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

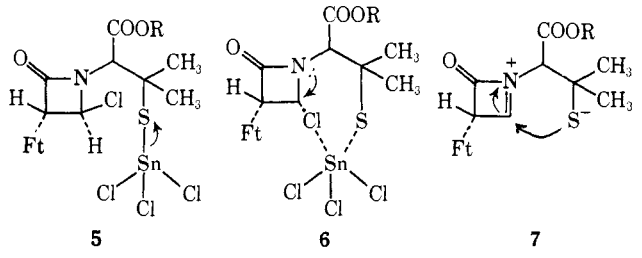
In order to prepare the corresponding 5-epipenicillin with a free carboxyl group in the molecule, a similar reductive cyclization starting with the benzhydryl ester **1b** has been carried out.

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.

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(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).

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.

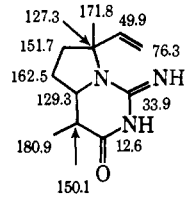
(3) The authors are indebted to Dr. B. C. Das (I.C.S.N., Gif-sur-Yvette) for the mass spectral determination.

(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).

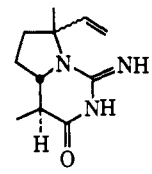
(5) L. R. Fowler, Z. Valenta, and K. Wiesner, *Chem. Ind. (London)*, 95 (1968), and references therein.

(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).

the alkaloid to possess three nonprotonated carbons—carbonyl and guanidine groups and an aminated tetrahedral site—three methines including an olefinic methine and an aminomethine, three methylenes—an olefinic methylene and two saturated ones whose highly shielded and deshielded positions each suggest them to be part of a $R_3CCH_2CH_2$ unit—and two methyl groups. These data yield formula **1** (or its tautomer) on whose carbons the observed chemical shifts (in parts per million upfield of carbon disulfide; $\delta^{CS_2} = \delta^{CHCl_3} + 115.2$ ppm) are denoted.[7]



1



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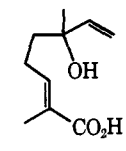

3

Structure **1** permits further interpretation of the pmr spectrum. The keto- and amino-methine signals appear at 2.10 (dd, J = 6.5, 13.0 Hz) and 3.51 ppm (ddd, J = 5.5, 11.0, 13.0 Hz), respectively. Coupling between the methine hydrogens indicates a trans relationship. Hence, **2** represents the relative stereochemical configuration of arenaïne. A solvolytic interaction of the linalool-derived acid **3** or its equivalent[8] with guanidine may represent the biogenesis of the alkaloid.

The above analysis bodes well for the future use of cmr spectroscopy in structure determinations of organic natural products.

(7) The unusual high-field position of one of the methyl groups must be due to an electronic effect of the neighboring carbonyl group [W. McFarlane, *Chem. Commun.*, 418 (1970)].

(8) For the related incorporation of hydroxygeraniol into indole alkaloids *cf.* S. Escher, P. Loew, and D. Arigoni, *ibid.*, 823 (1970), and A. R. Battersby, S. H. Brown, and T. G. Payne, *ibid.*, 827 (1970). *Cf.* also the structure of menthiafolin [A. R. Battersby, A. R. Burnett, G. D. Knowles, and P. G. Parsons, *ibid.*, 1277 (1968)].

(9) U.S. Public Health Service Predoctoral Fellow, 1967–1971.

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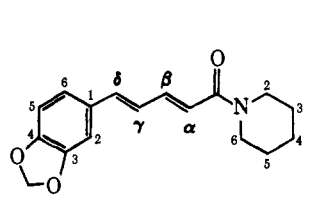
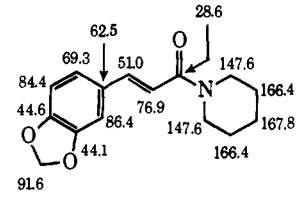
Carbon-13 Nuclear Magnetic Resonance Spectroscopy with the Aid of a Paramagnetic Shift Agent[1]

Sir:

