatographed on silica gel using toluene–ethyl acetate (3:1) as eluent system. First fractions gave the desired pure compound as an oil: yield 2.76 g (68%); IR 3.00, 5.65, 5.85 μ; NMR δ 6.85 (br, NH), 5.24 (dd, 1; J = 2 and 5 Hz), 3.46 (m, 1, J = 2, 5, and 15 Hz), 2.96 (m, 1, J = 2, 2, and 15 Hz), 2.58 (t, 2, J = 7 Hz), 1.20–1.90 (m, 6), 0.9 (t, 3, J = 7 Hz). Anal. Calcd for $C_9H_{15}NO_2S$ (201.28): C, 53.71; H, 7.51; N, 6.96; S, 15.93. Found: C, 53.82; H, 7.63; N, 6.83; S, 15.86.

7, R = Acetoxymethyl. 5 (8.5 g, 0.065 mol) was dissolved in 50 mL of dioxane, and a precooled solution of 13.4 g (0.1 mol) of acetoxythioacetic acid in 100 mL of 1 N NaOH was added. The reaction mixture was stirred at room temperature for 3 h, extracted with CH_2Cl_2 (3 × 100 mL), dried, and evaporated to dryness. The residue was chromatographed three times on SiO_2 using toluene–EtOAc (4:1) as solvent system, wt of the product 2.60 g (20%).

The product was contaminated with starting material to the extent of 9%. The separation was relatively difficult because of the closeness of R_f values. The product was used in this state of purity: R_f 0.34 (toluene–EtOAc (1:1)); IR 2.95, 5.60, 5.72, 5.90, 8.20 μ; NMR δ 6.96 (br, NH), 5.26 (dd, 1, J = 2 and 5 Hz), 4.74 (s, 2), 3.50 (m, 1), 2.98 (m, 1), 2.18 (s, 3).

7, R = Phenoxyacetaminomethyl. Phenoxyacetylaminothioacetic acid (6 g, 26.6 mmol) was dissolved in a precooled 26 mL of 1 N NaOH solution and 5 mL of dioxane, and was added to a cooled solution of 3.43 g (26.5 mmol) of **5** in 20 mL of dioxane. The reaction mixture was stirred at room temperature for 30 min and extracted with CH_2Cl_2 (3 ×50 mL). The organic extracts were dried and evaporated and the residue was chromatographed on a silica gel column using toluene–EtOAc (1:1) as solvent system, wt of the product 1.50 g (20%). The product was recrystallized from CH_2Cl_2–petroleum ether: mp 114–115 °C; IR 2.95, 5.60, 5.90, 6.25, 6.60, 6.70, 8.10 μ; NMR δ 6.70–7.50 (m, 6), 5.24 (m, 1), 4.59 (s, 2), 4.29 (d, 2, *J* = 6 Hz), 3.46 (m, 1), 2.94 (m, 1). Anal. Calcd for $C_{13}H_{14}N_2O_4S$ (294.33): C, 53.05; H, 4.80; N, 9.52; S, 10.90. Found: C, 52.96; H, 4.82; N, 9.40; S, 10.85.

7, R = 2-[*p*-Nitrocarbobenzoxyamino]ethyl. Crude thio acid **6d** (5.60 g, 20 mmol) was dissolved in 20 mL of precooled 1 N NaOH and was added drop by drop to a cooled solution of 2.2 g (17 mmol) of 4-acetoxyazetidin-2-one in 10 mL of dioxane. After the addition the reaction mixture was stirred at room temperature for 3 h and extracted with CH_2Cl_2 (3 × 50 mL) and the combined extracts were evaporated. The residue thus obtained was chromatographed on a column of silica gel using toluene–EtOAc (9:1 → 1:1) as solvent system: wt of the product 4.10 g (68% yield based on 4-acetoxyazetidinone); IR 2.95, 5.65, 5.80, 5.95, 6.60, 7.45, and 8.17 μ; NMR δ 8.18 (d, 2), 7.49 (d, 2), 6.78 (br, NH), 5.44 (br, NH), 5.27 (dd, 1, *J* = 2 and 4 Hz), 5.18 (s, 2), 3.52 (q, 2, *J* = 6 Hz), 3.44 (m, 1), 2.96 (m, 1), 2.86 (t, 2).

