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Antifungal Activity of Bischelates of 5-, 7-, and 5,7-Halogenated 8-Quinolinols with Copper(II). Determination of Approximate Dimensions of the Long and Short Axes of the Pores in the Fungal Spore Wall

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The effect on antifungal activity of simultaneously varying the substituents on the 5,5′ and 7,7′ axes of the Cu(II) bischelate of 8-quinolinol was studied. Calculations of approximate long and short dimensions of the pores of the spore walls of four fungi were made based on the geometry of the molecules in conjunction with their fungitoxicities. They were found to be: *A. niger*, 15.0, 10.8 Å; *T. viride*, 16.6, 10.7 Å; *A. oryzae*, 15.0, 10.8 Å; *T. mentagrophytes*, 16.6, 10.7 Å.

In a hypothesis proposed by Gershon, *et al.*,[1] it was suggested that the fungal spore wall behaved as a barrier with respect to certain potential antifungal agents. If the geometry and distribution of charge around a molecule are incompatible with the geometry and charge distribution around the peripheries of the pores in the fungal spore wall, penetration of the wall by the agent cannot take place, and toxic reactions within the spore do not occur. A further consequence of this hypothesis is that by altering the sizes and shapes of the toxicant molecules, and relating these geometrical forms with antifungal activity, it should be possible to arrive at an approximation in two dimensions of the appearance of the pores in the fungal spore wall.

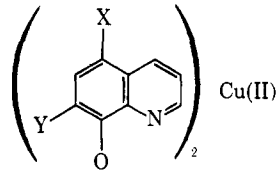
In these studies[1,2] which are concerned with five fungi it was shown by fungitoxicity studies with Cu(II) bischelates of 5-substituted 8-quinolinols that the minimal long dimensions of the pores of the spore wall in each species are as follows: *Aspergillus niger*, 15.0 Å; *Trichoderma viride*, 16.6 Å; *Aspergillus oryzae*, 15.0 Å; *Myrothecium verrucaria*, 16.6 Å; and *Trichophyton mentagrophytes*, 16.6 Å. If the hypothesis is sound, and the explanation of the nontoxicity of certain compounds is due to the long axes being greater than the major axes of the pores, alteration of a secondary axis of the compound should not cause the derivative to become toxic. This was found to be true by means of studies with the Cu(II) bischelates of 5-nitro-7-substituted 8-quinolinols.[3] It was further deduced from the dimensions and angles between the 5,5′ and 7,7′ axes of Cu(II) bischelates of 5-substituted 8-quinolinols and 5-substituted 7-nitro-8-quinolinols that the pores in the spore walls are not circular but may be elliptical or hexagonal.[2,4,†]

The present work is concerned with the effect on antifungal activity of simultaneously varying the substituents on the 5,5′ and 7,7′ axes of the Cu(II) bischelate of 8-quinolinol from H to F to Cl to Br to I. Based on these data, calculations can be made of approximate lengths of axes at the midpoint and perpendicular to the major axes of the pores in the fungal spore walls.

Of the ligands employed for preparing the chelates listed in Table II, compounds Ia, IIIa,c, IVa,d, and Va,e were commercially available. The remaining compounds were synthesized according to published methods as follows: Ib,[5] Ic,d,[6] Ie,[7] IIa,[8] IIb–d,[9] IIe,[8] IIIb,[9] IIId,[10] IIIe,[11] IVb,[9] IVc,[12] IVe,[9] Vb,[9] Vc,[11] and Vd.[9] The bischelates with Cu(II) were prepared by the methods described by Hollingshead.[13] The Cu(II) bischelates of the commercially available 8-quinolinols have been adequately reported in

†It was found that what was believed to be 5-bromo-7-nitro- and 5-iodo-7-nitro-8-quinolinols in ref 2 was incorrect. The corresponding compounds with correct structures were reported in ref 5 and 6. The data in ref 4 on the bis(5-halo-7-nitro-8-quinolinolato)copper(II) complexes were obtained with the new compounds, and it should be mentioned that bis(7-nitro-8-quinolinolato)copper(II) does not inhibit *T. mentagrophytes* below 1000 ppm as reported in ref 4 where inhibition was obtained with a decrepitated culture of the organism.

