(π-C_5H_5)$Co(CN)_2^{2-}$, a Co(I) complex that should have at least comparable stability to $Co(CN)_4^{3-}$, is unstable in acetonitrile on the cyclic voltametric time scale. Similar instability of low-valent cyanides in acetonitrile has been observed for other complexes.[16] It thus appears that cyanide has only limited ability to stabilize Co(I) in acetonitrile, and given the oxidizing power of Co(III) the disproportionation reaction above is probably thermodynamically unfavorable. A more interesting possibility is that coordination of the vinyl halide induces disproportionation. Electron-deficient alkenes are good ligands for low-valent cobalt.[17,18]

Thus it is not possible to choose from an abundance of possible reaction paths given the available evidence. There is evidence in both the aqueous and the acetonitrile reactions for π-coordination of the product nitriles, and coordination of the vinyl halides could well be important in one or both of the systems, but little is known about coordination of alkenes to Co(II) and even for Co(I) there are few well-characterized examples.[18]

Further mechanistic speculation concerning this reaction clearly is unwarranted at this time. The incomplete stereospecificity and lack of catalysis clearly distinguish our system from that of Funabiki et al., which appears to remain the method of choice for converting base-stable haloalkenes to α,β-unsaturated nitriles. The $(Et_3MeN)_3Co(CN)_5$ reaction may, however, be of value in organic synthesis when neither the aqueous base of the Funabiki reaction nor the high temperatures of the reaction with CuCN can be tolerated.

Experimental Section

General. All reactions were carried out in dry glassware under a nitrogen atmosphere. Acetonitrile was dried by distillation from P_4O_{10}. Dimethyl formamide (DMF) from Burdick and Jackson was stirred with activated 4-Å molecular sieves and filtered through a fine frit. Diethyl ether and THF for the preparation and purification of the cyanide salts were purified by distillation from sodium benzophenone. $(Et_3MeN)CN$,[19] (*E*)-C_6H_5CH=CHBr,[20] (*Z*)-C_6H_5CH=CHBr,[21] and (*Z*)-C_6H_5CH=$CHCl$[4a] were prepared and purified via literature procedures. Bromoethene, 2-bromopropene, 1-chloro-2-methylpropene, 2-bromo-3-phenylprop-2-enal, *p*-bromoanisole, and anhydrous $CoCl_2$ were commercial products. 1-Chloro-2-methylpropene was washed with Na_2SO_3 solution, filtered through activated alumina, and distilled. 2-Bromopropene was freshly distilled. Other halides were used as received.

Caution: Cyanides and nitriles should be assumed to be severe poisons and handled (wearing gloves) accordingly. No HCN should be produced in these reactions; however, safe laboratory practice requires that these reactions be carried out in a good fume hood or appropriately vented glovebox as a precaution against inadvertant HCN production.

Products, which are all known compounds, were identified by comparison with reported ^1H NMR data and also by GC comparison with authentic samples of those nitriles that were commercially available. Stereochemistry of the cinnamonitriles was assigned based on the reported ^1H NMR data.[4b] Quantitative analysis was by GC using the internal standard method. A 6 ft × $^1/_8$ in. 3% OV-210 on Chromosorb W column was used for halostyrene reaction analyses, a 6 ft × $^1/_8$ in. 1% SP-2100 on Carbopack B column was used for the 1-chloro-2-methylpropene reaction, and a 10% SP-2100 on Chromosorb W column was used for other analyses. Proton NMR was performed on a Varian EM-390 spectrometer. IR data were recorded on a Perkin-Elmer 683 spectrometer interfaced to a P-E 3500 Data Station.

$[(C_2H_5)_3(CH_3)N]_3[Co(CN)_5]$. A slight variant of the literature procedure for the synthesis of $[(C_2H_5)_4N][Co(CN)_5]$ was used.[8] A solution of $CoCl_2$ (1.04 g, 8.00 mmol) in 70 mL of DMF was slowly added to a stirred solution of $[(C_2H_5)_3(CH_3)N]CN$ (6.83 g, 4.0 mmol) in 250 mL of DMF. The flask holding the $CoCl_2$ solution was rinsed with 10 mL of DMF and the rinsings added to the reaction mixture, which was then stirred until its color stopped changing, ending as dark yellow. THF was added slowly with stirring until precipitation began, and the mixture was cooled to −35 °C. The yellow crystals that formed were collected by filtration and washed successively with 30 mL of a chilled 1:1 mixture of DMF and THF, 2 × 10 mL of THF, and 15 mL of ether. The product was recrystallized from a concentrated acetonitrile solution by addition of ether and cooling to −35 °C. After washing with chilled 1:1 acetonitrile–ether and then twice with ether, the solid was dried in vacuo for 1 h, to give $[(C_2H_5)_3(CH_3)N]_3Co(CN)_5$ (3.53 g, 82%) as opaque tan-yellow crystals. IR (mineral oil mull) 2070 cm^{-1}.

