concentration of 19-hydroxy and 19-oxo compounds was obtained whether I or II was the substrate for the organism. The results indicate that the reaction is indeed a reversible one, similar to that of the interconversion of steroidal ketones and alcohols.[3,6]

Experimental[7]

Transformation of Anhydrostrophanthidone (I) into 19-Dihydroanhydrostrophanthidone (II) by *Penicillium thomii*.—The fermentation medium consisted of corn steep liquor, 0.6%; $NH_4H_2PO_4$, 0.3%; calcium carbonate, 0.25%; corn oil, 0.22%; yeast extract, 0.25%; and glucose, 1.0%. *P. thomii* was grown in 4.8 l. of this medium (twelve 2-l. erlenmeyer flasks); after 24 hr. of incubation at 27° on a rotary shaker, 1.0 g. of anhydrostrophanthidone in 12 ml. of dimethylformamide was distributed equally among the flasks. The fermentation was allowed to continue for 96 hr.; the culture broth then was filtered and the filtrate extracted with chloroform. The chloroform extract was dried with sodium sulfate and evaporated to dryness to yield 0.96 g. of residue. An aliquot of the chloroform extract was chromatographed on Whatman no. 1 paper and developed in a benzene–chloroform–propylene glycol system[8] for 6 hr. The paper chromatogram showed only two spots, one of which corresponded to anhydrostrophanthidone, when viewed under the ultraviolet scanner. The other compound showed an R_f of 0.10; anhydrostrophanthidone has an R_f of 0.70 in this system. Direct crystallization from acetone yielded 552 mg. of crystals, m.p. 247–251°, λ_{max}^{MeOH} 219 mμ (ε 22,000); λ_{max}^{chf} 2.92, 5.60, 6.06, and 6.20 μ.

Anal. Calcd. for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.54; H, 7.83.

The melting point was not depressed upon admixture of a sample of 19-dihydroanhydrostrophanthidone (II) prepared by catalytic oxidation (described below) and the paper chromatographic behavior and solution infrared and ultraviolet spectra were identical with those of the synthetic sample.

Catalytic Oxidation of Strophanthidol (III) to 19-Dihydroanhydrostrophanthidone (II).—A solution of strophanthidol[9] (700 mg.) in acetone (100 ml.) and water (100 ml.) was treated with platinum black (from 400 mg. of platinum oxide) under oxygen. After 24 hr. the consumption of oxygen had ceased, and the reaction mixture was treated as usual to yield 720 mg.of residue. The residue in acetic acid (35 ml.) was heated under reflux for 15 min. under nitrogen. Evaporation to dryness gave a residue which was dissolved in chloroform and chromatographed on Woelm neutral alumina (20 g.). Elution with chloroform–methanol (98:2) gave a crude crystalline product (250 mg.). Two recrystallizations from acetone–ether yielded II (75 mg.), m.p. 247–251°, $[\alpha]^{25}D$ +91° (*c* 1.46, methanol).

Anal. Calcd. for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.36; H, 7.71.

19-Dihydroanhydrostrophanthidone Acetate (IV).—A solution of III (108 mg.) in acetic anhydride (1.5 ml.) and pyridine (1.5 ml.) was allowed to stand at room temperature for 17 hr. The excess acetic anhydride was decomposed by cautious addition of methanol (2 ml.) and the solution was evaporated to dryness under reduced pressure. Crystallization from ethyl acetate yielded 87 mg. of crude crystalline product. Recrystallization from ethyl acetate–ether afforded colorless needles (41 mg.), m.p. 186–187°, $[\alpha]D$ +101° (*c* 1.28, methanol).

Anal. Calcd. for $C_{25}H_{32}O_6$: C, 70.07; H, 7.53. Found: C, 69.77; H, 7.51.

(7) Melting points are corrected for stem exposure. Values of $[\alpha]D$ have been approximated to the nearest degree. Ultraviolet absorption spectra were determined in methanol on a Cary recording spectrophotometer (Model 11 MS). Infrared spectra were recorded on a Beckman IR5-A double beam infrared recording spectrophotometer. Microanalyses by Dr. S. M. Nagy, Cambridge, Mass., and Mr. J. Alicino, Metuchen, N. J. Whatman no. 1 paper was washed twice with 95% ethanol prior to use for paper chromatography. For quantitative determinations the spots were eluted with 95% ethanol and the absorbancy at 240 mμ was used in measuring concentrations. The culture, *Penicillium thomii*, was kindly supplied by Professor K. B. Raper, Department of Bacteriology, University of Wisconsin.