7, R = 3-(*p*-Nitrocarbobenzoxyamino)propyl. The crude thio acid (10 mmol) **6e** was dissolved in precooled 10 mL of 1 N NaOH and added to a cooled solution of 1.1 g (8.52 mmol) of **5** in 10 mL of dioxane. The reaction mixutre was stirred at room temperature until the disappearance of the thio acid spot on TLC (1.5 h). The reaction mixture was extracted with CH_2Cl_2 (3 × 40 mL), the organic phase was dried and evaporated, and the residue was chromatographed on a column of SiO_2 using toluene–EtOAc (9:1 → 7:3 → 1:1) as solvent system. Product was eluted with the 1:1 solvent mixture, and weighed 2.80 g (88%), foamy solid, yield based on 4-acetoxyazetidinone: IR 2.95, 5.65, 5.80, 5.92, 6.25, 6.60, 7.45, and 8.15 μ; NMR δ 8.18 (d, 2), 7.50 (d, 2), 6.88 (br, NH), 5.26 (m, 2), 5.20 (s, 2), 3.46 (m, 1), 3.26 (q, 2, *J* = 7 Hz), 2.94 (m, 1), 2.66 (t, 2, *J* = 7 Hz), 1.90 (quintet, 2, *J* = 7 Hz). Anal. Calcd for $C_{15}H_{17}N_3O_6S$ (367.38): C, 49.04; H, 4.67; N, 11.44; S, 8.73. Found: C, 49.10; H, 4.80; N, 11.19; S, 8.49.

7, R = Benzyl. Phenylthioacetic acid (5 g, 33 mmol) was dissolved in 33 mL of 1 N aqueous sodium hydroxide solution. This solution was slowly added dropwise to a solution of 4.24 g (33 mmol) of **5** in 20 mL of water. The reaction mixture was stirred at room temperature. After 1 h of stirring, a solid started to precipitate. While stirring was continued overnight, more of this solid precipitated and was collected by filtration. After drying under high vacuum, the precipitate was recrystallized twice from methylene chloride–hexane to afford 4.97 g (68% yield) of white crystals: mp 78 °C; IR 3.0, 5.65, 5.95, 6.73, 7.15, 7.5, 7.87, 8.65 μ; NMR δ 7.27 (m, 5), 6.56 (br, NH), 5.15 (dd, 1, *J* = 2 Hz), 3.82 (s, 2), 3.38 (dq, 1, *J* = 2, 5, and 14 Hz), 2.88 (dq, 1, *J* = 2, 2, and 14 Hz). Anal. Calcd for $C_{11}H_{11}NO_2S$ (221.28): C, 59.71; H, 5.01; N, 6.33; S, 14.49. Found: C, 59.37; H, 4.93; N, 6.48; S, 14.41.

7, R = *m*-Dimethylaminophenyl. **5** (616 mg, 4.77 mmol) was dissolved in 13 mL of water, and the mixture was cooled to 0 °C. Thio acid **6g** (864 mg, 4.77 mmol) dissolved in 4.77 mL of 1 N aqueous sodium hydroxide and 5 mL of tetrahydrofuran was added. The reaction mixture was then stirred at room temperature overnight. Then 50 mL of methylene chloride was added and after vigorous shaking the organic layer was separated, washed with water, and dried over sodium sulfate. Evaporation of the solvent afforded a crude product, which was chromatographed on silica gel. Elution with toluene–ethyl acetate yielded an oily product. This material was crystallized from methylene chloride–pentane. Thus 306 mg (27% yield) of green-yellow crystals, mp 117 °C, was isolated: IR 2.95, 3.5, 5.63, 6.03, 6.25, 6.68, 7.0, 7.40, 8.28, 8.62, 10.22, 10.82, 11.10 μ; NMR δ 7.22 (m, 3), 6.92 (m, 1), 6.59 (br, NH), 5.36 (dd, 1, *J* = 2 and 4 Hz), 3.52 (m, 1, *J* = 2, 5, and 15 Hz), 3.06 (m, 1, *J* = 2 and 15 Hz), 2.98 (s, 6). Anal. Calcd for $C_{12}H_{14}N_2O_2S$ (250.32): C, 57.58; H, 5.64; N, 11.19; S, 12.81. Found: C, 57.71; H, 5.68; N, 11.23; S, 12.78.

