ACTIDIONE, AN ANTIBIOTIC FROM STREPTOMYCES GRISEUS

Sir:

It has been found in this Laboratory that streptomycin-producing strains of *Streptomyces griseus* produce a second antibiotic which has little or no activity against bacteria but is very effective against many yeasts. The crude product was isolated from streptomycin beers by adsorbing on carbon, eluting with 80% acetone, distilling the acetone and extracting the remaining aqueous solution with chloroform. The chloroform extract was decolorized with carbon and evaporated. After purification of this crude product by counter-current distribution between benzene and water,[1] it was obtained in crystalline form. Several recrystallizations from amyl acetate yielded colorless plates, m.p. 115–116.5°, $[\alpha]^{25}D$ $-2.8°$ (*c* 9.6, methanol). Analytical data are in good agreement with the formula $C_{27}H_{42}N_2O_7$ (mol. wt. 507). The molecular weight (cryoscopic in benzene) varied from 420 to 875, depending upon the concentration.

TABLE I

	M. p., °C.	$\alpha^{25}D$ Deg.	c^a	Formula	Percentage composition C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
Actidione	115–116.5	−2.8	9.6	$C_{27}H_{42}N_2O_7$	64.01	63.74	8.36	8.35	5.53	5.44
Diacetate	143–145	+24.6	3.7	$C_{31}H_{46}N_2O_9$	63.03	62.98	7.85	7.89	4.74	4.70
Dioxime	203–204	....	...	$C_{27}H_{44}N_4O_7$	60.42	60.66	8.27	8.29	10.44	9.85
Disemicarbazone	176–178	....	...	$C_{29}H_{48}N_8O_7$	56.12	55.53	7.79	7.70	18.05	17.71

[a] In methanol.

Treatment of the compound with acetic anhydride and sodium acetate at room temperature produced a biologically inactive diacetate, m.p. 143–145°, $[\alpha]^{25}D$ $+24.6°$ (*c* 3.7, methanol). The dioxime melted at 203–204° and the disemicarbazone at 176–178°. We suggest that this compound be named *actidione* since it appears to be a diketone and is produced by an actinomycete.

Actidione is rapidly inactivated by dilute alkali at room temperature with the formation of a fragrant, dextrorotatory, volatile ketone; semicarbazone, m.p. 190–193°. Refluxing with dilute sulfuric acid does not produce the volatile ketone, but when the hydrolysate is made strongly alkaline a low molecular weight amine is evolved. Further degradation studies are now in progress.

An antibiotic spectrum of crystalline actidione was found to be very similar to that previously reported for crude preparations.[2] When tested against twelve representative bacteria it failed to inhibit at concentrations up to 1 mg. per ml. Crystalline actidione inhibits the fungal pathogen, *Cryptococcus neoformans*, in concentrations as low as 0.0002 mg. per ml. This high order of activity suggests its possible usefulness in the treatment of cryptococcosis, a rare but usually fatal disease. Toxicity tests, intravenously in mice, indicate an LD_{50} of approximately 150 mg. per kg.

Actidione has been assayed satisfactorily in concentrations as low as 0.001 mg. per ml. by an adaptation of the paper-disk plate method for streptomycin[3] using *Saccharomyces pastorianus* ATCC 2366 as the test organism.

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(1) Craig, Golumbic, Mighton and Titus, *J. Biol. Chem.*, **161**, 321 (1945).

(2) Whiffen, Bohonos and Emerson, *J. Bact.*, **52**, 610 (1946).

(3) Loo, Skell, Thornberry, Ehrlich, McGuire, Savage and Sylvester, *ibid.*, **50**, 701 (1945).

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THE POSSIBILITY OF FREE ROTATION IN THE SILICONES

Sir:

The low boiling points and small temperature coefficients of viscosity of the silicones have led to the view that siloxane bonds result in low cohesive forces.[1a,b] We have been determining the crystal structure of octamethylspiro[5.5]pentasiloxane[2] to see whether structural considerations would shed some light on this anomalous behavior.

Oxygen would be expected to form covalent *p* bonds at 90°. The Si–O–Si bond angle should be increased somewhat by repulsion resulting from the ionic character of the SiO bond. However, Sauer and Mead[3] calculate from the dipole moment of hexamethyldisiloxane an angle of 160 ± 15° and Frevel and Hunter[4] report a planar ring for the cyclic trimer $[(CH_3)_2SiO]_3$.

The spirosiloxane compound crystallizes with the space group $D_{4h}^{19}(I\frac{4}{a}md)$. There are four molecules in the unit cell, each molecule consisting of two planar six-membered rings linked at 90° through a common Si atom. The SiO distance is about 1.64 Å., comparable to distances found in the inorganic silicates and considerably less than the value 1.83 Å. obtained from the covalent radius sum for Si and O. The Si–C distance is 1.90 Å., the expected covalent sum.

Despite reasonable agreement between calculated and observed F^2 values for reflections with low *hkl* indices, it proved impossible to refine parameters by conventional Fourier methods. Electron density projections and sections indi-

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(1) (a) Hunter, Warrick, Hyde and Currie, THIS JOURNAL, **68**, 2284 (1946); (b) D. F. Wilcock, *ibid.*, **68**, 691 (1946).

(2) D. W. Scott, *ibid.*, **68**, 356 (1946).

(3) Sauer and Mead, *ibid.*, **68**, 1794 (1946).

(4) Frevel and Hunter, *ibid.*, **67**, 2275 (1945).