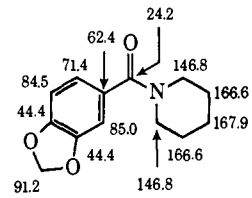
As part of a continuing ^{13}C nmr study of alkaloids[1,2] the cmr analysis of piperine (**1**) was initiated. Application of chemical-shift theory[3] to the noise resonance decoupled and single frequency decoupled spectra[2] of piperine and models **2** and **3** led to full signal assignment of the models[4] but only partial analysis of the alkaloid. Differentiation between the chemical shifts of piperine's aromatic C(6) and olefinic α and γ carbons as well as olefinic β and δ carbons remained difficult. Since such ambiguity has been circumvented in the realm of pmr spectroscopy by the expansion of the resonance range through use of paramagnetic shift agents,[5] introduction of the latter into cmr spectroscopy became important. Consequently an investigation of the pmr and cmr spectra of piperine and its La(dpm)$_3$ and Eu(dpm)$_3$ complexes[6] was undertaken.[7]



1



2



3

The results, collated in Table I, indicate that Eu(dpm)$_3$ is as useful a shift agent in cmr as in pmr spectroscopy and that the absolute magnitude of the shifts is comparable. The expanded cmr resonance range permitted assignment of all of piperine's carbon signals and bodes well for general, future structure analysis.

Shifts due merely to complexation may be as large as pseudocontact shifts especially at centers some distance removed from the coordination site, *cf.* cmr Δ_{La} and Δ_{Eu} values for γ-C and δ-C. However, pmr anisotropy effects of the piperine–Eu(dpm)$_3$ complex are mostly negligible and only noticeable in close proximity to the europium moiety, *cf.* pmr Δ_{La} values for β-C and pip-C(2). All Δ_{Eu} values, except the cmr value of the carbonyl group,[8] agree qualitatively with the *R*

(1) Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Naturally Occurring Substances. VII. For a previous article see A. Rabaron, M. Koch, M. Plat, J. Peyroux, E. Wenkert, and D. W. Cochran, *J. Amer. Chem. Soc.*, **93**, 6270 (1971).

(2) E. Wenkert, C.-J. Chang, A. O. Clouse, and D. W. Cochran, *Chem. Commun.*, 961 (1970).

(3) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 2, Pergamon Press, New York, N. Y., 1966; D. H. Marr and J. B. Stothers, *Can. J. Chem.*, **43**, 596 (1965); E. Lippmaa, T. Pekh, K. Anderson, and C. Rappe, *Org. Magn. Resonance*, **2**, 109 (1970).

(4) Individual chemical shifts from spectra of carbon tetrachloride solutions of the models are depicted on formulas **2** and **3** in parts per million upfield from carbon disulfide. The δ values of aromatic C(3) and C(4) of **2** may be reversed.

(5) For the utilization of one such agent, tris(dipivaloylmethanato)-europium(III) [Eu(dpm)$_3$], in the pmr analysis of organic natural products, see: P. V. DeMarco, T. K. Elzey, R. B. Lewis, and E. Wenkert, *J. Amer. Chem. Soc.*, **92**, 5734, 5737 (1970).

(6) The La(dpm)$_3$ study was included in order to ascertain the effect of complexation with piperine by a Eu(dpm)$_3$-like, diamagnetic agent. *Inter alia* electronic [*e.g.*, cmr δ changes of α,β-unsaturated ketones complexing with aluminum chloride (E. Wenkert and D. Doddrell, unpublished observations)], conformational [*cf.* T. H. Siddall, III, *Chem. Commun.*, 452 (1971)], and anisotropic [*cf.* A. C. Adams and E. M. Larsen, *Inorg. Chem.*, **5**, 228 (1966); T. J. Pinnavaia and R. C. Fay, *ibid.*, **5**, 233 (1966)] effects could be expected to modify the chemical-shift data of the alkaloid.

(7) A cmr study of borneol with paramagnetic shift agents just has been recorded [J. Briggs, F. A. Hart, G. P. Moss, and E. W. Randall, *Chem. Commun.*, 364 (1971)].

(8) This anomaly may be due to a strong contact-shift contribution.