***p*-Nitrobenzyl (4-Acylthio-2-azetidinon-1-yl)-triphenylphosphoranylideneacetate 10. 10, R = Methyl.** 4-Acetylthio-2-azetidinone (7, R = CH_3), 3.3 g (22.75 mmol), and the ethyl hemiacetal of *p*-nitrobenzyl glyoxylate[1] (12.9 g) were dissolved in 240 mL of dry toluene and 60 mL of dry dimethylformamide. After addition of freshly activated (250 °C, vacuum) molecular sieves (3 or 4 Å, 100 g) the mixture was stirred in a nitrogen atmosphere at room temperature overnight and for 2 hr at 50 °C. The sieves were filtered off and washed with toluene and the combined filtrate and washings were concentrated in vacuo. Column chromatography of the oily residue on 400 g of silica gel afforded first unconsumed glyoxylate (with toluene–ethyl acetate (9:1)) and then the adduct **8** (R = CH_3) as a mixture of diastereomers, 7.2 g (89%). The crude product was contaminated by a small amount of the glyoxylate reagent: IR 2.8, 5.62, 5.7 (sh), 5.90, 6.55, 7.40 μ; NMR δ 7.4–8.3 (compl 4 H), 5.2–5.6 (m, 4), 4.07 and 4.42 (d, 1), 2.9–3.6 (m, 2), 2.30 and 2.38 (s, 3).

Crude carbinolamine **8** (R = CH_3), 2 g, dissolved in 40 mL of absolute dioxane was added to 5.5 g of polymeric Hünig base[1] that had previously been stirred for 30 min in 20 mL of the same solvent. After addition of 1.87 mL (3.5 equiv) of thionyl chloride the mixture was stirred at room temperature in a nitrogen atmosphere for 5 h. The insoluble polymeric base was filtered off and the filtrate evaporated in vacuo to give the crude chloride **9** (R = CH_3). Redissolution of this material in 107 mL of dioxane and addition of the polymeric base (7 g) was followed by treatment of the resulting solution with 2.85 g of triphenylphosphine at 50 °C for 15 h in a nitrogen atmosphere. Filtration and evaporation of the filtrate under reduced pressure gave crude **10** (R = CH_3) which was purified by column chromatography on 150 g of silica gel. Elution with toluene–ethyl acetate (3:2) yielded 1.6 g of the phosphorane as a yellow foam: IR 5.67, 5.90, 6.15, 6.55, 7.42, 9.05, 9.25 μ. NMR spectra of phosphoranes **10**, owing to the presence of the phosphorus, are not amenable to meaningful interpretation.

10, R = Phenyl. 4-Benzoylthio 2-azetidinone (**7**, R = phenyl), 2.35 g (11.38 mmol), and 6.45 g of the ethyl hemiacetal of *p*-nitrobenzyl glyoxylate were dissolved in 30 mL of dry dimethylformamide and 120 mL of dry toluene. The reaction mixture was stirred overnight with freshly dried molecular sieves, at room temperature, and then at 50 °C for 2 h. The reaction mixture was filtered and the filtrate evaporated to dryness in vacuo. The residue was chromatographed on silica gel using toluene–ethyl acetate (9:1 and 3:1) as elution mixtures to obtain 5.2 g of product (**8**, R = phenyl) contaminated with some glyoxylate reagent: IR 2.85, 5.63, 5.70, 5.98, 6.20, 6.54, 7.40, 8.25, 11.0 μ.

The adduct mixture **8** (R = phenyl), 3.0 g, was converted to the mixture of epimeric chlorides **9** (R = phenyl) according to the procedure given above for **9** (R = CH_3). Further processing followed again the method described for **10** (R = CH_3). The obtained crude phosphorane **10** (R = phenyl) was chromatographed on silica gel. Unreacted triphenylphosphine was eluted first using toluene–ethyl acetate (9:1). The product was obtained by elution with toluene–ethyl acetate (3:2), 2.20 g (56% based on **8**, R = phenyl): IR 5.67, 6.00, 6.15, 6.55, 7.42, 8.30, 9.05, 11.05 μ.

10, R = Benzyl. 4-Phenacetylthio-2-azetidinone (**7**, R = benzyl), 1.244 g, and 2.87 g of *p*-nitrobenzyl glyoxylate ethyl hemiacetal were processed as described for **8** (R = phenyl). Chromatography on silica gel yielded 2.41 g of purified **8** (R = benzyl) using toluene–ethyl acetate (9:1 and 4:1) as eluant mixtures. The product (522 mg), still containing some reagent glyoxylate, was converted to the epimeric chlorides **9** (R = benzyl), 550 mg, following the procedure given for **9** (R = methyl): IR 5.61, 5.70, 6.25, 6.55, 7.45, 9.0 μ.

Using the standard procedure (see **10**, R = methyl) the chlorides (550 mg) were transformed to 268 mg of chromatographed phosphorane **10** (R = benzyl), as a yellowish foam (elution with toluene–ethyl acetate (9:1) gradually increased to 1:1): IR 3.33, 5.70, 5.90, 6.15, 6.57, 7.42, 9.05 μ.

