form extracts yielded 29 g. (39%) of **ethyl N-(2-ethoxycarbonylethyl)-glycinate-1-^{14}C**, b.p. 107–108° (2.5 mm.).

Anal. Calcd. for $C_9H_{17}O_4N$: C, 53.2; H, 8.4; N, 6.9. Found: C, 53.1; H, 8.4; N, 6.9.

The ethyl N-(2-ethoxycarbonylethyl)-glycinate-1-^{14}C (16 g., 0.08 mole) was added to a solution of 8 g. of sodium carbonate in 100 ml. of water and to this was added 8.4 g. of ethyl chloroformate. The reaction mixture was stirred at room temperature for 4 hours, then adjusted to *p*H 2.0 and extracted with five 50-ml. portions of benzene. Distillation of the dried benzene extracts yielded 20 g. (85%) of **ethyl N-ethoxycarbonyl-N-(2-ethoxycarbonylethyl)-glycinate-1-^{14}C (IIIb)**, b.p. 146–147° (3.5 mm.).

Anal. Calcd. for $C_{12}H_{21}O_6N$: C, 52.4; H, 7.7; N, 5.1; OC_2H_5, 49.1. Found: C, 52.4; H, 7.9; N, 4.9; OC_2H_5, 49.4.

Cyclization of the triester IIIb to the pyrrolidone IVb was carried out in 75% yield in the manner described above for the condensations in absolute ethanol.

Decarboxylation of radioactive IVa, IVb and IVc to the pyrrolidones VIa, VIb and VIc was carried out as reported.[8] The carbon dioxide was collected by using a nitrogen sweep and the gas stream was bubbled through molar potassium sulfate–potassium bisulfate (2:1) and then into standard sodium hydroxide solution. Barium chloride then was added to precipitate the barium carbonate for counting.

Radioactivity Measurements.—In every case, the starting esters IVa, IVb and IVc had specific activities of 30,000 ± 500 d.p.m./mmole. The decarboxylated pyrrolidones VIa, VIb and VIc had the same specific activities as the starting esters, and the evolved carbon dioxide had specific activities of 100 ± 30 d.p.m./mmole.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, BERKELEY 4, CALIF.]

The Synthesis of Prodigiosin[1]

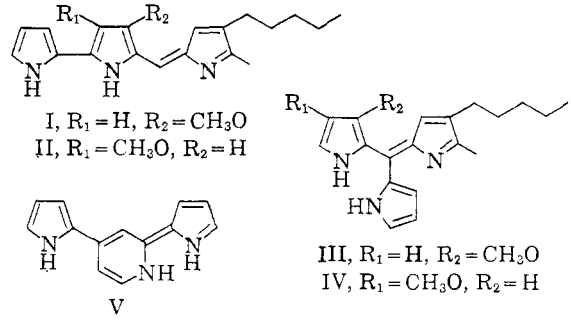
BY HENRY RAPOPORT AND KENNETH G. HOLDEN[2]

RECEIVED MAY 11, 1961

Prodigiosin, the red pigment of *S. marcescens*, has been synthesized. The pyrryldipyrrylmethene structure thus established for this pigment was built up through the following stages: (1) condensation of ethyl N-ethoxycarbonylglycinate with diethyl ethoxymethylenemalonate followed by treatment with diazomethane and selective hydrolysis gave ethyl 3-methoxypyrrole-2-carboxylate; (2) heating this ester with Δ^1-pyrroline led to the pyrrolidinylpyrrole which was dehydrogenated to ethyl 4-methoxy-2,2′-bipyrrole-5-carboxylate; (3) this bipyrrole ester was converted to the corresponding 4-methoxy-2,2′-bipyrrole-5-carboxaldehyde; and (4) acid-catalyzed condensation of this aldehyde with 2-methyl-3-amylpyrrole resulted in synthetic prodigiosin, identical with the natural pigment. This is the first synthesis of a pyrryldipyrrylmethene, and prodigiosin (and a related pigment) is the only example of the occurrence of such a skeleton in nature.

