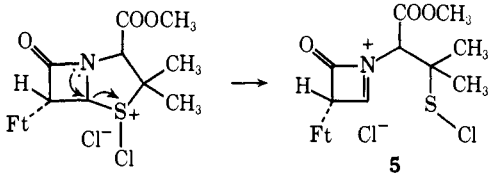
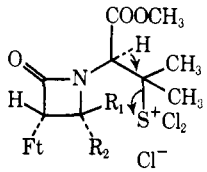
bonium ion is assisted by electron delocalization of the unshared electron pair of the nitrogen atom as depicted by **4** and **5**.[17] Theoretically, a nucleophilic chloride could approach the stabilized carbonium ion **5** from either side giving trans and cis isomers in equal amounts. However, in the case of **5** a bulky phthalimido group directs the nucleophilic displacement and as a result the trans and cis isomers **2a** and **2b** are formed in the ratio of *ca.* 4:1. The new olefin-forming reaction can be explained similarly by the good leaving characteristics of the dichlorosulfonium group and β elimination of hydrogen, as illustrated by **6**.



4 **5**



6

Further investigation of these reactions and utilization of described intermediates in eventual syntheses of new β-lactam compounds are in progress and will be reported subsequently.

(17) K. Kwart and R. W. Body, *J. Org. Chem.*, **30**, 1188 (1965).

Stjepan Kukolja
The Lilly Research Laboratories, Eli Lilly and Company
Indianapolis, Indiana 46206
Received August 2, 1971

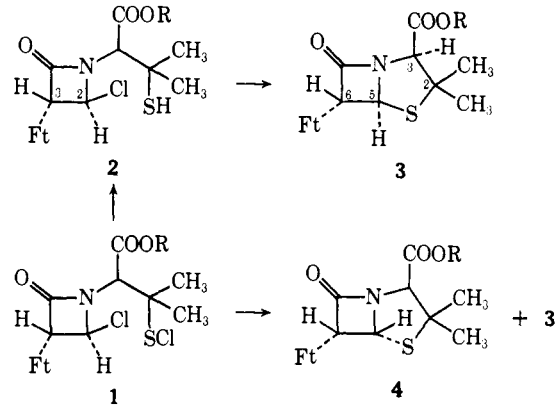
A Stereoselective Synthesis of 6-Phthalimido-5-epipenicillanates

Sir:

Structural studies of naturally occurring penicillins have shown that the bicyclic skeleton of the penicillin molecule is formed by joining azetidinone and thiazolidine rings in such a fashion that asymmetric carbon 5 has the *R* configuration. However, the fused bicyclic system can also exist with C-5 having the *S* configuration, and such penam systems may be called 5-epi- or 5*S* penicillins. In addition to the asymmetric center at C-5, the penicillin structure contains two asymmetric carbon atoms, C-3 and C-6, and eight stereoisomeric forms are possible. Thus far only penicillin V (natural) and its enantiomer, synthesized by Sheehan and Henery-Logan,[1] and 6-epipenicillin V, obtained by Bose, *et al.*,[2] have been accessible. Recently, 6-epipenicillins have also been prepared by several groups of investigators.[3-5]

(1) J. C. Sheehan and K. R. Henery-Logan, *J. Amer. Chem. Soc.*, **81**, 3089 (1959).
(2) A. K. Bose, G. Spiegelman, and M. S. Manhas, *ibid.*, **90**, 4506 (1968).
(3) D. A. Johnson, D. Mania, C. A. Panetta, and H. H. Silvestri, *Tetrahedron Lett.*, 1903 (1968).
(4) S. Wolfe and W. S. Lee, *Chem. Commun.*, 242 (1968).
(5) J. P. Clayton, J. H. C. Nayler, R. Southgate, and E. R. Stove, *ibid.*, 129 (1969).

The preceding communication[6] describes a method for preparing monocyclic azetidinone derivatives which have now been employed successfully in the synthesis of the hitherto unknown 5-epipenicillanates (**3**). Penicillanates (**4**) having the natural configuration have also been obtained in this sequence.



Ft = phthalimido
a, R = CH_3
b, R = $CH(C_6H_5)_2$
c, R = H

Reaction of methyl 2-chloro-α-(1-chlorothio-1-methylethyl)-4-oxo-3-phthalimido-1-azetidineacetate (**1a**) with 1 equiv of stannous chloride dihydrate in hot dioxane for 1 hr affords a mixture of **3a** and **4a** in 74% yield. The nmr spectrum shows that the compounds are present in the ratio of *ca.* 5:1. The diastereomers are separated by chromatography or by crystallization from methyl ethyl ketone or acetone. Methyl 6-phthalimido-5-epipenicillanate (**3a**) is isolated as colorless prisms, mp 174–175°, $[\alpha]D$ −192° ($CHCl_3$), in >50% yield.[7] The substance has ir maxima ($CHCl_3$) at 1795 (azetidinone CO), 1785 and 1733 (phthalimido CO), and 1752 cm^{-1} (ester CO); its mass spectrum is similar to **4a** and shows, in addition to the molecular ion at *m/e* 360, characteristic peaks at 332 (M^+, CO), 301 (M^+, $COOCH_3$), 273 (M^+, CO, $COOCH_3$), and 246 (M^+, HCN, CO, $COOCH_3$). The nmr spectrum ($CDCl_3$) is entirely in agreement with structure **3a**, since two geminal dimethyl singlets at 90 and 102, a methyl ester singlet at 231, a sharp H-3 peak at 234, doublets at 327 and 334 (J = 2.0 Hz) for the trans arrangement of azetidinone protons, and a signal at 471 Hz for the aromatic protons are indicated. Compound **4a**, mp 177–178°, $[\alpha]D$ +291° ($CHCl_3$), is isolated as the minor constituent and is identical with an authentic sample.[8]

