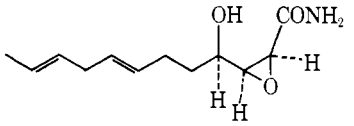
It is of interest to note that cerulenin (**1**), somewhat surprisingly, seems to exist both in the crystal and in solution primarily, if not exclusively, in the open form (two carbonyl absorbtions in the infrared), whereas related substances derived from the photooxygenation of pyrrole appear to prefer the closed aminol structure **12**.[17] This is presumably due to the greater stability of hemiacetals relative to hemiketals.



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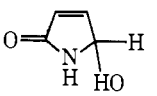

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(18) Fellow of the Alfred P. Sloan Foundation (1976–1978).

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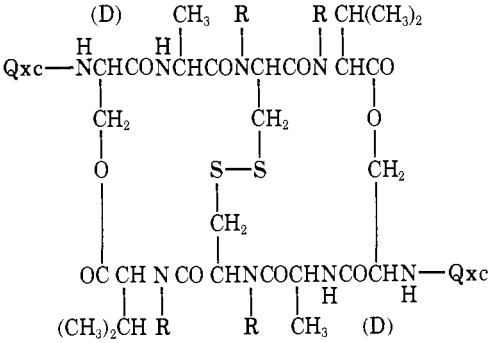
Synthesis of Des-*N*-tetramethyltriostin A, a Bicyclic Octadepsipeptide Related to the Quinoxaline Antibiotics

Sir:

The quinoxaline antibiotics are a group of bicyclic octadepsipeptides.[1] These antibiotics show activity against gram-positive bacteria[2] and certain animal tumors,[1c,3] and are potent inhibitors of RNA synthesis.[4] Their mechanism of action apparently occurs by binding to DNA in which they function as bifunctional intercalating agents.[5] Few reports[6,7] have appeared relating to synthetic studies on these substances. We report herein the first total synthesis of a close analogue of the quinoxaline antibiotics, namely, des-*N*-tetramethyltriostin A (**1**).

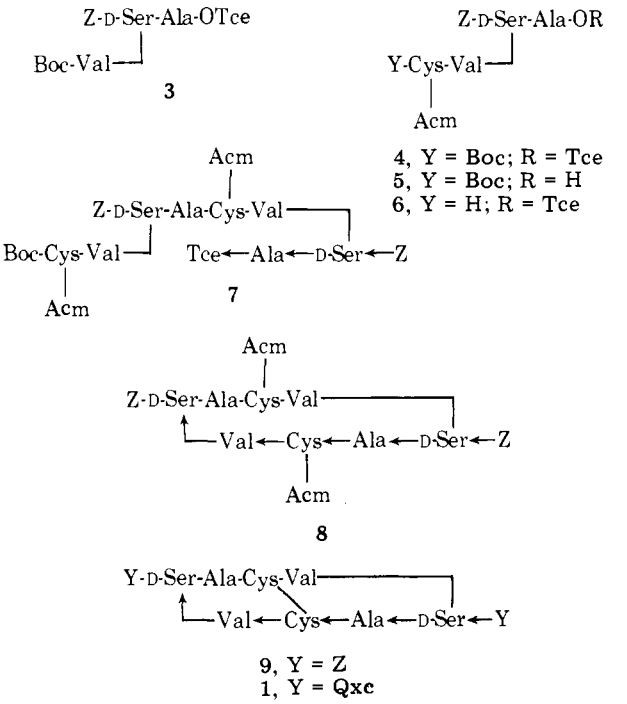
The title compound differs from the natural antibiotic, triostin A (**2**),[1d,e] by lack of *N*-methyl groups on the L-cysteine and L-valine residues. The synthesis of **1** proceeded as follows.[8] Coupling of *Z*-D-Ser-OH with the trichloroethyl ester[9] of L-alanine by use of *N,N'*-dicyclohexylcarbodiimide (DCC) in methylene chloride gave (71%) *Z*-D-Ser-Ala-OTce, which was converted in 76% yield to tridepsipeptide **3** by ester bond formation using DCC in pyridine.[6] Deprotection of **3** with trifluoroacetic acid (TFA), followed by neutralization and coupling to Boc-Cys(Acm)OH[10] using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide[11]:hydroxybenztriazole[12] gave tetradepsipeptide **4** in 69% yield.