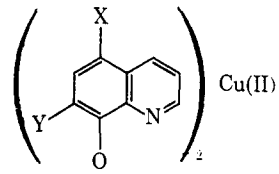
Table I. Bis(5,7-dihalo-8-quinolinolato)copper(II) Chelates



Compd	X	Y	Mp, °C dec[a]	Formula	Analyses[b]
Ib	H	F	Indistinct >350	$C_{18}H_{10}F_2N_2O_2Cu$	C, H, N
IIb	F	F	Indistinct >380	$C_{18}H_8F_4N_2O_2Cu$	C, H, F, N
IIc	F	Cl	320	$C_{18}H_8Cl_2F_2N_2O_2Cu$	C, H, F, N
IId	F	Br	Indistinct >370	$C_{18}H_8Br_2F_2N_2O_2Cu$	C, H, F, N
IIe	F	I	Indistinct >320	$C_{18}H_8F_2I_2N_2O_2Cu$	C, H, F, I, N
IIIb	Cl	F	368	$C_{18}H_8Cl_2F_2N_2O_2Cu$	C, H, Cl, I, N
IIId	Cl	Br	335	$C_{18}H_8Br_2Cl_2N_2O_2Cu$	C, H, N
IIIe	Cl	I	Indistinct >270	$C_{18}H_8Cl_2I_2N_2O_2Cu$	C, H, Cl, I, N
IVb	Br	F	Indistinct >270	$C_{18}H_8Br_2F_2N_2O_2Cu$	C, H, Br, F, N
IVc	Br	Cl	310	$C_{18}H_8Br_2Cl_2N_2O_2Cu$	C, H, N
IVe	Br	I	Indistinct >300	$C_{18}H_8Br_2I_2N_2O_2Cu$	C, H, Br, I, N
Vb	I	F	Indistinct >280	$C_{18}H_8F_2I_2N_2O_2Cu$	C, H, F, I, N
Vc	I	Cl	Indistinct >280	$C_{18}H_8Cl_2I_2N_2O_2Cu$	C, H, N
Vd	I	Br	Indistinct >270	$C_{18}H_8Br_2I_2N_2O_2Cu$	C, H, Br, I, N

[a]Analytical sample. [b]All analyses reported are within 0.3% of the theoretical value.

Table II. Minimal Antifungal Activity (mmol/l.) of Copper(II) Complexes of 5-, 7-, and 5,7-Substituted 8-Quinolinols in Sabouraud Dextrose Broth at 28° in Shake Flasks after 6 Days



			A. niger		*T. viride*		*A. oryzae*		*M. verrucaria*		*T. mentagrophytes*	
Compd	X	Y	S[b]	C	S	C	S	C	S	C	S	C
Ia	H	H[a]	0.0085	NA[c]	0.0085	NA	0.0085	NA	0.0085	0.0085	0.0057	0.0057
Ib	H	F	NA		0.036	NA	NA		0.036	0.037	0.018	0.023
Ic	H	Cl	NA		<0.0024[d]	<0.0024	NA		<0.0024	<0.0024	<0.0024	<0.0024
Id	H	Br	NA		<0.0020	<0.0020	NA		<0.0020	<0.0020	<0.0020	<0.0020
Ie	H	I	NA		<0.0017	NA	NA		<0.0017	NA	<0.0017	NA
IIa	F	H[a]	0.010	NA	0.0078	NA	0.013	NA	0.0078	0.010	0.0057	0.0078
IIb	F	F	NA		NA		NA		0.019	0.019	0.019	0.024
IIc	F	Cl	NA		0.035	NA	NA		<0.0022	0.0044	<0.0022	<0.0022
IId	F	Br	NA		0.018	NA	NA		<0.018	NA	<0.0018	<0.0018
IIe	F	I	NA		0.031	NA	NA		<0.0016	0.078	<0.0016	<0.0016
IIIa	Cl	H[a]	NA		0.0072	NA	NA		0.0072	0.079	0.012	0.017
IIIb	Cl	F	NA		NA		NA		0.0065	0.087	NA	
IIIc	Cl	Cl[a]	NA		NA		NA		0.012	0.16	NA	
IIId	Cl	Br	NA		NA		NA		NA		NA	
IIIe	Cl	I	NA		NA		NA		NA		NA	
IVa	Br	H[a]	NA		NA		NA		NA		NA	
IVb	Br	F	NA		NA		NA		NA		NA	
IVc	Br	Cl	NA		NA		NA		NA		NA	
IVd	Br	Br[a]	NA		NA		NA		NA		NA	
IVe	Br	I	NA		NA		NA		NA		NA	
Va	I	H[a]	NA		NA		NA		NA		NA	
Vb	I	F	NA		NA		NA		NA		NA	
Vc	I	Cl	NA		NA		NA		NA		NA	
Vd	I	Br	NA		NA		NA		NA		NA	
Ve	I	I[a]	NA		NA		NA		NA		NA	