10, R = *n*-Pentyl. 4-Hexanoylthio-2-azetidinone (**7**, R = *n*-pentyl), 2.38 g, yielded, using the standard procedure (see **7**, R = methyl), 6.7 g of chromatographed (toluene–ethyl acetate (9:1 to 4:1)) adduct **8**, which was converted to the chlorides **9** and hence to the phosphorane **10** (R = *n*-pentyl): 4.40 g (56% yield); IR 5.70, 5.90, 6.15, 6.96, 9.05 μ.

10, R = Acetoxyacetyl. 4-Acetoxyacetylthio-2-azetidinone (**7**, R = acetoxyacetyl), 0.44 g, gave 0.82 g of chromatographed adduct **8** which in turn led to 0.56 g (40%) of the phosphorane **10**: IR 5.70, 6.15, 6.55, 6.98, 8.20, 9.05 μ.

10, R = 2-Carbomethoxyethyl. 4-β-Carbomethoxypropionylthio-2-azetidinone (**7**, R = 2-carbomethoxyethyl) (266 mg) gave 446 mg of chromatographed adduct **8**, from which 490 mg of crude halide

9 was produced. Phosphorane **10** was obtained from **9**: 272 mg (37% yield); IR 5.70, 5.95, 6.20, 6.60, 7.45, 9.05 μ.

10, R = *m*-Dimethylaminophenyl. 4-*m*-Dimethylaminobenzoylthio-2-azetidinone (**7**, R = *m*-dimethylaminobenzoyl) (305 mg) gave 699 mg of chromatographed product **8**, yielding orange-colored plates: mp 148 °C from methylene chloride-ether; IR 2.86, 5.62, 5.69, 6.03, 6.23, 6.54, 7.41, 8.25, 10.83 μ; NMR δ 7.99 (d, 2 H, *J* = 9 Hz), 7.37 (d, 2 H, *J* = 9 Hz), 7.05 (m, 4 H), 5.64 (dd, 1 H, *J* = 3, 6 Hz), 5.60 (b, 1 H), 5.15 (AB, 2 H, *J* = 12 Hz), 4.72 (d, 1 H, *J* = 10 Hz), 3.53 (ABX, 1 H, *J* = 6, 16 Hz), 3.12 (ABX, 1 H, *J* = 3, 16 Hz), 2.96 (s, 6 H). Anal. Calcd for $C_{21}H_{21}N_3O_7S$ (459.48): C, 54.89; H, 4.61; N, 9.13. Found: C, 54.80; H, 4.48; N, 9.08.

8 (699 mg) (containing a small amount of the reagent glyoxylate) was converted to the chlorides **9** using 3.5 equiv of thionyl chloride and the polymeric base; 747 mg of crude product was obtained which was processed without further purification.

9 (747 mg of crude chloride mixture) yielded 500 mg (45%) of chromatographed phosphorane **10**: IR 5.69, 6.02, 6.23, 6.57, 7.42, 8.28, 9.03 μ.

10, R = 3-Pyridyl. 4-Nicotinoylthio-2-azetidinone (**7**, R = 3-pyridyl), 1 g, gave 1.2 g of chromatographed adduct **8**. **8** (3.6 g) yielded, by way of the mixture of chlorides **9**, 1.45 g of phosphorane **10** as a yellow foam, 25%: IR 5.67, 6.0, 6.15, 6.55, 6.95, 7.42, 9.05 μ.

10, R = 2-Furyl. 4-α-Furoylthio-2-azetidinone (**7**, R = 2-furyl), 2.4 g, produced 5.9 g of chromatographed adduct **8**, containing some reagent glyoxylate. This material (4.9 g) was converted to **9** and hence to the phosphorane **10**, 4.0 g (50% from **7**), yellowish foam: IR 5.67, 6.02, 6.15, 6.57, 7.42, 9.02, 11.80 μ.

10, R = Phenoxyacetaminoacetyl. 4-Phenoxyacetaminoacetylthio-2-azetidinone (**7**, R = phenoxyacetaminoacetyl), 1.40 g, gave 1.86 g (80%) of chromatographed adduct **8**: IR 2.95, 5.60, 5.70, 6.25, 6.55, 7.42, 8.20 μ.

8 (3.01 g) led to 680 mg (10%) of chromatographed phosphorane **10** (elution with ethyl acetate): IR 2.95, 5.70, 5.90, 6.20, 6.55, 6.70, 6.98, 7.45, 8.95 μ.