When **1a** is treated with *anhydrous* stannous chloride in tetrahydrofuran at room temperature for 2 hr, only 5-epipenicillanate **3a** is obtained. This result indicates the high stereoselectivity of reductive cyclization. However, the reaction of **1a** with stannous chloride *dihydrate* under the above conditions gives the reduced product **2a**, mp 156–157°, which is subsequently cyclized to **3a** with anhydrous stannous chloride in high yield. Apparently in the presence of water, only

(6) S. Kukolja, *J. Amer. Chem. Soc.*, **93**, 6267 (1971).
(7) Satisfactory analytical data were obtained for all new compounds.
(8) J. C. Sheehan and K. R. Henery-Logan, *J. Amer. Chem. Soc.*, **84**, 2983 (1962).

the reduction of the sulfenyl chloride group is accomplished, but not the cyclization to the thiazolidine ring.

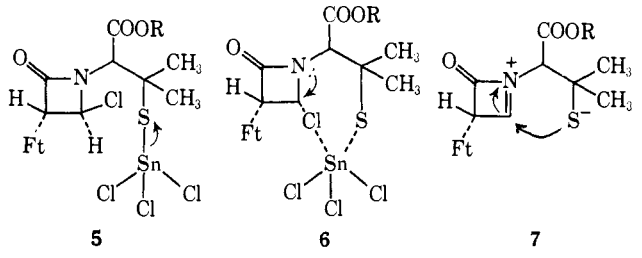
In order to prepare the corresponding 5-epipenicillin with a free carboxyl group in the molecule, a similar reductive cyclization starting with the benzhydryl ester **1b** has been carried out.

Esterification of 6-phthalimidopenicillanic acid with diphenyldiazomethane gives the appropriate benzhydryl ester as colorless silky needles, mp 161–163°, $[\alpha]_D$ +230.6° ($CHCl_3$). Treatment of this ester with chlorine in methylene chloride at 0° for 30 min yields **1b** as an amorphous solid, nmr ($CDCl_3$) 100 (s, 3 H), 104 (s, 3 H), 288 (s, 1 H), 328 (d, 1 H, J = 1.5 Hz), 360 (d, 1 H, J = 1.5 Hz), 422 (s, 1 H), 443 (m, 10 ArH), and 469 Hz (m, 4 ArH), in almost quantitative yield.

Reductive cyclization of **1b** with anhydrous stannous chloride in tetrahydrofuran at room temperature for 2 hr yields a crude mixture of **3b** and **4b** in the ratio of *ca.* 10:1. After separation by chromatography on silica gel, a colorless noncrystalline solid **3b** is isolated: $[\alpha]_D$ −75° ($CHCl_3$); $\nu_{max}^{CHCl_3}$ 1796 (azetidinone CO), 1785 and 1735 (phthalimido CO), and 1745 cm^{-1} (ester CO). The trans orientation of the azetidinone protons in **3b** is clearly established by doublets at 328 and 335 Hz and their coupling constant (J = 2.0 Hz).[9] The unchanged *S* configuration at C-3 is ascertained by measuring an internal nuclear Overhauser effect (NOE). Upon irradiation of the low-field methyl protons (99 cps), the H-3 signal at 240 Hz is increased by 17.6%, whereas saturation of the high-field methyl signal (76 Hz) does not increase the intensity of the H-3 peak. If we assume the assignment of Cooper, *et al.*,[10] for the 2β and 2α methyl groups, the observed relaxation of H-3 is due to the 2β methyl protons and the configuration at the chiral center **3** is *S*.

Cleavage of ester **3b** with trifluoroacetic acid in anisole at 0° for 10 min gives 6-phthalimido-5-epipenicillanic acid (**3c**) as a colorless solid: $[\alpha]_D$ −103.5° ($CHCl_3$); $\nu_{max}^{CHCl_3}$ 1795 (azetidinone CO) and 1782 and 1735 cm^{-1} (phthalimido CO). The coupling constant (J = 2.0 Hz) for the azetidinone doublets at 324.5 and 330.5 Hz indicates the trans stereochemistry of the corresponding protons. The *S* configuration of C-3 is again affirmed by internal NOE. The intensity of the H-3 singlet at 238.5 Hz is increased by 15.4% after irradiation of 2β CH_3 protons at 103 Hz, but there is no relaxation of H-3 upon irradiation of 2α CH_3 protons (94 Hz).

