3-Propyl-1,2,3,4,5,6-hexahydro-1,6-methano-3-benzazocine (1e) Hydrochloride. To 1.32 g (0.00763 mol) of 1a and 2.66 g (0.0193 mol) of K_2CO_3 in 16 mL of DMF (freshly distilled from CaH_2) was added 1.36 g (0.0080 mol) of propyl iodide. The mixture was stirred and heated at 110 °C for 2.5 h, cooled, and filtered. The recovered solid was washed with 15 mL of $CHCl_3$ and the filtrates were combined and concentrated under reduced pressure. Distillation of the residue [90–120 °C bath temperature (0.1 mm)] gave 0.81 g (49%) of free amine. The amine was dissolved in ether, dried over molecular sieves, filtered through Celite, and converted to the hydrochloride (HCl gas): mp 195–197 °C (acetone–Et_2O); *m/e* 215 (M^+ – HCl). Anal. ($C_{15}H_{22}NCl \cdot 0.5H_2O$) C, H, N.

3-(3-Methyl-2-butenyl)-1,2,3,4,5,6-hexahydro-1,6-methano-3-benzazocine (1g) Oxalate. To 1.00 g (0.00578 mol) of 1a were successively added 50 mL of DMF (distilled from CaH_2), 0.86 g (0.00577 mol) of 1-bromo-3-methyl-2-butene, and 0.73 g (0.00869 mol) of $NaHCO_3$. The mixture was refluxed 4.5 h, cooled, filtered through Celite (the filter cake washed with EtOH), and concentrated in vacuo. The residue was triturated with Et_2O and the solution filtered through Celite. After concentration, the residue was distilled [125–135 °C bath temperature (0.05 mm)] and the distillate (0.8 g, 57%) converted to the oxalate salt (ethereal oxalic acid): mp 173–176 °C (from CH_3OH–acetone). Anal. ($C_{19}H_{25}NO_4$) C, H, N.

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Hetacillin (*R*)- and (*S*)-Sulfoxides. Synthesis and Structure–Activity Relationships

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Hetacillin was oxidized with *m*-chloroperbenzoic acid to give the corresponding (*R*)- and (*S*)-sulfoxides. Ozonization of hetacillin not only oxidized the sulfide but caused unexpected oxidation of the imidazolidine ring to a 2*H*-imidazoline. The biological spectrum showed the (*R*)-sulfoxide to be appreciably more active than the (*S*)-sulfoxide.

Hetacillin,[1] a semisynthetic penicillin, offers a unique advantage in preparing penicillin (*R*)-sulfoxides. Other workers have extensively studied the stereochemistry of sulfoxide bond formation[2,3] and have indicated that the preferential formation of penicillin (*S*)-sulfoxides can be attributed to the directing effect of the carboxamido group present in the side chain. As with 6-phthalimidopenicillanic acid, hetacillin has a relatively bulky 6-substituent without an amide hydrogen available for hydrogen bonding. This allows steric effects to dominate and offers a convenient route to the preparation of penicillin (*R*)-sulfoxides. The imidazolidine moiety of hetacillin, however, offers a distinct advantage over the phthalimido group since it can be hydrolyzed easily to an α-aminophenylacetamido group, which is a side chain of a biologically active penicillanic acid derivative. It was our purpose to prepare both the hetacillin (*R*)- and (*S*)-sulfoxides and to compare their biological activities with those of their penicillin precursor, hetacillin.

The oxidation of penicillin derivatives has been extensively studied by other investigators. In contrast to oxidants such as sodium metaperiodate,[4] hydrogen peroxide,[5] and *m*-chloroperbenzoic acid[6] which have led to the isolation of only the (*S*)-sulfoxide, ozone has been found to afford a mixture of the (*R*)- and (*S*)-sulfoxides.[7] Therefore, the oxidation of hetacillin with ozone seemed to be the method of choice for the preparation of the (*R*)-sulfoxide. However, when ozone was found to attack the imidazolidine ring, oxidation with *m*-chloroperbenzoic acid was investigated.