10, R = 2-(*p*-nitrocarbobenzoxyamino)propionylthio-2-azetidinone, 4.10 g, yielded 6.33 g (96%) of chromatographed adduct. This was converted to the chloride mixture **9** and then to the phosphorane **10**, yield 3.78 g (40% from **7**): IR 2.90, 5.67, 5.77, 5.90, 6.12, 6.55, 7.40, 9.00 μ.

10, R = 3-(*p*-nitrocarbobenzoxyamino)butyrylthio-2-azetidinone, 2.724 g, yielded 3.676 g (86%) of chromatographed (toluene-ethyl acetate (1:1)) **8**. The chlorides **9** obtained gave 3.348 g (64%) of chromatographed phosphorane **10**: IR 2.95, 5.70, 5.80, 5.95, 6.25, 6.60, 7.00, 7.45, 8.15, 9.05 μ.

11. General Procedure. The phosphoranes **10** were heated in toluene solution (ca. 0.03 mol) to 90 °C in a nitrogen atmosphere in the presence of a catalytic amount of hydroquinone. The progress of the reaction was monitored by thin layer chromatography (SiO_2). The reaction solutions were eventually evaporated in vacuo and the products **11** isolated by column chromatography (SiO_2, separation from triphenylphosphine oxide).

R = Methyl. The reaction time was 14 h. Product was eluted from silica gel with toluene-ethyl acetate (19:1), yield 67%, and crystallized from ether-methylene chloride in yellow needles: mp 130-132 °C; UV 262 nm (ε 13 100), 308 (10 000); IR 5.57, 5.82, 6.3, 6.55, 7.4, 7.6, 8.3 μ; NMR δ 8.25 (m, 2 H), 7.65 (m, 2 H), 5.65 (dd, 1 H), 5.35 (m, 2 H), 3.4-3.9 (m, 2 H), 2.4 (s, 3 H); MS M 320, 305 (− CH_3), 292 (− CO), 279 (− CHCO), 278 (− CH_2CO). Anal. Calcd for $C_{14}H_{12}N_2O_5S$ (320.3): C, 52.50; H, 3.78; N, 3.75. Found: C, 52.51; H, 3.89; N, 8.86.

R = Phenyl. The reaction time was 2 days. The product was chromatographed on Merck silica gel using toluene-ethyl acetate (19:1): yield 57%; mp 182-183 °C; UV 258 nm (ε 17 250), 327 (8100); IR 5.55, 5.82, 6.55, 7.40, 7.65, 8.35, 8.45, 9.15, 9.85 μ; NMR δ 8.10 (d, 2 H, *J* = 9 Hz), 7.38 (m, 7 H), 5.78 (dd, 1 H, *J* = 2, 4 Hz), 5.29 (d, 1 H, *J* = 14 Hz), 5.12 (d, 1 H, *J* = 14 Hz), 3.88 (q, 1 H, *J* = 4, 16 Hz), 3.60 (q, 1 H, *J* = 3, 16 Hz). Anal. Calcd for $C_{19}H_{14}N_2O_5S$ (382.39): C, 59.68; H, 3.69; N, 7.33; S, 8.39. Found: C, 59.44; H, 3.87; N, 7.04; S, 8.25.

R = Benzyl. The reaction time was 36 h. The product was chromatographed as above: yield 50%; mp 115 °C; UV 258, 312 nm; IR 5.58, 5.83, 6.25, 6.36, 6.58, 7.45, 7.65, 8.37 μ; NMR δ 8.18 (d, 2 H, *J* = 9 Hz), 7.58 (d, 2 H, *J* = 9 Hz), 7.24 (s, 5 H), 5.57 (dd, 1 H, *J* = 2, 4 Hz), 5.35 (AB, 2 H), 4.17 (AB, 2 H), 3.59 (ABX, 2 H, J_{AX} = 2, J_{BX} = 4 Hz). Anal. Calcd for $C_{20}H_{16}N_2O_5S$ (306.42): C, 60.60; H, 4.07; N, 7.07. Found: C, 60.52; H, 4.25; N, 7.20.