Reactions of $[(C_2H_5)_3(CH_3)N]_3[Co(CN)_5]$ with Haloalkenes. The reaction with (*E*)-PhCH=CHBr is given as a representative procedure. The bromostyrene (85 μL, 0.66 mmol) was added by syringe to 6.00 mL of a 0.100 M solution of $[(C_2H_5)_3(CH_3)N]_3Co(CN)_5$ in acetonitrile. Within 15 min the initially yellow solution became green. The reaction mixture was placed in a 40 °C oil bath. In 2.5 h the solution color was blue. Heating was continued for a total of 43 h. After cooling, the blue-green solution was opened to the air and poured into 10 mL of 0.1 M aqueous NaOH. The products were extracted with diethyl ether, and the dried ether solution was analyzed by GC. A 72% yield of (*E*)-cinnamonitrile was found, with no starting material and a trace of the *Z* nitrile. A nonaqueous workup, vacuum distillation without exposure of the reaction mixture to air, was used to isolate the products of the 1-chloro-2-methylpropene reaction.

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Registry No. $[(C_2H_5)_3(CH_3)N]_3[Co(CN)_5]$, 98087-79-7; (*E*)-PhCH=CHBr, 588-72-7; (*Z*)-PhCH=CHBr, 588-73-8; (*Z*)-PhCH=CHCl, 4604-28-8; *p*-$CH_3OC_6H_4Br$, 104-92-7; $(CH_3)_2C$=CHCl, 513-37-1; (*E*)-PhCH=CHCN, 1885-38-7; (*Z*)-PhCH=CHCN, 24840-05-9; $(CH_3)_2C$=CHCN, 4786-24-7; $[(C_2H_5)(CH_3)N]CN$, 69666-99-5; $CoCl_2$, 7646-79-9; bromoethene, 593-60-2; 2-bromopropene, 557-93-7; 3-chlorocyclohex-2-enone, 5682-75-7; bromomaleic anhydride, 5926-51-2; 2-bromo-3-phenylprop-2-enol, 5443-49-2.

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A New Dihydrobenz[*a*]anthraquinone Antitumor Antibiotic (PD 116740)

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In the course of our anticancer drug discovery program, the fermentation broth of an as yet unidentified actinomycete isolate (WP 4669) was found to exhibit in vitro activity against L1210 lymphocytic leukemia and HCT-8

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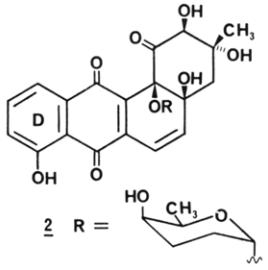
human colon adenocarcinoma cell lines. Bioactivity directed fractionation of subsequent broths resulted in the isolation of a new antibiotic, PD 116740 (1), possessing the benz[a]anthracene skeleton. Several similar antibiotics have recently been reported, including the sakyomycins,[1] X-14881A–E,[2] rabelomycin,[3] aquayamycin,[4] and tetrangomycin.[5] This report describes the isolation and structure elucidation of 1 which is the first reported benz[a]anthraquinone antibiotic possessing a 5,6-dihydrodiol moiety.

PD 116740 was isolated from filtered fermentation broths by adsorption onto Diaion HP-20, followed by elution with aqueous methanol. Chromatography of the concentrated eluate over C-18 silica gel and crystallization from methanol–acetone yielded PD 116740 as red plates.