Prodigiosin is the red pigment of *Serratia marcescens*, a widely distributed, non-pathogenic bacterium often found in soil and water. This bacterium, previously known as *Bacillus prodigiosus*, provided the excuse for frequent religious excesses during the Middle Ages when red colonies of the bacillus on consecrated wafers were mistaken for flecks of blood.[3] Prodigiosin itself has considerable antibiotic and antifungal activity,[4] but high toxicity precludes its use as a therapeutic agent.

The first degradative work reported[5] on prodigiosin, $C_{20}H_{25}N_3O$, indicated the presence of three pyrrole nuclei (pyrrole, 3-methoxypyrrole and 2-methyl-3-amylpyrrole) joined in some manner by means of the remaining carbon atom required by the empirical formula. On the basis of his work Wrede, in 1933,[5b] proposed structures I, III and IV for prodigiosin, favoring IV in his later publications[5c,d] without providing any further experimental justification. Nevertheless, because of Wrede's assignment of the tripyrrylmethene structure (IV), other plausible structures were ignored and attention was focused on the synthesis of tripyrrylmethenes.[6–8] However, comparisons of these synthetic model compounds with prodigiosin were inconclusive since the synthetic tripyrrylmethenes differed considerably from prodigiosin in extent and kind of substitution. In fact these comparisons have been interpreted both as evidence for[9] and against[7,8] the tripyrrylmethene structure. Synthesis of various other model compounds[10,11] led to the proposal[10] of a pyridine-containing nucleus (V) for prodigiosin. It was not until very recently[12,13] that a pyrryldipyrrylmethene structure was again considered for prodigiosin.



I, $R_1 = H$, $R_2 = CH_3O$
II, $R_1 = CH_3O$, $R_2 = H$

III, $R_1 = H$, $R_2 = CH_3O$
IV, $R_1 = CH_3O$, $R_2 = H$

V

(1) Presented in part as a communication; H. Rapoport and K. G. Holden, *J. Am. Chem. Soc.*, **82**, 5510 (1960).

(2) Public Health Service Predoctoral Research Fellow of the National Heart Institute.

(3) F. Mayer and A. H. Cook, "The Chemistry of Natural Coloring Matters," Reinhold Publishing Corp., New York, N. Y., 1943, p. 269.

(4) P. E. Thompson, D. A. McCarthy, A. Bayles, J. W. Reinertson and A. R. Cook, *Antibiotics and Chemotherapy*, **6**, 337 (1956); O. M. Efimenko, G. A. Kusnetsova and P. A. Yakimov, *Biokhim.*, **21**, 416 (1956); O. Felsenfeld, D. W. Soman, S. J. Ishihara, T. Waters and J. Norsen, *Proc. Soc. Exptl. Biol. Med.*, **77**, 287 (1951); for action against coccidioidomycosis, see A. Lack, *ibid.*, **72**, 656 (1949); R. E. Weir, R. O. Egeberg, A. Lack and G. M. Leiby, *Am. J. Med. Sci.*, **224**, 70 (1952).

(5) (a) F. Wrede and A. Rothhass, *Z. physiol. Chem.*, **215**, 67 (1933); (b) **219**, 267 (1933); (c) **222**, 203 (1933); (d) **226**, 95 (1934).

(6) H. Fischer and K. Gangl, *ibid.*, **267**, 201 (1941).

(7) A. Treibs and K. Hintermeier, *Ann.*, **605**, 35 (1957).

(8) A. J. Castro, A. H. Corwin, J. F. Deck and P. E. Wei, *J. Org. Chem.*, **24**, 1437 (1959).

(9) R. Hubbard and C. Rimington, *Biochem. J.*, **46**, 220 (1950).

(10) A. Treibs and R. Galler, *Angew. Chem.*, **70**, 57 (1958).

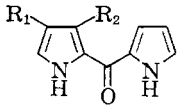
(11) A. Treibs and R. Zimmer-Galler, *Z. physiol. Chem.*, **318**, 12 (1960).