(8) H. R. Urscheler, Ch. Tamm, and T. Reichstein, *Helv. Chim. Acta*, **38**, 897 (1955).

(9) A Hunger and T. Reichstein, *Ber.*, **85**, 635 (1952).

The Structure Proof of 16α-Carboxypregnenolone

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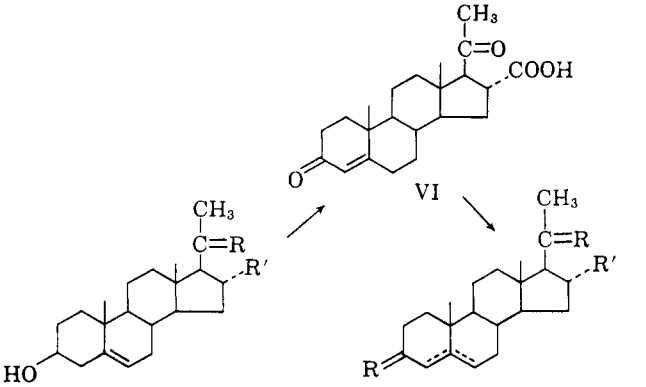
Received October 19, 1962

The recent publication of Heller, Stolar, and Bernstein[1] on the synthesis of 16α-hydroxymethylprogesterone prompts us to report some of our efforts in this area.

In the present work, we have converted 16α-carboxypregnenolone to the known 16α-methylprogesterone. Thus this sequence of reactions, for the first time, unequivocally establishes the configuration about carbons 16 and 17 in both the 16α-hydroxymethylprogesterone series of Heller, *et al.*,[1] and the 3β,20β-diacetoxypregn-5-ene-16α-carboxylic acid of Mazur and Cella.[2] This work also adds support to the evidence[2] that Romo[3] was working with 17α steroids substituted in the 16β position.

The synthesis of the acid IV and its conversion to 16α-methylprogesterone was accomplished in the following manner. The 20-cycloethylene ketal (II) of 16α-cyanopregnenolone was formed in the normal fashion. That no inversion had occurred at this step was confirmed by mild acid hydrolysis of the ketal to yield the starting cyano ketone I. When the ketal II was refluxed for 48 hours with ethanolic potassium hydroxide, there was obtained, in excellent yield after acid hydrolysis, the amide of 16α-carboxypregnenolone (III). When the hydrolysis of II was carried out in an



I. R = O, R′ = CN
II. R = 20-cycloethylene ketal, R′ = CN
III. R = O, R′ = $CONH_2$
IV. R = O, R′ = COOH
V. R = 20-cycloethylene ketal, R′ = COOH
VI. R = O, R′ = CH_2OH, Δ^5
VII. R = 20-cycloethylene ketal, R′ = $C(=O)-O-CH_2CH_2OH$, Δ^5
VIII. R = 20-cycloethylene ketal, R′ = CH_2OH, Δ^5
IX. R = O, R′ = CH_2OH, Δ^4
X. R = 20-cycloethylene ketal, R′ = CH_2—O—tosyl, Δ^5
XI. R = 20-cycloethylene ketal, R′ = CH_2I, Δ^5
XII. R = O, R′ = CH_3, Δ^4

(1) M. Heller, S. Stolar, and S. Bernstein, *J. Org. Chem.*, **27**, 2673 (1962).
(2) R. Mazur and J. Cella, *Tetrahedron*, **7**, 130 (1959).
(3) J. Romo, *ibid.*, **3**, 37 (1958).

autoclave at 100–110° for 90 hours, the ketal nitrile was hydrolyzed smoothly to the ketal acid V. The keto acid IV was obtained by acid hydrolysis of this ketal and when purified melted at 231.5–232°; $[\alpha]_D$, +3.0° (dioxane); reported[1] 235–238°; $[\alpha]_D$ +14° (chloroform). A mixed melting point with the acid obtained by the method of Romo[3] [m.p. 230–232.5°; $[\alpha]_D$ −115° (chloroform)] melted at 220–226°. These two isomeric acids possessed similar but different infrared spectra and different R_f values on thin layer plates; the acid IV had the lower R_f value. The crude acid IV, when analyzed *via* thin-layer chromatography, proved to be free of the 16β,17α isomeric acid, but did show a small amount of another acid presumably the *cis*, 16β, 17β acid.