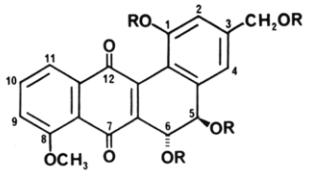
The ultraviolet absorption spectrum of 1 in methanol exhibited maxima at 255, 289, and 409 nm, indicating the presence of a substituted naphtho- or anthraquinone moiety. A pronounced bathochromic shift in base revealed the presence of at least one phenolic hydroxyl group. These data, together with other spectral and chemical evidence, suggested that a benz[a]anthraquinone structure could be assigned to PD 116740. In the infrared spectrum, a strong absorption peak at 1645 cm^{-1}, and the absence of a peak near 1670 cm^{-1}, indicated that both quinone carbonyls were chelated with neighboring hydroxyl groups.[6] Significantly, an IR band at 1700–1725 cm^{-1}, assigned to the C-1 carbonyl in related antibiotics, was absent in the spectrum of 1, suggesting that a hydroxyl group, hydrogen bonded to the C-12 quinone carbonyl, could be attached to the C-1 position.

The ^1H NMR spectrum of PD 116740 exhibited signals for an aromatic methoxy group, an allylic or benzylic hydroxymethyl group, and an aromatic ABX system with a pattern very similar to that observed for the D ring protons of sakyomycin A (2).[1] In addition, a pair of coupled signals



2 R =

at δ 4.30 and 4.87 (shifting to δ 6.0 and 6.33 in the spectrum of the tetraacetyl derivative 3) revealed the presence of a



1 R = H

3 R = Ac

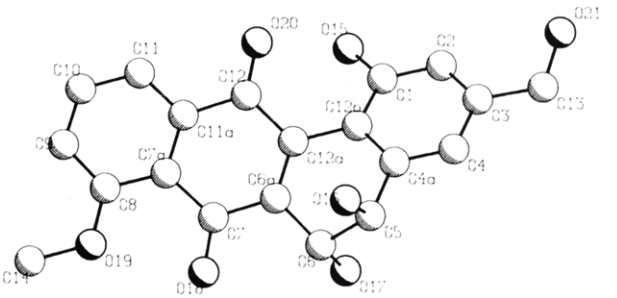


Figure 1. A computer-generated perspective drawing of the final X-ray model of PD 116740. Hydrogens are omitted for clarity, and no absolute configuration is implied.

CH(OH)CH(OH) moiety in 1. The remaining signals for nonexchangeable protons in the ^1H NMR spectrum of PD 116740 were observed as broad singlets at δ 6.78 and 6.79, each integrating for one proton, representing isolated (or long-range coupled) aromatic protons.

On the basis of the above data, several possible structures could be drawn for PD 116740. In particular, available evidence permitted the assignment of the vicinal dihydrodiol moiety to either the 1,2- or the 5,6-position. X-ray diffraction analysis conveniently provided a solution to this structure problem, establishing both the position and the relative configuration of the diol unit.

A computer-generated perspective drawing of the final X-ray model of PD 116740 less hydrogens is given in Figure 1. The X-ray analysis defined only the relative stereostructure, so the enantiomer shown is an arbitrary choice. As can be seen, the dihydrodiol moiety is located in the 5,6-position, and the resulting 5,6-dihydrobenz[a]anthraquinone is not planar. The aromatic D ring is rotated by approximately 25° to the naphthoquinone portion. This rotation relieves a potential steric congestion between O15 and O20, which are 2.68 Å apart in the solid state. This is certainly close enough for the H-bond suggested by the IR, but the hydrogen on O15 is oriented away from O20, participating in an *intermolecular* H-bond to O18 of a neighboring molecule. The O15–O18 distance is 2.82 Å, and the O15H···O18 distance is 1.85 Å. This, of course, does not rule out a H-bond in solution. The two aliphatic hydroxyl groups are oriented in an antiperiplanar fashion with a torsional angle of 171° between them. In general, bond distances and angles agree well with generally accepted values.

The structure assigned to PD 116740 is unique among the benz[a]anthraquinone class of antibiotics. Although fully aromatic compounds in this class are known, no antibiotics reduced only at the 5,6-position have been reported. PD 116740 is also the first representative of this class possessing 5,6-dihydroxy and 3-(hydroxymethyl) moieties. PD 116740 displays activity against both the L1210 and HCT-8 cell lines, exhibiting IC_{50} values of 2.1×10^{-6} M and 3.3×10^{-6} M, respectively. In vivo antitumor studies of this interesting new compound are in progress.

