reaction may be utilized in introducing an ether functionality under mild and neutral conditions. As an example, the simple esters (Me, Et, *i*-Pr, and *t*-Bu) were photolyzed in the corresponding alcohols to give ether esters of general structure $ROCH_2CO_2R$ in 65–80% yields. Further studies are in progress.

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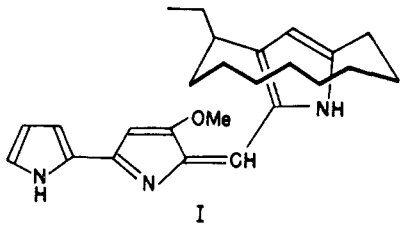
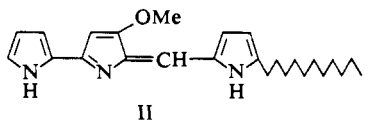
Metacycloprodigiosin, a Tripyrrole Pigment from *Streptomyces longisporus ruber*

Sir:

We have recently reported the structure and synthesis of undecylprodigiosin (II), a C-25 prodigiosin analog isolated from a strain of *Streptomyces*.[1] At that time it was noted that another more complex C-25 prodigiosin-like pigment was formed concurrently with II. In this communication we describe the isolation and structure determination of this product. Formulated as I,[2] this new tripyrrole pigment incorporates the unusual structural feature of a *meta*-bridged pyrrole, the first such system to be observed in a natural product. We propose the trivial name metacycloprodigiosin for this new pigment (I),[3] the synthesis of which is described in the accompanying report.[4]



I



II

Streptomyces longisporus ruber, strain M-3,[5] was grown on a soymeal–mannitol medium in shake culture for 1–3 weeks. Methylene chloride extraction of the lyophilized cells followed by acid and base washing and removal of the solvent *in vacuo* yielded a dark amorphous solid. Chromatography of the solid on basic alumina yielded two fractions, the first containing the new C-25 base (I), and the second containing a mixture of I and undecylprodigiosin (II). The new pigment was obtained as orange-brown crystals from petroleum ether, mp 208–209°, $[\alpha]^{20}_D$ −2370°; hydrochloride, mp 214–216°. *Anal.* Calcd for $C_{25}H_{33}N_3O \cdot HCl$: C, 70.12; H, 8.02; N, 9.81; Cl, 8.28. Found: C, 69.89; H, 8.10; N, 9.53; Cl, 8.08. The high-resolution mass spectrum of the hydrochloride has a molecular ion peak at *m/e* 391.2625 corresponding to the free base, $C_{25}H_{33}N_3O$ (*m/e* 391.2610).

The spectroscopic properties of the pigment and its hydrochloride clearly show it to be a member of the prodigiosin series.[6,7] In particular, the absorption spectrum of the free base exhibits a peak at $\lambda_{max}^{MeOH\ (0.5\%\ KOH)}$ 467 mμ (ε 30,600), while the hydrochloride has a peak at λ_{max}^{MeOH} 530 mμ (ε 75,900) as well as a shoulder at 500 mμ (ε 31,500). In the infrared, the free base of the new pigment shows bands at 1620, 1602, 1548, 1063, and 968 cm^{-1}. Likewise, the hydrochloride has characteristic bands at 1629, 1601, 1570, 1542, 1528, and 961 cm^{-1}.

The nmr spectrum of metacycloprodigiosin exhibits peaks due to N–H, and aromatic and methoxyl protons nearly identical with the corresponding absorptions shown by other prodigiosins,[6,7] and, in addition, the free base has a broad multiplet at τ 7.13–8.06 (3 H) and a multiplet at τ 8.13–9.42 (19 H). More specifically, the peak (1 H) at τ 4.08 is in accord with the presence of a β proton in the dialkylpyrrole residue.[6,7]

Pyrolysis of the pigment over soda lime gave a C-15 pyrrole containing four elements of unsaturation. *Anal.* Calcd for $C_{15}H_{25}N$: C, 82.13; H, 11.49; N, 6.38; mol wt, 219.1980. Found: C, 81.82; H, 11.80; N, 6.58; mol wt (high-resolution mass spectrum), 219.1985. The nmr spectrum clearly shows that the pyrrole is disubstituted, with one free α and one free β position: τ 2.69 (1 H), 3.71 (1 H multiplet, α-ring H), 4.18 (1 H multiplet, β-ring H), 7.5 (2 H triplet, J = 6 Hz), 7.8 (1 H multiplet), 8.3–9.2 (19 H, unresolved methyl–methylene region). Vapor phase reduction of the pyrrole (platinum-on-glass column)[8] yielded a hydrocarbon, $C_{15}H_{30}$, which was identified by mass spectrometry, nmr, and independent synthesis[9,10] as 1-ethyl-2-methylcyclododecane (III).