[a]Data taken from ref 1. [b]S = fungistatic; C = fungicidal. [c]NA = not active below 100 ppm. [d]< = inhibitory at 1 ppm, lowest level tested.

the past, and the analytical data characterizing compounds Ib, IIb–e, IIIb,d,e, IVb,c,e, and Vb–d are in Table I. Infrared spectra for all the Cu(II) bischelates have been obtained. (See paragraph at end of paper regarding supplementary material.)

All of the chelates were tested for antifungal activity according to published methods.[14] To Sabouraud dextrose broth (Difco) were added graded levels of test compound dissolved in dimethyl sulfoxide and inocula of each of *A. niger*, *A. oryzae*, *T. viride*, *M. verrucaria*, and *T. mentagrophytes*. After 6 days on a rotary shaker at 28°, records were made of all flasks that showed no apparent growth. These were diluted 1–100 in Sabouraud dextrose broth and incubated at 28° for 2 weeks to determine whether the inoculum was inhibited or killed. Thus, both fungistatic and fungicidal levels of test compound were established. The results are compiled in Table II, and Table III contains the lengths between the 5,5′ and 7,7′ axes and the

Table III. Lengths and Angles between the 5,5′ and 7,7′ Axes of the Bischelates of Copper(II) with 8-Quinolinols due to Substituents[a]

5,5′ axis		7,7′ axis		
Substituent	Length, Å	Substituent	Length, Å	Angle, deg
H	14.2	H	11.5	59
F	15.0	H	11.5	60
Cl	16.6	H	11.5	62
Br	17.4	H	11.5	63
I	18.0	H	11.5	64
H	14.2	F	12.2	62
F	15.0	F	12.2	63
Cl	16.6	F	12.2	65
Br	17.4	F	12.2	66
I	18.0	F	12.2	67
H	14.2	Cl	13.5	67
F	15.0	Cl	13.5	68
Cl	16.6	Cl	13.5	70
Br	17.4	Cl	13.5	71
I	18.0	Cl	13.5	72
H	14.2	Br	14.1	69
F	15.0	Br	14.1	70
Cl	16.6	Br	14.1	72
Br	17.4	Br	14.1	73
I	18.0	Br	14.1	74
H	14.2	I	14.7	70
F	15.0	I	14.7	71
Cl	16.6	I	14.7	73
Br	17.4	I	14.7	74
I	18.0	I	14.7	75
H	14.2	NO_2	14.9	70
F	15.0	NO_2	14.9	71
Cl	16.6	NO_2	14.9	73
Br	17.4	NO_2	14.9	74
I	18.0	NO_2	14.9	75

[a] Computations were based on ref 15 and 16.

angles formed between them, assuming square planarity of all the Cu(II) chelates. These calculations were based on the X-ray crystallographic studies on bis(8-quinolinolato)copper(II)[15] together with the van der Waals radii of the substituents.[16] It should be noted that the chelates containing 7-bromo and 7-iodo substituents are not square planar, as determined by stability constant measurements, and the 7-chloro derivatives might also be nonplanar.[17]