Experimental Section

General Methods. Infrared spectra were determined on a Nicolet SX-60 FTIR spectrometer. Ultraviolet spectra were recorded on a IBM Model 9420 UV–vis spectrophotometer. ^1H and ^{13}C NMR spectra were run on a Varian XL-200 spectrometer; chemical shifts are reported in parts per million downfield from internal Me_4Si. The optical rotation of PD 116740 was measured on a Perkin-Elmer Model 141 polarimeter. The course of isolation and chromatographic steps was monitored by HPLC using a Waters Assoc. μBondapak C-18 column (0.4 × 30 cm) and 0.05 M pH 6.5 ammonium acetate buffer–methanol (70:30) as the mobile phase at a flow rate of 2.0 mL/min. The retention time

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of PD 116 740 in this system is 4.1 min.

Isolation of PD 116 740. Filtered fermentation broth (12 L) of culture WP 4669 was passed over 500 mL of Diaion HP-20 resin packed in water. After washing with methanol-water (2:8, 1 L), PD 116 740 was eluted with methanol-water (1:1). The eluates containing most of the PD 116 740 were combined and concentrated to dryness to give 3.2 g of crude concentrate. The residue was dissolved in methanol, filtered, diluted with water, and chromatographed over 900 g of C-18 silica gel (20 μm, Analytichem International). Elution with 3.5 L of water-methanol (9:1), followed by 2.5 L of water-methanol (85:15) and 3 L of water-methanol (3:1), resulted in the concentration of 1 in the 25% methanol eluates. After concentration to dryness, the residue (1.15 g) was crystallized from methanol and recrystallized from methanol-acetone to yield crystalline 1 (560 mg) as red plates: mp >300 °C; $[\alpha]_D$ +311° (*c* 0.44, MeOH); λ_{max} (MeOH) 255 nm (ϵ 14 500), 289 nm (ϵ 10 800) and 409 nm (ϵ 6 300); λ_{max} (MeOH + NaOH) 238 nm (ϵ 22 300), 321 nm (ϵ 7 000), 341 nm (ϵ 5 900), 389 nm (ϵ 4 970), 541 nm (ϵ 2 800); ν_{max} (KBr) 1645, 1620, 1590, 1270, and 1030 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 3.91 (3 H, s, OCH_3), 4.30 (1 H, dd, *J* = 2.0, 2.0, H-5), 4.44 (2 H, d, *J* = 5.8, H-13), 4.87 (1 H, dd, *J* = 2.0, 2.0, H-6), 5.21 (3 H, m, 3 × OH, signal disappears upon addition of D_2O), 6.78 and 6.79 (1 H each, s, H-2 and H-4), 7.47 and 7.49 (each 1 H, d, *J* = 7.5, H-9 and H-11), 7.76 (1 H, dd, *J* = 7.5, 7.5, H-10) and 9.7 (1 H, br s, OH); ^{13}C NMR (CD_3OD) δ 54.7, 62.4, 62.6, 70.7, 113.6, 115.0, 117.0, 118.1, 118.5, 119.3, 134.2, 135.4, 138.3, 140.1, 140.8, 145.4, 155.3, 158.6, 182.2, 185.1.

Anal. Calcd for $C_{20}H_{16}O_7$·1.39CH_3OH: C, 62.38; H, 5.22. Found: C, 62.39; H, 5.09.

Preparation of PD 116 740 Tetraacetate. PD 116 740 (10 mg) was treated with acetic anhydride (0.25 mL) in pyridine (0.75 mL) at room temperature for 2.5 h. The residue obtained after removal of excess reagents in vacuo was crystallized as yellow needles from methanol to yield 11.5 mg of **3**: mp 210–13 °C; ν_{max} ($CHCl_3$) 1746, 1677, 1656, 1589, 1371, 1282, 1114, 1035 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.91 (3 H, s), 1.92 (3 H, s), 2.14 (3 H, s), 2.21 (3 H, s), 4.02 (3 H, s, OCH_3), 5.13 (2 H, s, H-13), 6.00 (1 H, d, *J* = 2.6, H-5), 6.33 (1 H, d, *J* = 2.6, H-6), 7.28 (1 H, br s, H-2 or H-4), 7.32 (1 H, dd, *J* = 2.0, 7.0, H-11), 7.48 (1 H, br s, H-2 or H-4), and 7.7 (2 H, m, H-9 and H-10).