(12) G. Narni and R. A. Nicolaus, *Rend. accad. sci. fis. e mat. (Soc. nazl. sci. Napoli)*, **26**, 3 (1959).

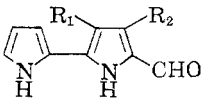
(13) H. H. Wasserman, J. E. McKeon, L. Smith and P. Forgione, *J. Am. Chem. Soc.*, **82**, 506 (1960).

Of profound importance to the elucidation of the structure of prodigiosin is a compound, $C_{10}H_{10}N_2O_2$, isolated[14] from a mutant strain of *S. marcescens*. This compound was shown[14] by tracer experiments, to be a true precursor of prodigiosin and to contain a methoxyl and carbonyl group and a pyrrole ring. Furthermore, it was shown later[13] that acid-catalyzed condensation of this precursor with 2-methyl-3-amylpyrrole gave prodigiosin.

The most reasonable structure for the precursor than seemed to be either a methoxy-2,2′-dipyrryl ketone (VI or VII), if prodigiosin were a tripyrrylmethene (III or IV), or a methoxy-2,2′-bipyrrole aldehyde (VIII or IX), if a pyrryldipyrrylmethene structure (I or II) were correct.

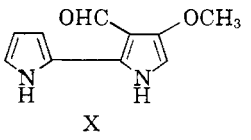


VI, $R_1 = H$, $R_2 = CH_3O$
VII, $R_1 = CH_3O$, $R_2 = H$

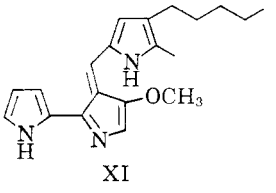


VIII, $R_1 = H$, $R_2 = CH_3O$
IX, $R_1 = CH_3O$, $R_2 = H$

Synthesis of 4-methoxy-2,2′-dipyrryl ketone (VII)[15] eliminated this structure for prodigiosin precursor and therefore structure IV for prodigiosin. Also, the physical properties of this substance and other dipyrryl ketones led to the conclusion[15] that the precursor could not be a dipyrryl ketone. The isolation of pyrrole-2-carboxamide from oxidation of the precursor[13] provided strong evidence for the 2,2′-linkage of the pyrrole rings, and together with n.m.r. data led to the proposal[13] that prodigiosin precursor was either the bipyrrole α-aldehyde VIII or the β-aldehyde X, with the former being favored, and leading to structure I or XI, respectively, for prodigiosin.



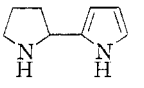
X



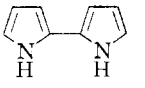
XI

From a consideration of all the above data structure I or II appeared to be the most probable for prodigiosin. We therefore focused our attention on the synthesis of the methoxy-2,2′-bipyrrole aldehydes VIII and IX, one of which should then be the prodigiosin precursor. A review of the literature revealed no method for the synthesis of a 2,2′-bipyrrole which appeared applicable to the present problem. However, condensation of Δ^1-pyrroline with pyrrole to give 2,2′-pyrrolidinylpyrrole (XII) has been reported,[16] and it seemed likely that this compound could be dehydrogenated to 2,2′-bipyrrole (XIII). This was indeed the case, for XII was dehydrogenated readily in refluxing xylene in the presence of 5% palladium-on-carbon, thus providing a route to the 2,2′-bipyrrole system.

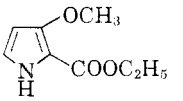
Because of the mild, neutral conditions of both the initial condensation and the dehydrogenation, this method seemed extensible to appropriately substituted pyrroles in order to arrive at the methoxy-2,2′-bipyrrole aldehydes VIII and IX. To establish beyond question the position of the formyl group in the final product, the methoxypyrrole esters XIV and XV were required as starting materials, since we anticipated subsequently converting the ester function to an aldehyde. The question of which aldehyde, VIII or



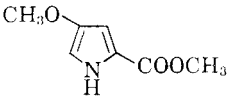
XII



XIII



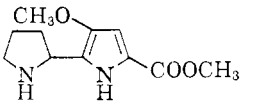
XIV



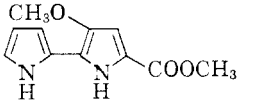
XV

IX, to synthesize first was answered by the availability of starting materials, XV being readily available[15] while XIV was unknown.

