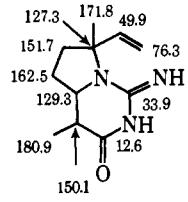
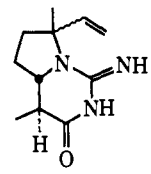
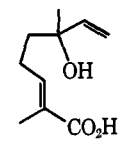
the alkaloid to possess three nonprotonated carbons—carbonyl and guanidine groups and an aminated tetrahedral site—three methines including an olefinic methine and an aminomethine, three methylenes—an olefinic methylene and two saturated ones whose highly shielded and deshielded positions each suggest 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



2



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.

Alain Rabaron, Michel Koch, Michel Plat*
U.E.R. de Chemie Thérapeutique
Faculté de Pharmacie, Université de Paris
Paris 6e, France

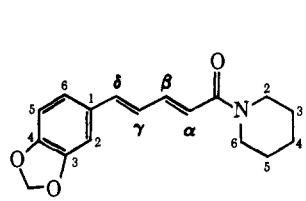
J. Peyroux
U.E.R. des Sciences, Pharmaceutiques et Biologiques
Faculté de Pharmacie, Université de Paris
Paris 6e, France

Ernest Wenkert,* David W. Cochran[9]
Department of Chemistry, Indiana University
Bloomington, Indiana 47401
Received July 6, 1971

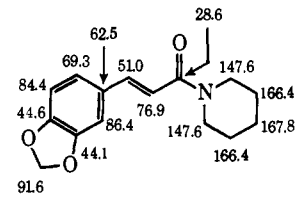
Carbon-13 Nuclear Magnetic Resonance Spectroscopy with the Aid of a Paramagnetic Shift Agent[1]

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



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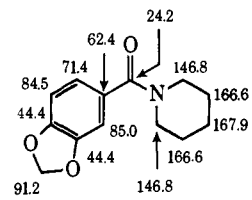


3

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.

Table I. Nmr Spectra of Piperine

	^{1}H magnetic resonance[a]							^{13}C magnetic resonance[b]			
	CCl_4[c]			$CHCl_3$[d]				CCl_4			$CHCl_3$
	δ[e]			δ[e]							
	Obsd[l]	Extrap[m]	Δ_{Eu}[f]	Obsd[l]	Extrap[m]	Δ_{Eu}[f]	Δ_{La}[f]	δ[g]	Δ_{Eu}[f,h,i]	Δ_{La}[f,h,i]	δ[k]
Ar–C(1)								61.4	−1.1	−0.5	61.6
Ar–C(2)	6.87	6.88	+0.12	6.92	6.93	+0.10	0	86.9	−0.3	0	87.0
Ar–C(3)								44.6	0	0	44.5
Ar–C(4)								44.6	0	0	44.5
Ar–C(5)	*n*	6.63	+0.32	6.72	6.71	+0.27	0	84.3	−0.4	0	84.3
Ar–C(6)	6.81	6.83	+0.86	6.82	6.81	+0.77	*n*	70.6	0	+0.3	70.2
α-C	6.29	6.26	−9.26	6.38	6.38	−8.32	+0.08	72.4	+16.5	−3.5	72.5
β-C	7.26	7.26	−9.54	7.38	7.38	−9.42	−0.17	50.5	+20.3	+4.5	50.4
γ-C	*n*	6.69	−2.39	*n*	6.80	−2.24	>0	67.0	+1.4	−0.9	67.4
δ-C	*n*	6.64	+2.50	*n*	6.73	+2.21	<0	55.1	+2.9	+2.9	54.6
C=O								29.0	−6.0	+1.8	27.4
Pip–C(2)	3.50	3.50	−13.53	3.49[o]	3.49	−11.43	−0.14[p]	147.8	+13.8	−0.9	149.2
Pip–C(3)	1.61	1.58	−3.84	1.62	1.70	−3.36	~0	166.4	+4.8[q]	−0.5	166.7
Pip–C(4)	1.61	1.66	−2.28	1.62	1.56	−2.14	~0	167.7	+3.3[q]	+0.7	168.1
Pip–C(5)	1.61	1.58	−3.44	1.62	1.70	−2.70	~0	166.4	+4.8[q]	−0.5	166.7
Pip–C(6)	3.50	3.60	−6.42	3.59[o]	3.56	−5.73	+0.06[p]	147.8	+10.1	+1.9	146.2
Dioxy–CH_2	5.92	5.89	−0.09	5.92	5.92	−0.09	0	91.7	0	0	91.4