Single-Crystal X-ray Diffraction Analysis of PD 116 740 (1). Suitable crystals, in the form of dark red retangular solids, could be grown by slow evaporation of methanol-acetone solutions. A crystal of approximate dimensions 0.7 × 0.5 × 0.2 mm was selected for the analysis. Preliminary X-ray photographs displayed monoclinic symmetry, and accurate lattice constants of a = 9.157 (1) Å, b = 7.243 (1) Å, c = 14.064 (2) Å, and β = 82.78 (1)° were determined from a least-squares fit of 15 diffractometer-measured 2θ values. The systematic extinctions, crystal density, and optical rotation were uniquely accommodated by space group $P2_1$ with one molecule of composition $C_{20}H_{16}O_7$·CH_3OH forming the asymmetric unit. All unique diffraction maxima with $2\theta \leq 114°$ were collected on a computer-controlled four-circle diffractometer using variable speed, 1° ω scans and graphite-monochromated Cu K$\bar{\alpha}$ radiation (1.54178 Å).

Of the 1357 reflections measured in this fashion, 1250 (92%) were judged observed ($|F_o| \geq 3\sigma(F_o)$) after correction for Lorentz, polarization, and background effects.[7] A phasing model, consisting of all of the non-hydrogen atoms, was found uneventfully using direct methods. Hydrogens were located on a difference synthesis following partial refinement. Block-diagonal, least-squares refinements with anisotropic non-hydrogen atoms and isotropic hydrogens have converged to a standard crystallographic residual of 0.048 (R_w = 0.060) for the observed reflections. Additional crystallographic details are available and are described in the paragraph entitled Supplementary Material Available at the end of this paper.

Acknowledgment. The authors at Warner-Lambert/Parke-Davis thank Dr. J. B. Tunac and Dr. R. C. Jackson and their respective microbiology and tumor biology sections for their valuable contributions to this work. The portion of this work performed at Warner-Lambert/Parke-Davis was supported in part by contract NO1-CM-37614 from the National Cancer Institute. The Cornell authors thank NSF INT14133 and NIH CA24487 for partial support of this work.

Registry No. 1, 98015-54-4; 3, 98015-55-5.

Supplementary Material Available: Tables of fractional coordinates, thermal parameters, bond distances, and bond angles for PD 116 740 (4 pages). Ordering information is given on any current masthead page.

(7) All crystallographic calculations were done on a PRIME 850 computer operated by the Cornell Chemistry Computing Facility. Principal programs employed were REDUCE and UNIQUE, data reduction programs by M. E. Leonowicz, Cornell University, 1978; MULTAN 78, MULTAN 80, and RANTAN 80, systems of computer programs for the automatic solution of crystal structures from X-ray diffraction data (locally modified to perform all Fourier calculations including Patterson syntheses) written by P. Main, S. E. Hull, L. Lessinger, G. Germain, J. P. Declercq, and M. M. Woolfson, University of York, England, 1978 and 1980; DIRDIF written by P. T. Beurskens et al., University of Nijmegen, Netherlands, 1981; MITHRIL, an automatic solution package written by C. J. Gilmore, University of Glasgow, Scotland, 1983; BLS78A, an anisotropic block-diagonal least-squares refinement written by K. Hirotsu, and E. Arnold, Cornell University, 1980; PLUTO78, a crystallographic illustration program by W. D. S. Motherwell, Cambridge Crystallographic Data Centre, 1978; and BOND, a program to calculate molecular parameters and prepare tables written by K. Hirotsu, Cornell University, 1978.

Communications

Nitrones by Heterolytic Fragmentation of γ-*N*-Hydroxyamino Sulfonates. Conversion of a Decahydroquinoline to a Perhydroazaazulene

Summary: (*E,Z*)-1-Azacyclodeca-1,6-diene 1-oxide (**4**) was generated by fragmentation of 1-hydroxy-*cis,cis*-5-[(*p*-tolylsulfonyl)oxy]decahydroquinoline (**3a**) under basic conditions. The nitrone **4** underwent in situ intramolecular cycloaddition to a 1-aza-11-oxatricyclo[5.3.1.0^{2,6}]undecane (**5**), and it could be trapped with styrene in an intermolecular dipolar cycloaddition to give **6**. This concerted fragmentation reaction represents a useful nitrone synthesis.

Sir: Heterolytic fragmentation reactions have come to be accepted as valuable stereospecific processes in the synthesis of many compounds, including natural products.[1] Grob and co-workers have demonstrated that the synchronous fragmentation of γ-amino alcohol derivatives requires an extended, anti-periplanar relationship between the C_α–X bond, the C_β–C_γ bond which is undergoing cleavage, and the nitrogen lone pair electrons.[2] Among the many systems with which this postulate has been

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