R = *n*-Pentyl. The reaction time was 2 days. The product was chromatographed as above: yield 65%; oil; UV 310 nm (ε 9700), 270 (13 600); IR 5.60, 5.85, 6.35, 6.57, 7.43, 7.65, 8.37 μ; NMR δ 8.20 (d, 2 H, *J* = 8 Hz), 7.60 (d, 2 H, *J* = 8 Hz), 5.62 (dd, 1 H, *J* = 2, 4 Hz), 5.44 (d, 1 H, *J* = 14 Hz), 5.20 (d, 1 H, *J* = 14 Hz), 3.80 (q, 1 H, *J* = 4, 16 Hz), 3.48 (q, 1 H, *J* = 2, 16 Hz), 2.84 (m, 2 H, *J* = 7, 14 Hz), 1.1-1.7 (m, 6 H), 0.88 (t, 3 H). Anal. Calcd for $C_{18}H_{20}N_2O_5S$ (376.43): C, 57.44; H, 5.36; N, 7.44; S, 8.52. Found: C, 57.24; H, 5.44; N, 7.29; S, 8.08.

R = Acetoxymethyl. The reaction time was 35 h. The product was chromatographed as above (toluene-ethyl acetate (9:1)): yield 55%; mp 127-128 °C (methylene chloride-ether); UV 319 nm (ε 9200), 262 (11 900); IR 5.60, 5.75, 5.85, 6.30, 6.55, 7.45, 7.60, 8.20 μ; NMR δ 8.22 (d, 2 H, *J* = 9 Hz), 7.63 (d, 2 H, *J* = 9 Hz), 5.72 (dd, 1 H, *J* = 2, 4 Hz), 5.00-5.60 (two overlapping AB quartets, 4 H), 3.84 (dd, 1 H, *J* = 4, 16 Hz), 3.58 (dd, 1 H, *J* = 2, 16 Hz), 2.14 (s, 3 H). Anal. Calcd for $C_{16}H_{14}N_2O_7S$ (378.36): C, 50.79; H, 3.73; N, 7.40; S, 8.47. Found: C, 50.95, H, 3.67; N, 7.45; S, 8.39.

R = *m*-Dimethylaminophenyl. The reaction time was 90 h. The product was chromatographed with toluene-ethyl acetate (19:1): yield 45% (based on consumed starting material); mp 77 °C (methylene chloride-ether-pentane); UV 256 and 325 nm; IR 5.58, 5.86, 6.25, 6.58, 7.40, 7.68 μ; NMR δ 8.06 (d, 2 H, *J* = 10 Hz), 7.25 (m, 4 H), 6.75 (d, 2 H, *J* = 10 Hz), 5.75 (dd, 1 H, *J* = 4, 2 Hz), 5.18 (AB, 2 H, *J* = 14 Hz), 3.9 (dd, 1 H, *J* = 16, 4 Hz), 3.56 (dd, 1 H, *J* = 16, 2 Hz), 2.88 (s, 6 H). Anal. Calcd for $C_{21}H_{19}N_3O_5S$ (425.46): C, 59.28; H, 4.50; N, 9.88. Found: C, 59.26; H, 4.70; N, 9.92.

R = 2-Carbomethoxyethyl. The reaction time was 2 days. The product was chromatographed as above: yield 32%; mp 125 °C (methylene chloride-ether); UV 262 and 312 nm; IR 5.60, 5.78, 5.85, 6.33, 6.56, 7.45, 7.65 μ; NMR δ 8.28 (d, 2 H, *J* = 9 Hz), 7.65 (d, 2 H, *J* = 9 Hz), 5.70 (dd, 1 H, 2, 4 Hz), 5.40 (AB, 2 H, *J* = 14 Hz), 3.85 (ABX, 1 H, *J* = 16, 4 Hz), 3.74 (s, 3 H), 3.55 (ABX, 1 H, *J* = 16, 2 Hz), 3.20 (t, 2 H), 2.64 (t, 2 H). Anal. Calcd for $C_{17}H_{16}N_2O_7S$ (392.39): C, 52.04; H, 4.11; N, 7.14. Found: C, 52.22; H, 4.26; N, 7.15.

R = α-Furyl. The reaction time was 48 h. The product was chromatographed as above: yield 79%; mp 161-163 °C (ether-methylene chloride); UV 260 nm (ε 12 350), 294 (10 570), 307 (9470), 358 (11 900); IR 5.57, 5.85, 6.55, 7.42, 7.62, 8.20, 8.52 μ; NMR δ 8.22 (m, 2 H), 7.75-7.50 (m, 4 H), 6.55 (dd, 1 H), 5.68 (dd, 1 H), 5.37 (m, 2 H), 3.70 (m, 2 H). Anal. Calcd for $C_{17}H_{12}N_2O_6S$ (372.35): C, 54.84; H, 3.25; N, 7.52. Found: C, 54.70; H, 3.13; N, 7.55.