Extension of the Δ^1-pyrroline condensation from the simple case of pyrrole to a pyrrole carboxylic ester raised some questions since the electron-withdrawing character of the ethoxycarbonyl group would be expected to decrease the electron density of the pyrrole nucleus, discouraging electrophilic attack by Δ^1-pyrroline. As expected, ethyl pyrrole-2-carboxylate failed to condense with Δ^1-pyrroline under the previous conditions. However, this deactivation was offset by the electron-releasing nature of the methoxyl group, and condensation of Δ^1-pyrroline with methyl 4-methoxypyrrole-2-carboxylate (XV) gave methyl 4-methoxy - 5 - (2′ - pyrrolidinyl) - pyrrole - 2 - carboxylate (XVI) in high yield. This material was dehydrogenated to methyl 3-methoxy-2,2′-bipyrrole-5-carboxylate (XVII).



XVI



XVII

Although diethoxy lithium aluminum hydride[17] failed to reduce either pyrrole-2-carboxdimethylamide or pyrrole-2-carboxpyrrolidide to pyrrole-2-carboxaldehyde, conversion of the ester function to an aldehyde was achieved by the method of MacFadyen–Stevens.[18] Thus methyl 3-methoxy-2,2′-bipyrrole-5-carboxylate (XVII) was converted to its hydrazide in high yield; the tosylate of the hydrazide then was decomposed to give 3-methoxy-2,2′-bipyrrole-5-carboxaldehyde (IX) in 34% overall yield. However, this compound was not the desired prodigiosin precursor as was clearly shown by its ultraviolet absorption spectrum, which had a maximum at 386 mμ. The precursor was reported[14] to have its longest wave length absorption at 363 mμ; furthermore, the precursor was reported[14] to

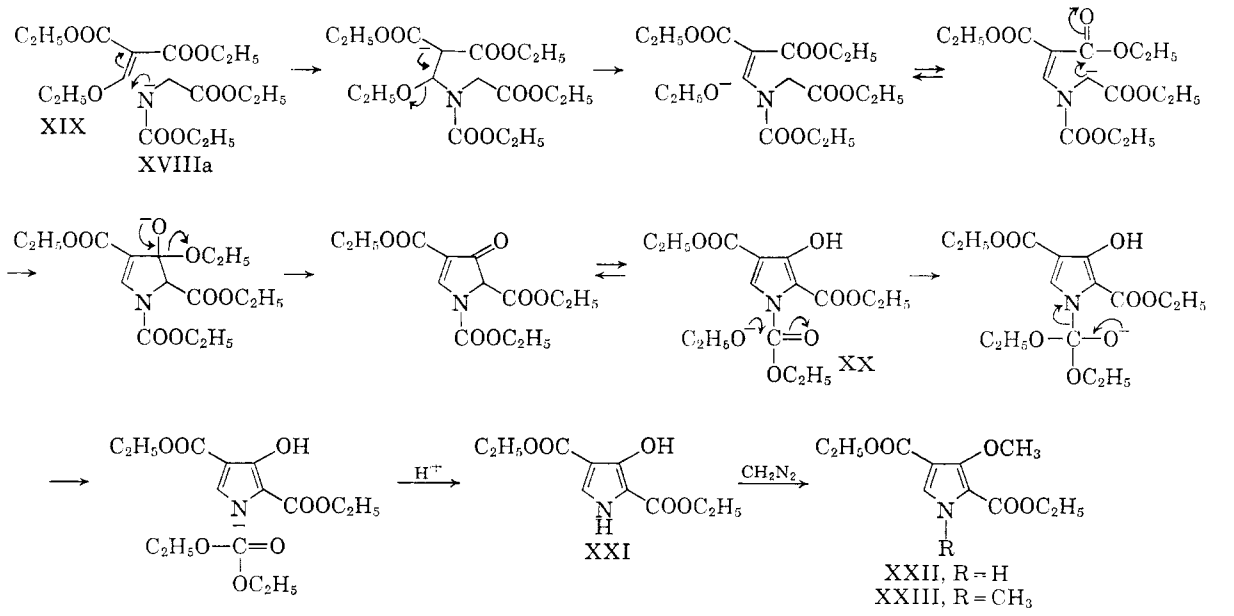
(14) U. V. Santer and H. J. Vogel, *Federation Proc.*, **15**, 1131 (1956); *Biochim. Biophys. Acta*, **19**, 578 (1956).