The acid IV was converted to 16α-carboxyprogesterone (VI) by the method of Julian, Cole, Magnani, and Meyer.[4] Ketalization of 16α-carboxyprogesterone with ethylene glycol in the usual fashion gave β-hydroxyethyl pregn-5-ene-16α-carboxylate-3,20-dionebiscycloethylene ketal (VII). Lithium aluminum hydride reduction of the glycol ester yielded 16α-hydroxymethyl-pregn-5-ene-3,20-dione biscycloethylene ketal (VIII). Dilute acid hydrolysis of this bisketal resulted in conversion to 16α-hydroxymethylprogesterone (IX).

Attempts to prepare the tosyl derivative X of 16α-hydroxymethyl-pregn-5-ene-3,20-dionebiscycloethyleneketal (VIII) by the action of *p*-toluenesulfonyl chloride and pyridine gave only unchanged starting material. When triethylenediamine was substituted as the base and benzene as the solvent, the tosyl derivative X was obtained in excellent yield. If this tosyl derivative was treated with lithium aluminum hydride in ether, the reduction was incomplete. The tosyl derivative was converted to the iodo derivative XI by the action of sodium iodide in refluxing methyl ethyl ketone. The iodo derivative was reduced with lithium aluminum hydride in ether, and after acid hydrolysis of the bisketal, the product proved to be identical to 16α-methylprogesterone (XII) by comparisons with the melting point, mixed melting point, infrared spectra, and gas chromatographic analysis of an authentic sample.

Experimental[5]

16α-Carboxy-3β-hydroxy-5-pregnen-20-one (IV).—A mixture of 37.82 g. (0.098 mole) of ketal nitrile (II), 1.4 l. 95% ethanol, 185 g. potassium hydroxide and 185 ml. water was heated in an autoclave for 90 hr. at 100–110°. The brownish ethanolic solution was concentrated to 750 ml. *in vacuo* and diluted to 1500 ml. with water. After cooling to 0°, the solution was acidified with glacial acetic acid. The finely divided ketal acid V was filtered and washed with water. The total solid was suspended in 1.4 l. of acetone and 100 ml. of 10% aqueous hydrochloric acid added. After standing overnight, the solution was concentrated to 200 ml. and the slurry diluted to 2.0 l. with water. The filtered, dried product, IV, weighed 33.4 g. (94.5%) and melted at 229–231° with softening at 225°. One recrystallization from chloroform gave 28.4 g. (80%) of material melting at 231–231.5° (gas evolved); reported[1] m.p. 235–238°. The acetate of IV melted at 176–178°.

Anal. Calcd. for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51; O, 19.88. Found: C, 71.42; H, 8.61; O, 19.45.

The methyl ester of IV was obtained as colorless crystals melting, after short path distillation (180°, 0.5 mm.), at 130–132°.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15; O, 17.09. Found: C, 73.46; H, 9.20; O, 17.44.

16α-Carbamoyl-3β-hydroxy-5-pregnen-20-one (III).—A solution of 300 mg. (0.00084 mole) of II, 15 ml. 95% ethanol, 1 ml. water and 1.0 g. of potassium hydroxide was refluxed for 48 hr. The ethanol was stripped *in vacuo*. The residue was diluted to 200 ml. with water, warmed to coagulate the precipitate, and filtered. The filtrate was acidified yielding a slightly murky solution showing the absence of any appreciable amounts of acidic material. The precipitate was dried, dissolved in 100 ml. of acetone, and treated with 30 ml. of 5% hydrochloric acid. After 2 hr. at room temperature, the acetone was concentrated *in vacuo* and the residue diluted with water. The dried product, 0.223 g., melted at 264–267° dec. The analytical sample melted at 265–268° dec.; $[\alpha]_D$ +3.6° (*c*, 0.46, ethanol).

Anal. Calcd. for $C_{22}H_{33}NO_3$: C, 73.50; H, 9.25. Found: C, 73.53; H, 9.35.