R = β-Pyridyl. The reaction time was 24 h. The product was chromatographed as above (but using toluene-ethyl acetate (3:2) as eluant): yield 52%; mp 160-161 °C (ether-methylene chloride); UV 259 nm (ε 15 520), 333 (6680); IR 5.55, 5.78, 6.55, 7.42, 7.63, 8.35, 8.50 μ; NMR δ 8.6-8.7 (m, 2 H), 8.16 (m, 2 H), 7.78 (m, 1 H), 7.25-7.5 (m, 3 H), 5.84 (m, 1 H), 5.24 (m, 2 H), 4.04-3.5 (m, 2 H). Anal. Calcd for $C_{18}H_{13}N_3O_5S$ (383.38): C, 56.39; H, 3.42; N, 10.96; O, 20.87; S, 8.36. Found: C, 56.31; H, 3.62; N, 10.76; O, 20.60; S, 8.19.

R = Phenoxyacetaminomethyl. The reaction time was 17 h. The product was chromatographed and eluted with toluene-ethyl acetate (4:1): yield 57%; mp 163-165 °C (methylene chloride-petroleum ether); UV (dioxane) 261 nm (ε 14 870), 266 (14 870), 272 sh (12 680), 318 (10 020); IR 2.95, 5.55, 5.85, 5.90, 6.30, 6.55, 6.70, 7.40, 7.60, 8.25-8.35 μ; NMR δ 6.80-8.30 (m, 10 H), 5.33 (dd, 2 H, *J* = 14 Hz), 4.66 (dd, 1 H, *J* = 2, 4 Hz), 4.34-4.90 (m, 2 H), 4.52 (s, 2 H), 3.84 (dd, 1 H, *J* = 4, 16 Hz), 3.44 (dd, 1 H, *J* = 2, 16 Hz). Anal. Calcd for $C_{22}H_{19}N_3O_7S$ (469.46): C, 56.28; H, 4.08; N, 8.95; S, 6.83. Found: C, 56.14; H, 4.06; N, 8.86; S, 7.10.

R = 2-(*p*-Nitrocarbobenzoxamino)ethyl. The reaction time was 24 h. The product was chromatographed and eluted with toluene-ethyl acetate (4:1): yield 60%; mp 143-144 °C (methylene chloride-ether); UV (dioxane) 264 nm (ε 22 100), 314 (9540); IR 2.95, 5.58, 5.80, 6.22, 6.32, 6.57, 7.42, 7.62, 8.35 μ; NMR δ 7.40-8.30 (m, 8 H), 5.65 (dd, 1 H, *J* = 2, 4 Hz), 5.33 (dd, 2 H, *J* = 14 Hz), 5.18 (s, 2 H), 3.84 (dd, 1 H, *J* = 4, 16 Hz), 2.80-3.60 (m, 5 H). Anal. Calcd for $C_{23}H_{18}N_4O_9S$ (526.48): C, 52.47; H, 3.45; N, 10.64; S, 6.09. Found: C, 52.67; H, 3.90; N, 10.49; S, 5.74.

R = 3-(*p*-Nitrocarbobenzoxamino)propyl. The reaction time was 24 h. The product was chromatographed as above: yield of analytically pure material as a foam 65%; UV 264, 300 sh nm; IR 2.90, 5.55, 5.80, 6.20, 6.37, 6.55, 7.40, 7.60, 8.35 μ; NMR δ 7.40-8.20 (m, 8 H), 5.64

(dd, 1 H, J = 2, 4 Hz), 5.40 (b, 1 H), 5.30 (dd, 2 H, J = 14 Hz), 5.17 (s, 2 H), 3.82 (dd, 1 H, J = 4, 16 Hz), 3.47 (dd, 1 H, J = 2, 16 Hz), 3.24 (q, 2 H, J = 7 Hz), 2.90 (m, 2 H), 1.80 (quintet, 2 H, J = 7 Hz). Anal. Calcd for $C_{24}H_{22}N_4O_9S$ (542.52): C, 53.13; H, 4.09; N, 10.33; S, 5.91. Found: C, 53.03; H, 4.22; N, 10.40; S, 5.58.