[a] Spectra taken on a Varian HA-100 spectrometer. [b] Spectra taken at 15.077 MHz on a Fourier Transform spectrometer. [c] 0.200 *M* solution at 32°. [d] 0.25 *M* solution at 32°. [e] In parts per million downfield from internal TMS. [f] $\Delta_M = \delta_1 + \delta_{complex}$, where complex = 1:1 M(dpm)$_3$/**1**; pmr + Δ_M values and cmr − Δ_M values signify upfield shifts. [g] 0.20 *M* solution at 38°; chemical shifts in parts per million downfield from CS_2; $\delta^{CS_2} = \delta^{CCl_4} + 96.5$ ppm. [h] 0.25 *M* solution at 38°. [i] δ values of the methyl groups of H(dpm), Eu(dpm)$_3$, and the 1:1 Eu(dpm)$_3$–**1** complex are 164.7, 163.0, and 163.9, respectively. [j] Values extrapolated from plots extending up to 3:4 La(dpm)$_3$–**1** concentration ratio. [k] 0.5 *M* solution at 35°; chemical shifts in parts per million downfield from CS_2; $\delta^{CS_2} = \delta^{CHCl_3} + 115.2$ ppm. [l] Observed values. [m] Extrapolated values (see Figure 1). [n] Overlapping multiplets prevent measurement. [o] Determined at 220 MHz and 13° (below the coalescence temperature). [p] Values may be reversed. [q] Extrapolated values (see Figure 2); direct observation obscured by overlapping signal of the methyl groups of Eu(dpm)$_3$.

and θ relationships of the pseudocontact-shift phenomenon.[9] Thus, there is observed not only a change in the magnitude of the chemical shifts of both hydrogens and carbons dependent on their distance from europium bonded to the amide oxygen, but also a change in direction of those shifts outside 54° of the magnetic axis of the complex, *e.g.*, the upfield shifts of the aro-

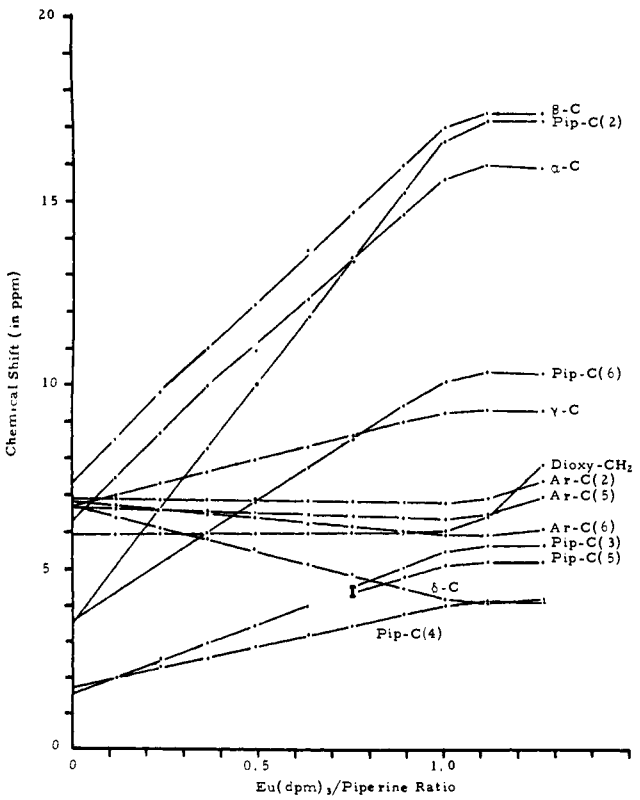


Figure 1. Effect of Eu(dpm)$_3$ on pmr chemical shifts.