16α-Carboxy-4-pregnene-3,20-dione (VI)—A solution composed of 3.80 g. (0.0105 mole) of IV in 50 ml. of glacial acetic acid was treated with 15 ml. of glacial acetic acid containing 1.68 g. (0.0105 mole) of bromine.[4] After 2 min., a solution containing 0.88 g. (0.0088 mole) chromium trioxide, 2 ml. of water, and 15 ml. of acetic acid was added. The oxidation was allowed to proceed at room temperature for 2 hr. followed by the addition of 15 ml. of methanol. The system was purged with nitrogen and treated with 200 ml. of 0.5 *N* chromous chloride. The debromination was allowed to proceed overnight a room temperature in a nitrogen atmosphere. Dilution with 1800 ml. of water, methylene chloride extraction, washing, drying and concentration yielded a nearly colorless oil. This material defined crystallization from many solvents, but did yield broad solvated prisms from ethyl acetate (2.13 g.) melting at 133–138° (gas evolution). A second crop (0.41 g.) melted at 128–137° (gas evolution). The analytical sample was obtained from ethyl acetate as broad prisms melting at 134–137° (gas evolution); $[\alpha]_D$ +116.9° (*c*, 1.0, ethanol), $\lambda_{max}^{CH_3OH}$ 239 mμ (ε 17,500). The infrared spectra showed a strong acetate band confirming the presence of ethyl acetate of crystallization.

Crabbé and Romo[6] have reported the preparation of unsolvated 16α-carboxyprogesterone by a different route; m.p. 182–184°; $[\alpha]_D$ (methanol) +129°.

Anal. Calcd. for $C_{22}H_{30}O_4 \cdot 1/2CH_3COOC_2H_5$: C, 71.61; H, 8.51; O, 19.88. Found: C, 71.61; H, 8.61; O, 19.81.

β-Hydroxyethyl Pregn-5-ene-16α-carboxylate-3,20-dionebiscycloethyleneketal (VII).—A mixture of 1.66 g. (0.0041 mole) VI (solvated with 1/2 mole of ethyl acetate), 250 ml. of thiophene-free benzene, 30 ml. of ethylene glycol and 200 mg. of *p*-toluenesulfonic acid monohydrate was refluxed for 17 hr. while removing water *via* a Dean–Stark water separator. The reaction mixture was cooled and washed successively with saturated sodium bicarbonate solution and water. Concentraton, *in vacuo*, following addition of a few milliliters of pyridine gave 2.46 g. of a sticky solid. Crystallization from ether gave solvated colorless needles of VII which melted at 131–134° (gas evolution). Crystallization from benzene–petroleum ether gave VII which melted at 153–156°.

Anal. Calcd. for $C_{28}H_{42}O_7$: C, 68.54; H, 8.63. Found: C, 68.34; H, 8.68.

16α-Hydroxymethyl-5-pregnene-3,20-dionebiscycloethyleneketal (VIII).—Nine hundred milligrams of VII (ether solvated) in 100 ml. of dry ether was added to a stirred, refluxing suspension of 2.0 g. lithium aluminum hydride in 100 ml. of dry ether. After refluxing and stirring for 2 hr., the suspension was allowed to stand overnight. Decomposition of the complex by the addition of 12 ml. of water, followed by removal of the inorganic salts by filtration and concentration of the filtrates, gave 740 mg. of crude VIII; m.p. 223–235°. Recrystallization from methanol gave solvated colorless needles (520 mg.) melting at 238–240°.

(4) P. Julian, W. Cole, A. Magnani, and E. Meyer, *J. Am. Chem. Soc.*, **67**, 1728 (1945).

(5) Melting points are not corrected and unless specified were taken in evacuated capillary tubes. Rotations were carried out at 25° ± 3° in the solvents specified.

(6) P. Crabbé and J. Romo, *Chem. Ind.* (London), 408 (1962).

A second crop amounted to 100 mg. and melted at 233–236°; $[\alpha]_D$ −35.2° (*c*, 0.53 ethanol).[7]

Anal. Calcd. for $C_{26}H_{40}O_5 \cdot 1/2CH_3OH$: C, 70.99; H, 9.44. Found: C, 71.01; H, 9.43.

A sample dried for 17 hr. at 100° (0.5 mm.) melted at 236–240°; $[\alpha]_D$ −38.6° (*c*, 0.57. ethanol).