12, R = Methyl. The corresponding ester **11** (R = methyl), 700 mg (2.18 mmol), was dissolved in 42 mL of ethyl acetate. To this solution 28 mL of a 0.2 *m* aqueous sodium bicarbonate solution and 1 g of palladium on charcoal (10%) catalyst were added. The mixture was stirred vigorously for 90 min in a hydrogen atmosphere and the catalyst removed by filtration over Hyflo. The filter aid was washed once with bicarbonate solution and three times with ethyl acetate. Washings and filtrate were combined, the phases were separated, and the aqueous one was washed with methylene chloride. Acidification with 5% aqueous citric acid and four extractions with methylene chloride yielded after drying over sodium sulfate and evaporation in vacuo 184 mg of the crude product (45%). Crystallization from ether–acetone gave the pure product: mp 140–167 °C dec; UV 302 nm (ϵ 6050) and 260 (3930); IR (KBr) 3.4, 3.6, 3.95, 5.62, 6.0, 6.37, 7.0, 7.6, 7.85, 8.15 μ; NMR (Me_2SO-d_6) δ 5.65 (dd, 1 H), 3.3–3.9 (m, 2 H), 2.28 (s, 3 H); MS M 185, 168, 157, 144, 143. Anal. Calcd for $C_7H_7NO_3S$ (185.2): C, 45.40; H, 3.81; N, 7.56. Found: C, 45.40; H, 3.88; N, 7.64.

R = *n*-Pentyl. The corresponding ester **11** (800 mg, 2.1 mmol) was dissolved in 48 mL of ethyl acetate and 32 mL of a 0.2 *m* sodium bicarbonate solution. Hydrogenation was effected as described for **12**, R = methyl, using 1.60 g of the same catalyst. **12** (160 mg, 28%) was obtained following the workup procedure given for **12**, R = methyl: mp 99–100 °C, recrystallized from ether–petroleum ether; UV 307 nm (ϵ 5320) and 257 (3710); IR 2.75–4.25, 5.60, 5.97, 6.40, 7.05, 7.70, 8.25, 8.32 μ; NMR δ 9.20 (b, 1 H), 5.63 (dd, 1 H, J = 2, 4 Hz), 3.80 (q, 1 H, J = 4, 16 Hz), 3.46 (q, 1 H, J = 2, 16 Hz), 2.83 (m, 2 H), 1.1–1.8 (m, 6 H), 0.89 (t, 3 H). Anal. Calcd for $C_{11}H_{15}NO_3S$ (241.31): C, 54.75; H, 6.27; N, 5.81; S, 13.29. Found: C, 54.23; H, 6.40; N, 5.84; S, 12.72.

R = Phenyl. The corresponding ester **11** (200 mg, 0.52 mmol) was hydrogenated as above, using 12 mL of ethyl acetate, 8 mL of the bicarbonate solution, and 350 mg of the catalyst. There resulted 44 mg (37%) of product, recrystallized from acetone–ether: mp 127–128 °C; UV 323 nm (ϵ 7310), 246 sh (9570), 235 (10 470); IR (KBr) 3.50, 5.60, 6.00, 6.45, 6.72, 6.97, 7.67, 7.85, 8.27, 9.65, 11.05, 13.95 μ; NMR δ 7.42 (m, 5 H), 5.78 (dd, 1 H, J = 2, 4 Hz), 3.88 (q, 1 H, J = 4, 16 Hz), 3.60 (q, 1 H, J = 2, 16 Hz). Anal. Calcd for $C_{12}H_9NO_3S$ (247.27): C, 58.29; H, 3.67; N, 5.66; S, 12.97. Found: C, 58.52; H, 3.82; N, 5.64; S, 12.75.

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The Penems, a New Class of β-Lactam Antibiotics. 3. Synthesis of Optically Active 2-Methyl-(5*R*)-penem-3-carboxylic Acid

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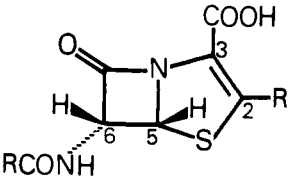
Abstract: 2-Methyl-(5*R*)-penem-3-carboxylic acid (**3**) has been synthesized from the natural 6(*R*)-amino-(5*R*)-penicillanic acid as an optically active representative of the novel group of 6-unsubstituted penems. It proved to be the biologically active component of the previously reported, racemic, 2-methylpenem-3-carboxylic acid. The general necessity of a 5*R*(6*R*) configuration for the biological activity of bicyclic β-lactam antibiotics is briefly discussed.

In the preceding paper of this series,[1] a second generation of penem-3-carboxylic acids **2**, lacking the 6-acylamino substituent of the previously reported penems **1**,[2] has been described.

Acids **2** proved to be substantially more stable than their predecessors **1**, and they displayed activity against a remarkably broad spectrum of bacteria including both Gram-positive and Gram-negative microorganisms. Since all the tested acids



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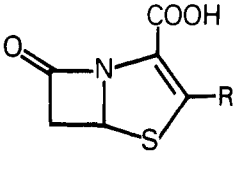

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