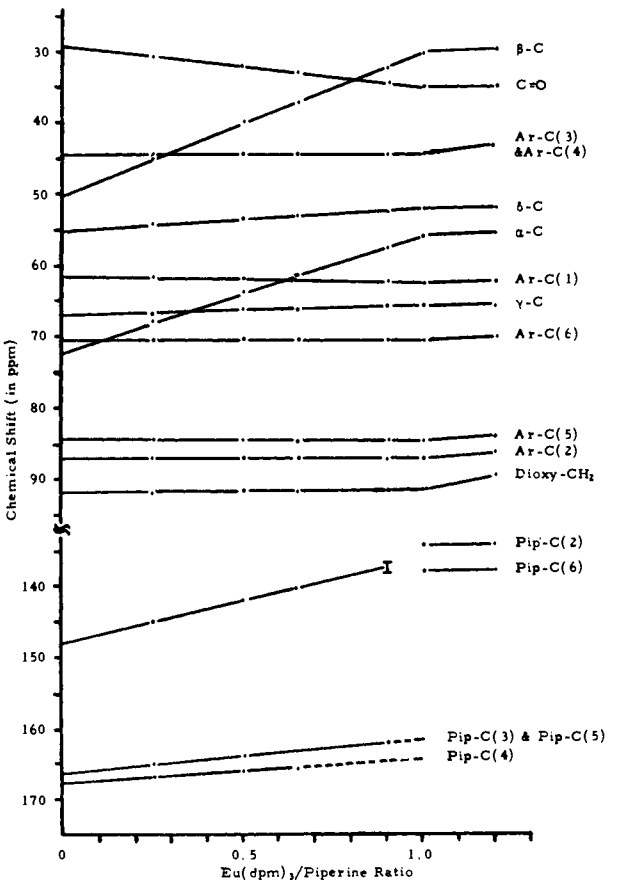


Figure 2. Effect of Eu(dpm)$_3$ on cmr chemical shifts.

(9) H. M. McConnell and R. E. Robertson, *J. Chem. Phys.*, **29**, 1361 (1958); G. N. LaMar, *ibid.*, **43**, 1085 (1965).

matic hydrogens and the δ hydrogen.[10] The data indicate the magnetic axis to pass approximately through the δ carbon and the aromatic C(2)–hydrogen bond and piperine to possess a freely rotating aromatic ring (on the nmr time scale) with preponderant rotamer population as depicted in **1**.

As the increasing dissimilarity of the aminomethylene hydrogens and carbons with increasing concentration of europium agent indicates (Figures 1 and 2), lanthanide association freezes piperine into unique rotamers.[11] After a 1:1 piperine–Eu(dpm)$_3$ concentration ratio is reached, chemical shifts change drastically, as complexation at the methylenedioxy group commences (Figures 1 and 2).

Pmr solvent effects are slight, but distinct. All Δ_{Eu} values are of the same sign and of nearly the same magnitude, when normalized to the Δ_{Eu} value of the 2-aminomethylene hydrogens, for carbon tetrachloride and chloroform solutions. The lower absolute magnitude of chloroform's Δ_{Eu} values reflects less tendency toward complexation in this solvent in view of its competing hydrogen bonding property (Table I). Chloroform's H bonding may be responsible also for the earlier separation of the aminomethylene signals in chloroform than in carbon tetrachloride and the sharper breaks in the Δ_{Eu} plots (hence, the more selective complexation) in carbon tetrachloride than in chloroform (Figures 1 and 2).

(10) In view of the experimental error of ±0.2 for the cmr δ values and the low cmr $\Delta_{Eu} - \Delta_{La}$ values the cmr Δ_{Eu} data are not as revealing about the θ dependence as the corresponding pmr data.

(11) Not only is the piperidine unit affected in this manner, but the olefinic side chain behaves in this fashion. The sharp signals due to the hydrogens of α-C and β-C undergo initial line broadening and subsequent resharpening on addition of Eu(dpm)$_3$.

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

(13) U. S. Public Health Service Predoctoral Fellow, 1969–1971.

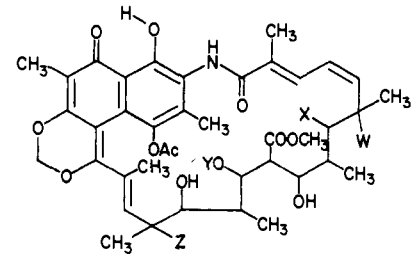
(14) U. S. Public Health Service Predoctoral Fellow, 1969–present.

Ernest Wenkert,* David W. Cochran[12]
Edward W. Hagaman, R. Burton Lewis,[13] F. M. Schell[14]
Department of Chemistry, Indiana University
Bloomington, Indiana 47401
Received July 6, 1971

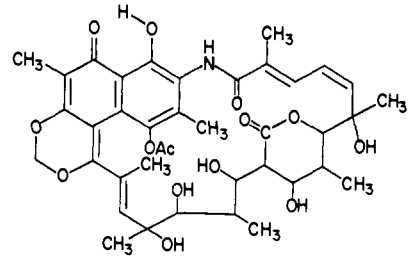
Chemistry of the Streptovaricins. VIII. Structures of Streptovaricins A, B, D, E, F, and G[1a]