Anal. Calcd. for $C_{26}H_{40}O_5$: C, 72.19; H, 9.32; O, 18.49. Found: C, 71.81; H, 9.21; O, 19.04.

16α-Hydroxymethylprogesterone (IX).—A solution containing 320 mg. (0.000715 mole) of the solvated biscycloethylene ketal (VIII), 50 ml. of acetone and 10 ml. of 10% aqueous hydrochloric acid was warmed slightly to attain solution and allowed to stand at room temperature for 75 min. The acetone was removed in a stream of nitrogen and the residue diluted with water. The colorless needles thus obtained (228 mg.) melted at 160–161°. A sample purified by recrystallization from methanol and water melted at 161–162.5°; $[\alpha]_D$ +164° (*c*, 1.04, chloroform); reported m.p.[1] 163–164°; $[\alpha]^{25}_D$ +160° (chloroform).

16α-Hydroxymethyl-5-pregnene-3,20-dionebiscycloethyleneketal Tosylate (X).—A solution of 1.0 g. (0.0023 mole) VIII, 2.260 g. of triethylene diamine in 300 ml. of thiophene-free benzene was stirred at room temperature until complete solution was attained. To this was added 2.20 g. of *p*-toluenesulfonyl chloride in 75 ml. of benzene. After 5 min., the clear homogeneous solution became hazy and a finely divided solid separated; stirring was continued overnight. The suspension was decomposed with ice and water and the organic layer washed with water. Concentration (*in vacuo*) in the presence of pyridine followed by dilution with water gave 1.36 g. of colorless needles X; *decomposition point* 150–153°.

Anal. Calcd. for $C_{33}H_{46}O_7S$: C, 67.55; H, 7.90. Found: C, 67.42; H, 7.60.

16α-Iodomethyl-5-pregnene-3,20-dionebiscycloethyleneketal (XI).—A mixture of 200 mg. of X, (0.00034 mole) 400 mg. of sodium iodide, 125 ml. of methyl ethyl ketone and 25 mg. of anhydrous sodium bicarbonate was refluxed for 48 hr. The solution was concentrated *in vacuo* and the residue diluted with water giving 0.184 g. of XI melting at 165.5–167°. The analytical sample was obtained as colorless needles melting at 168–169.5°; $[\alpha]_D$ −51.0° (*c*, 0.4, ethanol).

Anal. Calcd. for $C_{26}H_{39}O_4I$: C, 57.56; H, 7.24; I, 23.39. Found: C, 57.79; H, 7.00; I, 23.50.

16α-Methylprogesterone (XII).—A solution 100 mg. of XI (0.000184 mole) in 10 ml. of diglyme (distilled from calcium hydride) was added to a stirred solution of 400 mg. of lithium aluminum hydride in 75 ml. of dry diglyme. After stirring overnight at 65°, 4.8 ml. of water was added dropwise. The inorganic salts were removed by filtration and the cake was washed well with ether. The solvents were removed *in vacuo*. The solid residue (70 mg.) gave a negative Beilstein test. This crude product was hydrolyzed by treatment with 40 ml. of acetone and 4 ml. of 10% aqueous hydrochloric acid at room temperature for 60 min. Concentration *in vacuo* followed by addition of water and filtering gave 33 mg. of colorless needles melting at 133–141°. Chromatography on silica gel using 4–6% ether in benzene as the eluting agent gave 14.7 mg. of colorless needles melting at 138–139° (Fisher–Johns block). A mixed melting point with an authentic sample (m.p. 136–137.5°) melted at 136–137°. The infrared pattern was identical with authentic material. A sample submitted for high temperature (237°) gas–liquid chromatography, using an 8-ft. glass column packed with 0.5% Pluronic F-68 on siliconized Chromasorb W (60–80 mesh), showed identical retention time when compared to authentic material.

Acknowledgment.—The author is indebted to Mr. E. F. Shelberg and Mr. W. Washburn and their associates for the microanalyses and infrared spectra, respectively, and to Dr. I. Merits for the gas–liquid chromatographic analysis of 16α-methylprogesterone. The autoclave reactions were carried out by Messrs. G. Stone and M. Freifelder. The clarifying discussions with Dr. W. Cole are gratefully acknowledged.

(7) The ethanol used in the rotation of ketals contained a trace of pyridine.