Chemistry. Oxidation of hetacillin with *m*-chloroperbenzoic acid afforded a 7:3 mixture of the isomeric sulfoxides **2** and **3** (Scheme I). These could be easily separated by fractional crystallization, and the major isomer was assigned the (*R*)-sulfoxide configuration, **2**. Treatment of hetacillin with ozone unexpectedly led to oxidation of both the imidazolidine ring and the sulfide, affording compound **1** in high yield. The assignments of sulfoxide configurations on compounds **1**–**3** are based primarily on the hypothesis that the thermodynamically more stable (*S*)-sulfoxide arises from a strong oxidant directing effect and sulfoxide stabilizing effect by a 6β-

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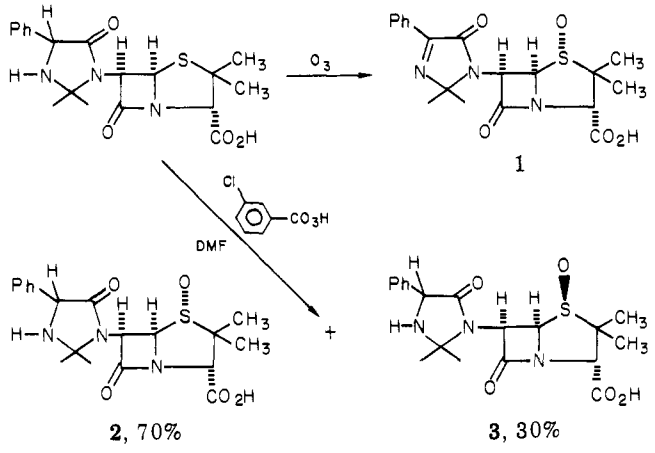
Table I. Minimum Inhibitory Concentration (μg/mL)[a]

Compd	St.p.	St.py.	S.a.	S.a.(R)	E.c.	P.m.	P.v.	Mouse PD_{50} vs. S. pyogenes, mg/kg sc[b] im	po
1	1	1	>8	>125	>125	>125	>125		
2	0.13	0.13	1	>125	8	1	1	3.1	9.4
3	0.5	0.5	4	>125	32	4	4	9.6	>25
Hetacillin	0.004	0.004	0.016	>125	1	0.13	0.13	0.2	0.3

[a] The in vitro antibacterial activities are reported as minimum inhibitory concentrations (MIC) in μg/mL. The MIC's were determined by a twofold serial dilution technique in nutrient broth. Organisms selected for inclusion in this table are *St.p.*, *Streptococcus pneumonia* 9585; *St.py.*, *Streptococcus pyogenes* 9604; *S.a.*, *Staphylococcus aureus* 9537; *S.a.*(R), *Staphylococcus aureus* (penicillin resistant) 9606; *E.c.*, *Escherichia coli* 15119; *P.m.*, *Proteus mirabilis* 9900; *P.v.*, *Proteus vulgaris* 9716. [b] The PD_{50} values are expressed as the total dose of compound in mg/kg which afforded protection of 50% of the mice challenged intraperitoneally with approximately 1.3×10^3 organisms per mouse of *S. pyogenes* A9604 diluted in brain heart infusion broth to produce a uniform lethal infection. Fourfold dilutions of each compound were injected intramuscularly or orally at 1 and 3.5 h postinfection. Survivors were observed for 5 days and the mean protective dose (PD_{50}) was calculated by the method of Spearman-Karber, "Statistical Methods in Biological Assay", D. J. Finney, Ed., 2nd ed, Hafner Publishing Co., New York, N.Y., 1964.

Scheme I



carboxamido group. X-ray crystallographic analysis and extensive NMR studies have not been carried out on these compounds; however, the NMR data obtained are consistent with the assignments.

Biology. The in vitro antibacterial activities of the penicillin sulfoxides are shown in Table I. Compound 1 showed very poor activity against all organisms. Compound 2 was four- to eightfold more active than 3 but 64-fold less active than the control, hetacillin.[9] These relative activities are reflected in the mouse infection–protection activities (PD_{50} values) against *Streptococcus pyogenes* in which the (*R*)-sulfoxide 2 gave better protection to the mouse both orally and intramuscularly than the (*S*)-sulfoxide 3. Quantitative thin-layer bioautograms[8] indicated that hetacillin contamination in 2 and 3 was considerably less than 1%.

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. The IR spectra were recorded on a Beckman 5240 spectrophotometer using KBr pellets; NMR spectra were obtained on a Varian HA-100 spectrometer using Me_4Si as an internal standard. The IR and NMR data on all compounds were consistent with the assigned structure. The ^{13}C NMR spectrum of 1 was obtained on a Varian XL-100A in Me_2SO-d_6 and was consistent for the assigned structure. The elemental analyses were within ±0.4% of the theoretical values for all compounds. The ozone oxidations were run using a Welsbach Model T-23 ozonizer with an output of 1.1 mm of O_3/min. No attempt was made to monitor the uptake of ozone.