A plausible mechanism for the reduction of **1** with stannous chloride to **2** as well as the subsequent cyclization to **3** and **4** can be explained by electron transfer from tin(II) to the sulfur as shown in **5**. In the case of reduction, probably the hydrolysis of intermediate **5** takes place. We have indeed observed that the reduction of **1** to **2** is facilitated by increasing the polarity of solvent and that the reaction is terminated at this step. However, in an aprotic solvent most likely a stabilized carbonium ion **7** is formed *via* **6** and subsequently cyclized to **3** and/or **4**. The high stereoselectivity of reductive cyclization can be explained by the bulkiness of the neighboring phthalimido group.



The present work describes the synthesis of the fourth isomer of penicillin. By applying the described methods for ring opening and closure of the penicillin molecule and the known epimerization of C-6, other stereoisomeric penicillins can be synthesized. The described 6-phthalimido-5-epipenicillanic acid is devoid of antibiotic activity.

Stjepan Kukolja
The Lilly Research Laboratories, Eli Lilly and Company
Indianapolis, Indiana 46206
Received August 2, 1971

Structure Analysis by Carbon-13 Nuclear Magnetic Resonance Spectroscopy. Arenaïne[1]

Sir:

We wish to report the structure determination of an organic natural product of unknown constitution in which a natural abundance ^{13}C nmr spectral analysis plays a major role.

The seeds of *Plantago arenaria* Waldst and Kit. have yielded[2] narcotine and a new $C_{11}H_{17}ON_3$ alkaloid, arenaïne, mp 208–210°; $[\alpha]^{22}_D$ +305° (*c* 1.7, chloroform); *m/e* 207.1367 (calcd 207.1372);[3] uv (ethanol) λ_{max} 213 (3.81), 244 nm (log ϵ 4.07); ir NH 2.90 (m), 3.25 (m), C=O 6.09 μ (s). The 220-MHz pmr spectrum of arenaïne reveals methyl [δ 1.50 (s)] and vinyl [5.33 (d, J = 11 Hz), 5.36 (d, J = 18 Hz), 5.98 (dd, J = 11, 18 Hz)] groups on quaternary carbon sites, a methyl function [1.15 (d, J = 6.5 Hz)] on a methine center, and several difficultly interpretable multiplets. The presence of monoterpene alkaloids in various Plantago species[4] and representation of the unusual $C_{11}N_3$ combination in the guanidyl monoterpene chaksine[5] suggests that arenaïne may possess a related structure.

Application of chemical-shift theory[6] to the noise resonance decoupled and single frequency decoupled spectra[1] of a chloroform solution of arenaïne shows

(1) Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Naturally Occurring Substances. VI. Previous publications: F. R. N. Gurd, P. J. Lawson, D. W. Cochran, and E. Wenkert, *J. Biol. Chem.*, **246**, 3725 (1971); A. Allerhand, D. Doddrell, V. Glushko, E. Wenkert, P. J. Lawson, and F. R. N. Gurd, *J. Amer. Chem.*, **93**, 544 (1971); E. Wenkert, C.-J. Chang, A. O. Clouse, and D. W. Cochran, *Chem. Commun.*, 961 (1970); E. Wenkert, A. O. Clouse, D. W. Cochran, and D. Doddrell, *ibid.*, 1433 (1969); E. Wenkert, A. O. Clouse, D. W. Cochran, and D. Doddrell, *J. Amer. Chem. Soc.*, **91**, 6879 (1969).

(2) J. Peyroux, M. Hachem-Mehri, M. Platt, P. Rossignol, and G. Valette, *Ann. Pharm. Fr.*, in press.

(3) The authors are indebted to Dr. B. C. Das (I.C.S.N., Gif-sur-Yvette) for the mass spectral determination.

(4) A. V. Danilova and R. A. Konovalova, *Zh. Obshch. Khim.*, **26**, 2307 (1956); R. Torsell, *Acta Chim. Scand.*, **22**, 2715 (1968); Z. F. Ahmed, A. H. Rizk, and F. M. Hammouda, *J. Pharm. Pharmacol.*, **17**, 395 (1965).

(5) L. R. Fowler, Z. Valenta, and K. Wiesner, *Chem. Ind. (London)*, 95 (1968), and references therein.

(6) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 2, Pergamon Press, New York, N.Y., 1966; W. Horsley, H. Sternlicht, and J. S. Cohen, *Biochem. Biophys. Res. Commun.*, **37**, 47 (1969).

(9) D. A. Johnson and D. Mania, *Tetrahedron Lett.*, 267 (1969), and references cited therein.

(10) R. D. G. Cooper, P. V. Demarco, J. C. Cheng, and N. D. Jones, *J. Amer. Chem. Soc.*, **91**, 1408 (1969); R. D. G. Cooper, P. V. Demarco, and D. O. Spry, *ibid.*, **91**, 1528 (1969).