1, R = H
2, R = Me

Qxc = quinoxaline-2-carbonyl

Removal of the Tce ester function in **4** by use[9] of zinc in acetic acid yielded (87%) **5**, while removal of the Boc group in **4** gave (88%) **6**. Fragment coupling of **5** and **6** was effected by either the mixed anhydride[13] (from isobutyl chloroformate) (78%) or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide[11]: hydroxybenztriazole[12] (93%) methods to furnish the linear octadepsipeptide **7**. A sequence of deprotection (Zn in AcOH, then TFA), neutralization, and cyclization (*N*-hydroxysuccinimide:DCC,[14] high dilution of compound **7** at concentration of 2.6×10^{-3} M in THF:DMF (190:15), 4 days at room temperature) provided, following chromatography on a silica gel column and recrystallization, the cyclic depsipeptide **8** in 43% yield from **7**. Treatment of **8** with iodine in methanol[15] effected conversion (89%) to the disulfide **9**, which upon acidolysis of the benzyloxycarbonyl group (HBr in acetic acid)



4, Y = Boc; R = Tce
5, Y = Boc; R = H
6, Y = H; R = Tce

7

8

9, Y = Z
1, Y = Qxc

and acylation[7] with 2-quinoxoyl chloride gave, following chromatography (silica gel) and recrystallization, des-*N*-tetramethyltriostin A (**1**) in a yield of 57%: mp 226–229 °C; TLC R_f ($CHCl_3$:MeOH:AcOH, 85:10:5) 0.60, R_f ($CHCl_3$:ethanol, 80:20) 0.69; amino acid analysis, Ala 1.08, Cys 0.87, Ser 1.06, Val 1.00; $[\alpha]^{25}_D$ −43° (*c* 1.5, $CHCl_3$); $\lambda_{max}^{CH_3CN}$ 315 nm (ϵ 1.13 × 10^4), 325 (ϵ 1.11 × 10^4); NMR ($CDCl_3$) δ 1.1 (q, 12 H, valyl methyl), 1.3 (d, 6 H, alanyl methyls), 2.5 (m, 2 H, valyl methines), 2.8 (d, 4 H, cystinyl methylenes), 4.4–5.1 (m, 10 H, seryl methylenes, 6 α-hydrogens), 5.6 (m, 2 H, α-hydrogens), 6.4 (d, 2 H, NH), 7.3 (d, 2 H, NH), 7.7–8.3 (m, 8 H, quinoxaline H_5–H_8), 8.5 (d, 2 H, NH), 8.7 (d, 2 H, NH), 9.6 (s, 2 H, quinoxaline H_3); M^+ 1031 (field desorption). The electron impact spectrum of **1** had peaks in the low mass region at *m/e* 102, 129, 157, 226, 297, 366, and 482; a similar fragmentation pattern was observed in the reported[1b] spectrum for the quinoxaline antibiotic echinomycin. Analysis[16] of **1** indicated 2% racemization of the alanine residues, which racemization likely occurred upon activation of the alanine carboxyl in the fragment coupling and cyclization procedures.

Des-*N*-tetramethyltriostin A (**1**) has been shown[17] to bind as a bifunctional intercalating agent to DNA. In contrast to triostin A (**2**), analogue **1** showed[17] no activity toward *Staphalococcus aureus*.

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The He I Photoelectron Spectrum of 3,7-Dimethyl-*p*-quinodimethane. A Non-Koopmans Theorem Effect

Sir:

Interpretations of observed bands of photoelectron spectra are most frequently cast in terms of Koopmans' approximation.[1] This has come to be the case in spite of the unrealistic restriction which this method places on the wave functions for the ionic states and the dependency of the whole procedure on the fortuitous cancellation of the errors due to correlation and electronic reorganization.[2] The adoption of such a scheme implies all pertinent information for highly excited ionic states is given through the orbital approximation as it is applied to the neutral ground state molecule, which seems a somewhat drastic assumption.[3]

We have previously reported[4] our observation of the PE spectrum of *p*-quinodimethane (**1**) by flash vacuum pyrolysis of 2,2-paracyclophane.[5] The most interesting feature of this study was the apparently low energetic position and intensity of the third band. We rationalized this observation as being a manifestation of the interaction between ionic structures (b_{2g}^0, b_{2g}^1) derived from the quinoid **1** and diradical **1a** contributors to the ground state. The purpose of this paper is to discuss the spectrum of the 3,7-dimethyl derivative **2** which confirms the previous assignment and appears to establish a strong effect outside of those encompassed through the Koopmans' approximation procedure.

The 3,7-dimethyl derivative[6] **2** was chosen for these studies because of the predictions of the simple structure representation[7] (SR) procedure of the effects of the added methyl groups. In this (SR) procedure, the shifts due to methyl or methylene substitution are attributed *entirely* to hyperconjugation. The parameters associated with the interaction in the ionic states were determined from studies of other alkylated olefins.[8] The calculated shifts (Table I) of the first, second, and fourth (zero order) II ionic states are significant while the third is predicted to be unaffected by 3,7-dimethyl substitution. Huckel wave functions and the INDO[9] Koopmans approximation methods (Table I) give similar results. All three criteria indicate that 3,7-dimethyl substitution would uncover a (weak) band near 9.8 eV if our original rationalization were correct. The SR