(1*R*)-6-(2,2-Dimethyl-5-oxo-4-phenyl-2*H*-imidazolinyl)-penicillanic Acid 1-Oxide (1). A solution of 2 g (0.0047 mol) of potassium hetacillin in 20 mL of acetone and 1.5 mL of water was ozonized at 23 °C for 10 min and cooled in an ice bath to 5 °C, and the ozonization was continued for 2 h. The acetone was evaporated at 30 °C (15 mm) to a viscous residue which was slurried with 20 mL of water and acidified dropwise to pH 2 with concentrated HCl. The solid which crystallized was collected, washed with water, and dried in vacuo over P_2O_5 to yield 1.1 g (58%) of 1: mp 125 °C dec; IR 2300–3100 (OH), 2980, 2930 (CH_3), 1810 (β-lactam), 1745 (carboxyl), 1690–1710 (CONH), 695 cm^{-1} (Ph); NMR (Me_2SO-d_6) δ 8.2–8.5 (m, 2, ortho aromatic protons), 7.3–7.7 (m, 3, aromatic), 5.8 (d, 1, C_6-H), 4.85 (d, 1, C_5-H), 4.43 (s, 1, C_3-H), 1.65, 1.58, 1.23 [s, 3, s, 6, s, 3, *gem*-dimethyl and $NC(CH_3)_2N$]; ^{13}C NMR (Me_2SO-d_6) δ 158.799 (>C=N), all other peaks were consistent for the assigned structure.

(1*R*)-6-(2,2-Dimethyl-5-oxo-4-phenyl-1-imidazolidinyl)-penicillanic Acid 1-Oxide (2). To a suspension of 15.6 g (0.04 mol) of hetacillin in 40 mL of DMF at 0–5 °C was added 8.4 g (0.048 mol) of *m*-chloroperbenzoic acid. Slowly the mixture became clear. The solution was stirred for 2.5 h and diluted with 500 mL of ether. The crystalline solid which separated was collected and air-dried to constant weight yielding 9 g (56%). The dry solid was purified by dissolving in 15 mL of MeOH, cooling, and collecting the precipitate: yield 5 g (31%). This was found to contain about 1% hetacillin by quantitative thin-layer bioautogram. A 1-g sample was slurried with 2 mL of Me_2SO and collected to yield 521 mg: mp >120 °C slow dec; $[\alpha]^{22}_{436}$ +352° (*c* 0.99, DMF). This was found to possess less than 0.5% hetacillin and was used for the MIC assay and determining the PD_{50} values: IR 1795 (β-lactam), 1720 (carboxyl C=O), 1700 (–CONH–), 708 cm^{-1} (Ph); NMR (Me_2SO-d_6) δ 7.4–7.7 (m, 5, ArH), 5.38 (d, 1, C_6-H), 4.72 (s, 1, –CHC=O), 4.68 (d, 1, C_5-H), 4.24 (s, 1, C_3-H), 1.1–1.6 [m, 12, *gem*-dimethyl and $NC(CH_3)_2N$].

(1*S*)-6-(2,2-Dimethyl-5-oxo-4-phenylimidazolidinyl)-penicillanic Acid 1-Oxide (3). A suspension of 7.8 g (0.02 mol) of hetacillin in 20 mL of DMF at 5 °C was stirred with 4.2 g (0.0243 mol) of *m*-chloroperbenzoic acid. The solution became clear and was stirred for 2.5 h. The solution was then diluted with 500 mL of ether and a white crystalline precipitate was collected which weighed, after air drying to constant weight, 6.2 g. The solid was stirred with 30 mL of water and the solution was adjusted to pH 2 by dropwise addition of concentrated HCl. A white solid was collected, washed with acetone, and dried to constant weight to yield 450 mg (5.6%): mp >120 °C slow dec; $[\alpha]^{22}_{436}$ +289.9° (*c* 1, DMF). The bioautographic assay indicated less than 0.5% hetacillin present in the sample: IR 1810 (β-lactam), 1725 (carboxyl), 1695 (CONH), 695 cm^{-1} (Ph); NMR (Me_2SO-d_6) δ 8.4 (s, 1, NH), 7.3 (s, 5, ArH), 5.1 (d, 1, C_6-H), 4.6 (d, 1, C_5-H), 4.5 [s, 1, CHC(=O)–], 4.2 (s, 1, C_3-H), 1.50, 1.40, 1.43, 1.45 [m, 12, *gem*-dimethyl and $NC(CH_3)_2N$].

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(9) Phenoxymethylpenicillin (*R*)-sulfoxide has been reported to have five times greater gram-positive antibacterial activity than the corresponding (*S*)-sulfoxide: "Cephalosporins and Penicillins: Chemistry and Biology", E. H. Flynn, Ed., Academic Press, New York, N.Y., 1972, p 540.

Book Reviews

Venoms: Chemistry and Molecular Biology. By Anthony T. Tu. Wiley, New York, N.Y. 1977. x + 560 pp. 18 × 25 cm. $34.50.