The data of Table II indicate that either the compounds are toxic at low concentrations or are inactive. Many of the chelates were tested at 1000 ppm, and good fungal growth was observed. It appears that this is an "all or none phenomenon" which is consistent with the concept that toxic reactions result upon penetration of the spore by the agent, and nontoxicity is due to exclusion of the potential toxicant.[1,4] It is also apparent from the data in Table II that none of the Cu(II) bischelates of 5-bromo- or 5-iodo-8-quinolinols or derivatives is fungitoxic and this is in agreement with similar observations based on bis(5-nitro-8-quinolinolato)copper(II).[3] It should be mentioned that fresh preparations of the Cu(II) bischelates of some of the 5-bromo- and 5-iodo-8-quinolinol derivatives were inhibitory to some of the fungi, but repeated boilups with dimethylformamide (DMF) yielded products which no longer inhibited the test organisms. These products possessed the expected elemental and ligand compositions. This is similar to an earlier observation made with the 5-nitro-8-quinolinol Cu(II) chelates.[3]

It can be noted from the data in Table II that for the *Aspergilli* when the 7 and 7′ positions are occupied by H the pores can accommodate compounds in which the 5 and 5′ positions are occupied by F, and when the 7 and 7′ positions contain F, the pores will allow passage only of the chelate containing H in the 5 and 5′ positions. With respect to *T. viride*, when the 7 and 7′ positions are occupied by H, the chelate in which the 5 and 5′ positions are filled by Cl can pass through the pores in the fungal spore wall, but when the 7 and 7′ positions contain F, chelates containing H in the 5 and 5′ positions are permitted passage. As for *T. mentagrophytes*, when the 7 and 7′ positions are occupied by H, the 5 and 5′ positions holding Cl can pass through the pores, and when the 7 and 7′ positions are filled with F, the 5 and 5′ positions containing F can pass into the fungal spore. An analysis of the comparable results for *M. verrucaria* does not lead to definite conclusions, due to the uncertainty as to whether the 7- and 7′-chloro derivatives are square planar. Thus, by shortening the long axis of the chelate, longer short axes can be accommodated by the pores in the spore wall. This can be visualized by considering the copper atom of the chelate as a pivotal point in the center of the pore, and as the long axis becomes shorter, the molecule can rotate about the point to accommodate longer short axes.

Table IV. Approximate Long and Short Dimensions of Holes in Fungal Spore Wall

Organism	Length, Å	Width, Å
A. niger	15.0	10.8
T. viride	16.6	10.7
A. oryzae	15.0	10.8
T. mentagrophytes	16.6	10.7

Based on the geometry of the molecules that are square planar, possess the largest dimensions, and are still fungitoxic, it is possible to calculate approximate dimensions that are perpendicular to the long dimensions of the pores in the four fungi: *A. niger*, *T. viride*, *A. oryzae*, and *T. mentagrophytes*. Knowing the lengths of two axes and the angle between them for each toxicant (Table III), they can be circumscribed by a symmetrical geometric figure. As a first approximation, an ellipse would be suitable. The major axis of the ellipse would be related to the long axis of the toxicant, whereas the shorter axis of the toxicant would be a diameter. The minor axis of the ellipse would be related to the shortest diameter of the pore in the spore wall, and it would also be perpendicular to the long axis of the pore. The semiminor axis of the ellipse can be calculated by rearranging the equation of the ellipse to $b = [a^2y^2/(a^2 - x^2)]^{1/2}$, in which b = semiminor axis of the ellipse, a = semimajor axis = $\frac{1}{2}$ of the length of the 5,5′ axis of the bischelate, x and y are the coordinates of the point on the circumference of the ellipse which intersects with the diameter $2r$, the 7,7′ axis of the chelate, $x = r \cos\theta$ and $y = r \sin\theta$, and θ = angle between 5,5′ and 7,7′ axes. By the appropriate substitutions for x and y in terms of the 7,7′ axis ($2r$) and the angle (θ) between the 5,5′ and 7,7′ axes the formula, $b = [a^2r^2 \sin^2\theta/(a^2 - r^2 \cos^2\theta)]^{1/2}$, can be obtained from which the shortest diameters ($2b$) of the pores in the fungal spore wall can be computed. Table IV contains the approximate long and perpendicular short dimensions of the pores in the spore walls of the four fungi.

Although the short diameters of the pores in the fungal spore walls were obtained by means of calculations with ellipses, it is not being implied that the pores are elliptical. It is anticipated that further study with the 3,3′ together with the 5,5′ axes might allow the assignment of shape to the pores of the fungal spore wall.