Prodigiosin[1a]

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Received November 13, 1961

In a preceding paper[2a] it was shown that the properties of model compounds do not support the Wrede and Rothhaas[3] 2,2′,2″-tripyrrylmethane structure for prodigiosin[2b,c] isolated from the Stanford Z-4 strain of *Serratia marcescens*. During our continuation of the structural study, the partial synthesis of prodigiosin was described and a formula essentially that considered as an alternate possibility earlier by Wrede and Rothhaas,[4] along with that of an analog, were suggested from an investigation[5] of a precursor derived from a colorless mutant of the bacterium. The complete synthesis of prodigiosin identifying it as 2,2′-[3-methoxy-4′-amyl-5′-methyl-5-(2″-pyrryl)] dipyrrylmethene (I), the formula favored from the precursor study, has been recently reported.[6] Interestingly, isomeric formulas have been proposed from a permanganate oxidation of a product derived from a particular strain of the bacterium.[7] The possibility of variations arising from aberrant strains exists. Our own results are hence of interest from this standpoint as well as for other reasons. The compound obtained from the Stanford Z-4 strain is evidently identical[8] with the synthetic product and

(1) (a) This investigation was supported by research grants E-1335 and E-1335(C2) from the National Institute of Allergy and Infectious Diseases, Public Health Service, to the University of Santa Clara. (b) National Science Foundation Undergraduate Research Participant (NSF-G11923).

(2) (a) A. J. Castro, A. H. Corwin, J. F. Deck, and P. E. Wei, *J. Org. Chem.*, **24**, 1437 (1959). For other comparisons see: (b) A. Treibs and K. Hintermeier, *Ann.*, **605**, 35 (1957); (c) A. Treibs and R. Zimmer-Galler, *Z. physiol. Chem.*, **318**, 12 (1960).

(3) F. Wrede and A. Rothhaas, *Z. physiol. Chem.*, **226**, 95 (1934).

(4) F. Wrede and A. Rothhaas, *ibid.*, **219**, 267 (1933).

(5) H. H. Wasserman, J. E. McKeon, L. Smith, and P. Forgione, *J. Am. Chem. Soc.*, **82**, 506 (1960).

(6) H. Rapoport and K. G. Holden, *ibid.*, **84**, 635 (1962).

(7) G. Narni and R. A. Nicolaus, *Rend. accad. sci. fis. mat.* (*Soc. naz. sci. Napoli*), **26**, 471 (1959).

(8) Chromic acid oxidation of the carefully purified natural product yielded maleimide and methoxymaleimide (the major product), and 2-methyl-3-amylpyrrole was obtained from a soda-lime distillation. The imides[9] and alkylpyrrole[3] were similarly derived earlier by Wrede and Rothhaas. However, because of the impure nature of their product and the low yields of the imides apparently obtained, conclusions reached therefrom have been questionable. It should be mentioned that permanganate oxidation at different conditions, including those of Narni and Nicolaus,[7] as well as the use of a variety of oxidants in addition to the application of other procedures to obtain products suitable for structure elucidation were unsuccessful. Hydrogenation with an Adam's catalyst in dioxane at room temperature resulted in the ready uptake of one mole of hydrogen followed by a subsequent slow hydrogenation in agreement with initial reduction of the dipyrrylmethene unit, indicated by salt formation[1,11] and zinc complex formation as concluded earlier,[12] followed by the more difficult hydrogenation of the pyrrole rings.[4,13,14] Zerevitinov analysis gave values of 0.45 and 0.46% active hydrogens corresponding to 1.47 active hydrogen per mole of monomer, although the proton magnetic resonance spectrum shows a typical low, broad absorption at $\tau = -0.98$, assignable to two pyrrole NH protons in a total of twenty-five.[15] Moreover, the synthetic product is described as identified by comparison with a reported authentic sample and *the properties of prodigiosin given by* Treibs and Zimmer-Galler.[2c] From the infrared and visible–ultraviolet absorption spectra of our compound and those reported by the latter workers, their product and ours are apparently the same, even though their product is described as decomposing at 90° and individual samples of our red, crystalline compound melt with decomposition near 150°.[16] Similarly, the visible–ultraviolet absorption for their hydrochloride and ours[11] appear to be the same, while they describe this derivative as dark violet needles melting at 135° and we find it is a magenta colored solid that melts with decomposition at 148.5–150.0°. Their per-