It takes but a cursory examination of this volume to recognize that the title does not do justice to the breadth of material contained therein. While our all too limited knowledge of the chemistry and molecular biology of venoms is thoroughly reviewed, there is also a great deal of information about the biological effects of the various venoms at the subcellular, cellular, tissue, and organ levels. In preparing this volume, the author has reviewed the rather extensive literature on venoms from many disciplines.

Most of this book is devoted to snake venoms, where the literature is most abundant; however, arachnid and insect venoms are also covered, and there is a brief discussion of Gila monster venoms. The book is organized into four sections, the first presenting a discussion of nonprotein components of snake venoms. This is preceded by a very brief, but helpful introduction to snakes, their occurrence, their classification, and the general properties of their venoms. Eight chapters devoted to snake venom enzymes and one chapter on enzyme inhibitors comprise the second section of the book. The third section, which occupies almost 60% of the book, is devoted largely to the properties and actions of nonenzymatic proteins found in snake venoms. This section has five chapters devoted to the five families of venomous snakes, eleven chapters dealing with the pharmacological and pathological effects of snake venoms and some of their purified constituents, and a chapter which summarizes attempts at chemical detoxification of snake venoms. There are several chapters in section three which are of particular interest to the medicinal chemist. These present extensive discussions of the chemistry and actions of the neurotoxic, cardiotoxic, and cytotoxic components of snake venoms; and also the effects of venom components on the blood clotting system, the immune system, and nerve growth. Surprisingly, however, one of the few clinical uses of snake venoms, the use of cobra neurotoxin as an analgesic, is not mentioned. The fourth section, some 75 pages, is devoted to venoms from creatures other than snakes. Most of this section is divided between scorpion venoms, spider venoms, and the venoms of bees, hornets, and wasps.

The author has succeeded in providing a broad overview of venoms by incorporating into this volume information abstracted from a very large body of literature. At times, however, it is difficult not to lose sight of the larger picture. There is a tendency to incorporate too much detail and too many examples without adequate discusion. In some instances, detailed factual material is presented which, when read out of the context of the original literature, is confusing or misleading. In some places, the text is so punctuated by examples and references that reading becomes quite tedious. The chapters of greatest interest to medicinal chemists are, fortunately, among the better written ones, thus making for easy as well as interesting reading.

This volume can provide the medicinal chemist with a very good overview of a fascinating class of pharmacologically active natural products. As a reference book on venoms, its value is more limited but it does provide a useful guide to the literature on venoms.

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Analysis of Drugs and Metabolites by Gas Chromatography–Mass Spectrometry. Volume 1. By Benjamin J. Gudzinowicz and Michael J. Gudzinowicz. Marcel Dekker, New York, N.Y. 1977. vii + 223 pp. 15 × 22.5 cm. $23.75.

This is the first in a series of volumes (five are already in publication and others are in preparation) devoted to the GC–MS analysis of drugs and metabolites. In the particular case of volume 1, however, the title is misleading, as the use of mass spectrometry is hardly mentioned. The book is divided into two chapters with 145 and 253 literature references, respectively, and including both author and subject indexes. Chapter 1 is subdivided into three sections: (1) respiratory and blood gases; (2) volatile anesthetics; and (3) a collection of miscellaneous volatile compounds which includes sterilizing agents, organic solvents, and riot-control aerosol irritants. Much of the information presented is a historical review of the development of GC methods (equipment, columns, and detectors) for analyzing these highly volatile substances. The literature cited ranges from work published in the late 1950's to 1974 publications. Representative gas chromatograms, diagrams of specialized equipment, and tables of data (retention times, quantitative determinations, etc.) supplement the discussion. In addition to GC information, the authors present a review of sample preparation and injection techniques. Examples of applications of the GC data to problems in cardiopulmonary research and in anesthesiology are also included.

Chapter 2 is divided into a section on the analysis of ethyl alcohol and a section on the analysis of volatile constituents in human breath, fluids, and tissues. The first section begins with a description of the biochemistry and pharmacology of ethanol, followed by a lengthy discussion of methods for analyzing ethanol in various specimens (blood, urine, tissue, and breath). GC techniques and sampling methods are reviewed. While the focus is on ethanol, analytical data on drugs and other compounds are also presented. Although the authors review metabolic profile analysis in the second section of chapter 2, the treatment is very sketchy. They devote insufficient space to the analysis of volatile metabolites (which is consistent with the subject matter of volume 1), while including a discussion of the analysis of nonvolatile metabolites such as organic acids and steroids (which is an inappropriate inclusion).