Of the $C_{15}H_{25}N$ pyrroles which may lead to III on reduction, only structures IV and V would exhibit nmr spectra consistent with that observed. To distinguish between these possibilities, the 2-formyl derivative was prepared[11] for nmr examination. *Anal.* Calcd for

(1) H. H. Wasserman, G. C. Rodgers, and D. D. Keith, *Chem. Commun.*, 825 (1966); see also K. Harashima, N. Tsuchida, T. Tanaka, and J. Nagatsu, *Agr. Biol. Chem.*, **31**, 481 (1967); K. Harashima, N. Tsuchida, and J. Nagatsu, *ibid.*, **30**, 309 (1966).

(2) Structure I is not stereochemically definitive, as the absolute configuration of the pigment has not been determined.

(3) There have been numerous reports of C-25 analogs of prodigiosin of undetermined structure; these substances, some of which show considerable antibiotic activity, most probably correspond to I or II, or mixtures of the two pigments. (a) E. Dietzel, *Naturwissenschaften*, **35**, 345 (1948); (b) E. Dietzel, *Z. Physiol. Chem.*, **284**, 262 (1949); (c) F. Arcamone, A. DiMarco, M. Chione, and T. Scotti, *Giorn. Microbiol.*, **4**, 77 (1957); (d) R. A. Nicolaus, R. Nicoletti, and F. Arcamone, *Ric. Sci.*, **28**, 2314 (1958); (e) J. J. Perry, *Nature*, **191**, 77 (1961); (f) Yu. M. Khokhlova, A. V. Puchnina, and O. I. Artamonova, *Biokhimya*, **29**, 841 (1964); (g) Y. Chi-sheng, *Mikrobiologiya*, **31**, 254 (1962); (h) N. A. Krasil'nikov and G. I. El'-Registan, *ibid.*, **35**, 581 (1966); (i) M. N. Bekhtereva, Yu. M. Khokhlova, N. V. Tarasova, V. E. Khizhanovskaya, and G. A. Kasymova, *ibid.*, **35**, 586 (1966); (j) E. P. Feofilova and E. I. Filippovich, *ibid.*, **36**, 396 (1967), and references contained therein; (k) N. F. Kirillova, *ibid.*, **36**, 274 (1967).

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(5) We thank Dr. K. Haider, Institut fur Biochemie des Bodens, Braunschweig, Germany, for providing us with strains of *Streptomyces longisporus ruber*.

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(7) D. J. Friedland, Ph.D. Thesis, Yale University, 1968.

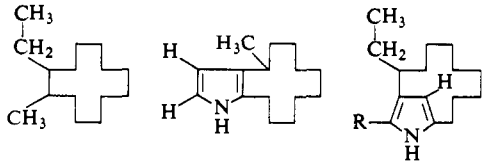
(8) C. J. Thompson, H. J. Coleman, C. C. Ward, and H. T. Rall, *Anal. Chem.*, **34**, 151 (1962). Reduction of model pyrroles by this method indicated no rearrangement of alkyl substituents.

(9) Synthesized by Dr. Jeffrey Nadelson from 2-methylcyclododecanone.

(10) Satisfactory analytical and spectral data were obtained for all new compounds.

(11) R. M. Silverstein, E. E. Ryskiewicx, C. Willard, and R. C. Koehler, *J. Org. Chem.*, **20**, 668 (1955).

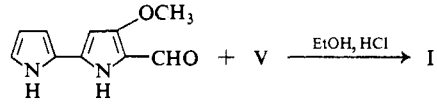
$C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66. Found: C, 77.48; H, 9.97; N, 5.64. The nmr spectrum of the formyl derivative shows the presence of a single β-ring hydrogen, the chemical shift of which (τ 4.00) is not significantly altered from that observed for the β proton in the parent pyrrole (τ 4.18).



III IV V, R=H VI, R=CHO

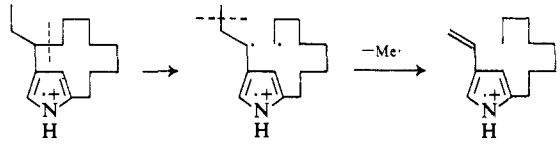
Studies of model systems[6] show that a formyl group at the 2 position of a pyrrole ring has a pronounced deshielding effect on the adjacent hydrogen at the 3 position, causing a downfield shift of about 0.8 ppm. On the other hand, the corresponding effect of a 2-formyl group on a β hydrogen at the 4 position is very slight (0.1–0.2 ppm). The formyl derivative, therefore, clearly has structure VI, and the C-15 dialkylpyrrole must accordingly have structure V.[12]