Sir:

In other communications we have assigned a revised structure, **3**, to streptovaricin C ($C_{40}H_{51}NO_{14}$), the most abundant component of the streptovaricin complex.[1a] The activities of the individual components of the complex as inhibitors of pox virus[2] and leukemia virus[3] vary widely,[2b,3b] as do their antibacterial activities,[4] and streptovaricin C is by no means the most active in all these tests. In the present report we assign structures to streptovaricins A (**1**, $C_{42}H_{53}NO_{16}$),[5a-c] B (**2**, $C_{42}H_{53}NO_{15}$),[5a,b] D (**4**, $C_{40}H_{51}NO_{13}$),[5a,b] E (**5**, $C_{40}H_{49}NO_{14}$),[5a,b] F (**6**, $C_{39}H_{47}NO_{14}$),[5b] and G (**7**, $C_{40}H_{51}NO_{15}$),[5a,b]

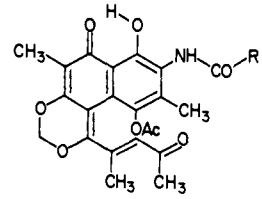


1(A), W = OH; X = H, OH; Y = Ac; Z = OH
2(B), W = H; X = H,OH; Y = Ac; Z = OH
3(C), W = H; X = H,OH; Y = H; Z = OH
4(D), W = H; X = H,OH; Y = H; Z = H
5(E), W = H; X = =O; Y = H; Z = OH
7(G), W = OH; X = H,OH; Y = H; Z = OH



6(F)

Electronic spectra of the streptovaricins indicate a common chromophore for the antibiotics[6] and osmium tetroxide–sodium periodate oxidation of streptovaricins A–C and E–G (but not D) give the same aromatic compound, streptovarone (**8**).[1a,7,8] Moreover, high-resolution mass spectral data indicate the common structural unit a for streptovaricins A–C and E–G (but not D), since the most prominent peaks in the mass spectra of prestreptovarone (**9**)[7-9]—those at *m/e* 390.133



8, R = $-COCH_3$
9, R = $-C(CH_3)=CHCH=CHCOCH_3$

($C_{23}H_{20}NO_5$), 324.087 ($C_{18}H_{14}NO_5$), 297.100 ($C_{17}H_{15}NO_4$), and 269.079 ($C_{16}H_{13}O_4$)—are also found in the spectra of streptovaricins A–C and E–G.[10]

(1) (a) Paper VII: K. L. Rinehart, Jr., and F. J. Antosz, *J. Antibiot.*, in press; (b) A. H.-J. Wang, I. C. Paul, K. L. Rinehart, Jr., and F. J. Antosz, *J. Amer. Chem. Soc.*, **93**, 6275 (1971).

(2) (a) N. A. Quintrell and B. R. McAuslan, *J. Virol.*, **6**, 485 (1970); (b) K. B. Tan and B. R. McAuslan, *Biochem. Biophys. Res. Commun.*, **42**, 230 (1971).

(3) (a) W. W. Brockman, W. A. Carter, L.-H. Li, F. Reusser, and F. R. Nichol, *Nature (London)*, **230**, 249 (1971); (b) W. A. Carter, W. W. Brockman, and E. C. Borden, *ibid.*, *New Biol.*, **232**, 212 (1971); (c) E. C. Borden, W. W. Brockman, and W. A. Carter, *ibid.*, **232**, 214 (1971).

(4) (a) P. Siminoff, R. M. Smith, W. T. Sokolski, and G. M. Savage, *Amer. Rev. Tuberc. Pulm. Dis.*, **75**, 576 (1957); (b) L. E. Rhuland, K. F. Stern, and H. R. Reames, *ibid.*, **75**, 588 (1957).

(5) In agreement with the molecular formula assigned are (a) microanalyses, (b) low-resolution mass spectral data, and (c) high-resolution mass spectral data.

(6) P. K. Martin, Ph.D. Thesis, University of Illinois, 1965.

(7) K. L. Rinehart, Jr., C. E. Coverdale, and P. K. Martin, *J. Amer. Chem. Soc.*, **88**, 3150 (1966).

(8) K. L. Rinehart, Jr., P. K. Martin, and C. E. Coverdale, *ibid.*, **88**, 3149 (1966).

(9) The structure **9** shown for prestreptovarone has been revised to accord with the revised structure of streptovarone (**8**).[1a]