The significance of this study is that if sound data concerning the shape, dimensions, and electrical character of

the pore in the fungal spore wall were developed, such information could be used in the design of antifungal agents other than the 8-quinolinols and derivatives.

Experimental Section

Melting points were taken in a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were obtained with a Perkin-Elmer Model 221 spectrophotometer.

Preparation of Substituted Bis(8-quinolinolato)copper(II) Derivatives. To a solution of 0.02 mol of ligand in MeOH or MeOH–DMF mixture was added 0.01 mol of $Cu(OAc)_2 \cdot H_2O$ dissolved in MeOH, and the mixture was stirred for 1 hr. The product was removed by filtration, washed with H_2O followed by Me_2CO, and dried at 60° overnight. The materials were usually pure enough for analysis.

Acknowledgments. This work was supported in part by U. S. Public Health Service Grant No. AI-05808. Thanks are due to P. Pechukas, Columbia University, for helpful discussion; M. LaCorte, 1967 summer assistant at Boyce Thompson Institute, for assistance in calculating the data of Table III; A. T. Grefig for obtaining the infrared spectra; and P. K. Godfrey and J. Baricko for carrying out the antifungal testing.

Supplementary Material Available. Infrared spectra will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JMED-74-824.

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Antiviral Agents. Chemical Modifications of a Disulfide Antibiotic, Acetylaranotin†

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The reactivity of the cyclic disulfide linkage in acetylaranotin (1) was investigated. Novel insertion reactions with elemental sulfur and hydrogen cyanide gave tetrasulfide 8 and dithiocarbamate 16. Cleavages with methanethiol and dimethyl disulfide gave dithiol 5 and bis(methyl disulfide) 7. Because of lability of the disulfide linkage of acetylaranotin toward acids and bases, acetoxy groups were removed by an indirect method to give diol 26. When atmospheric oxygen was present in a basic medium a sulfur disproportionation reaction gave tetrasulfide diol 29. Diol 26 was oxidized to diketone 30 and acylated to give di- and monocarbethoxy derivatives 31 and 32. In mice, tetrasulfide 8 and trisulfide 10 gave protection equivalent to that of acetylaranotin against a lethal respiratory virus, Coxsackie A-21. Carbethoxy derivatives 31 and 32 were less active. Marginal activities of trithiocarbonate 18 and monosulfide 22 give the first indication that an S–S linkage may not be an absolute requirement for antiviral activity in this family of compounds. In an enzyme inhibition assay against an RNA polymerase system from Coxsackie A-21 virus, several compounds were more than 1000 times more inhibitory toward the viral polymerase than they were toward the RNA polymerase of the uninfected host cells. An improved color test for the detection of thiols is described.

Earlier reports from these laboratories and from workers at Eli Lilly and Co. have described the isolation,[1b,2a] characterization,[1b,2] and antiviral activities[3,4] of acetylaranotin (AAS_2, 1). The structural elucidation of 1 was completed by X-ray crystallography,[5] revealing the indicated absolute configuration. The same central epidithiopiperazinedione grouping also is found in gliotoxin (2), sporidesmin (3),[6a] oryzachlorin,[7] the chaetocins,[8a] verticillin,[8b] the melinocidins,[8c] and chetomin.[8d] Although these fungal metabolites are generally more toxic to mammals than acetylaranotin, gliotoxin has shown some prophylactic antiviral activity *in vivo*[9] as well as *in vitro*.[9-12]

The relatively few chemical modifications of gliotoxin (2) and sporidesmin (3) have led predominantly to sulfur-free or nonbridged structures which lacked significant biological activity.[6a] This report describes an investigation of the reactivity of the disulfide linkage of AAS_2, aimed primarily at the preparation of sulfur-retaining and ring-bridged derivatives. As a working hypothesis, such derivatives were considered to be of special interest when they retained a potentiality for reaction with enzymatic thiol groups, *i.e.*, Enz-SH + RSSR′ → Enz-SSR.‡ As a practical matter, the range of synthetic procedures applicable to AAS_2 derivatives was found to be fairly limited due to the

†For a preliminary communication of this work, see ref 1a.

‡Susequent biochemical evidence inicates that acetylaranotin does indeed inhibit a viral RNA polymerase by reacting with enzymatic sulfhydryl groups.[6b]