As a member of the prodigiosin series, metacycloprodigiosin would be expected to incorporate residues corresponding to pyrrole (V) and the methoxybipyrrole aldehyde (VII) as shown in structure I.[14-16] The validity of this assignment was established when the parent pigment was reconstituted by the HCl-catalyzed condensation of the alkylpyrrole V, with the C-10 prodigiosin precursor (VII) obtained from a mutant strain of *Serratia*.[17] This reaction yielded metacycloprodigiosin hydrochloride iden-

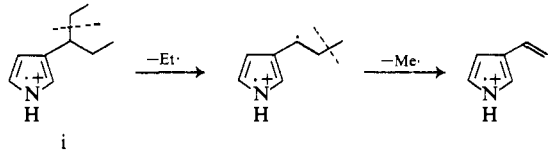


VII

(12) The mass spectrum of V exhibits peaks at *m/e* 204 (loss of methyl) and 190 (loss of ethyl). Although the $M^+ - 15$ peak seems on first consideration to be exceptional, it is readily explained in terms of the sequence



As would be expected from the above, we have observed that the mass spectrum of 3-(3-pentyl)pyrrole (i)[13] exhibits peaks at *m/e* 137, 108, and 93.



i

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(14) H. H. Wasserman, J. E. McKeon, L. A. Smith, and P. Forgione, *J. Am. Chem. Soc.*, **82**, 506 (1960).
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(16) H. Rapoport and K. G. Holden, *J. Am. Chem. Soc.*, **84**, 635 (1962).
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tical (nmr and infrared absorption spectra, mass spectrum) with the natural material.

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(18) National Science Foundation Cooperative Graduate Fellow, 1962–1963; National Science Foundation Predoctoral Fellow, 1963–1965.
(19) National Institutes of Health Predoctoral Fellow, 1966–1968.

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The Synthesis of Metacycloprodigiosin

Sir:

In the accompanying communication[1] we have reported the isolation and structure determination of metacycloprodigiosin (**1**), a tripyrrole pigment from *Streptomyces*. We now describe the synthesis of the racemic form of this pigment which confirms the structural assignment.

Cyclododecanone (**2**) was converted by sodamide in glyme followed by ethyl bromide to the 2-ethyl derivative **3** (45%): bp 80° (0.1 mm); $\nu_{max}^{liquid\ film}$ 1706 cm^{-1}; τ_{CCl_4} 7.38–7.83 (m, 3 H), 9.18 (t, 3 H).[2] Treatment of **3** with ethylene glycol–*p*-toluenesulfonic acid monohydrate in benzene afforded the ketal **4**[3] (70%): bp 114° (0.5 mm); τ_{CCl_4} 6.20 (s, 4 H, OCH_2CH_2O). Treatment of **4** with pyridine hydrobromide perbromide[4] in dry THF yielded 2-bromo-12-ethylcyclododecanone ethylene ketal **5**[3] (~100): mp 59.5–60.5°. The location of bromine at the less substituted position[5] was shown by the nmr spectrum exhibiting five protons (two multiplets) in the region τ 5.6–5.9, associated with the groups $-OCH_2CH_2O-$ and $-CHBr-$. Dehydrobromination of **5** with 1,5-diazabicylo[4.3.0]non-5-ene[6] at 110° for 72 hr furnished the α,β-unsaturated ethylene ketal **6**[3] (90%): bp 84–85° (0.03 mm); $\nu_{max}^{CCl_4}$ 1667, 992 cm^{-1}; τ_{CCl_4} 4.5 (m, 1 H), 4.80 (d, 1 H), 6.37 (s, 4 H). Acid hydrolysis of **6** gave 12-ethyl-2-cyclododecenone (**7**)[3] (95%): bp 98–101° (0.2 mm); semicarbazone mp 157–159°; λ_{max}^{EtOH} 230 mμ (ν 10,200); $\nu_{max}^{CCl_4}$ 1692, 1666, 1625, 990 cm^{-1}; τ_{CCl_4} 3.31 (m, 1 H), 3.72 (d, 1 H), 7.7 (m, 3 H).

When **7** was treated with H_2O_2 and NaOH in MeOH at 5°[7] the α,β-epoxy ketone **8**[3] was obtained (94%); bp 115–117° (0.1 mm); $\nu_{max}^{CCl_4}$ 1717 cm^{-1}; τ_{CCl_4} 6.73 (d, 1 H, J = 2 Hz), 7.2 (m, 2 H). Gas chromatographic analysis (SE 30 column, 200°) indicated that the product was a mixture of two diastereomers. It was possible to obtain one isomer as a crystalline solid[3] from MeOH, mp 67.5–

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(2) L. I. Zakharin, and V. V. Korneva, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2102 (1964).
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