(15) H. Rapoport and C. D. Willson, *J. Am. Chem. Soc.*, **84**, 630 (1962).

(16) D. W. Fuhlhage and C. A. VanderWerf, *ibid.*, **80**, 6249 (1958).

(17) H. C. Brown and A. Tsukamoto, *ibid.*, **81**, 502 (1959).

(18) E. Mosettig in "Organic Reactions," Vol. VIII, John Wiley and Sons, Inc., New York, N. Y., 1954, p. 218; R. G. Jones and K. C. McLaughlin, *J. Am. Chem. Soc.*, **71**, 2444 (1949).



decompose above 250°, while the bipyrrole aldehyde IX melted at 186° without decomposition.

At this point our primary objective became preparation of the methoxypyrrole ester XIV. A series of reactions parallel to those applied above should then result in the isomeric bipyrrole aldehyde VIII which now seemed to be the correct structure for prodigiosin precursor. The successful route by which the key intermediate XIV was prepared will now be discussed in detail.

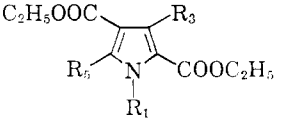
Condensation of the sodium salt of ethyl N-ethoxycarbonylglycinate (XVIIIa) with diethyl ethoxymethylenemalonate (XIX) gave directly diethyl 3-hydroxypyrrole-2,4-dicarboxylate (XXI). This transformation presumably took place by Michael addition followed by loss of ethoxide and ring closure to give as an intermediate the N-carbethoxypyrrole XX. Ethoxide attack on this compound would then result in the product, XXI.

Treatment of the reaction product, presumably XXI, with diazomethane gave three compounds, A, B and C, in the ratio of 15:1:12, which were readily separated by chromatography on alumina. The last substance off the column, C, eluted with benzene–chloroform (1:1), was the desired diethyl 3-methoxypyrrole-2,4-dicarboxylate (XXII). The first two substances from the column, A and B, eluted with benzene–hexane (1:1), were isomeric, $C_{12}H_{17}O_5N$, and both had three alkoxyl and two C–methyl groups. Neither compound showed N–H or O–H absorption in the infrared, nor was there any shift in their ultraviolet spectra on addition of acid. These data are consistent with either compound being diethyl 1-methyl-3-methoxypyrrole-2,4-dicarboxylate (XXIII), the product resulting from N- as well as O-methylation of XXI.

Since A was produced in much larger amount than B (15:1), and in almost equal amount with C, it seemed probable that A was the expected dimethylated derivative XXIII, while B arose from an impurity in the starting material XXI. However, their ultraviolet absorption spectra suggest the opposite. It is known[19] that the N-methyl derivatives of pyrroles have ultraviolet spectra very similar to the parent pyrrole. For 2-carbonylpyrroles, N-methylation causes a 3–8 mμ bathochromic shift of the short wave length peak with an increase in extinction coefficient of 200–1800; the longer wave length peak is also shifted bathochromically, 1–2 mμ, but with a decrease of 300–4,000 in extinction coefficient. A closer analogy to the case at hand is offered by the diethyl pyrrole-2,4-dicarboxylates XXIV and XXV with which compound C, diethyl 3-methoxypyrrole-2,4-dicarboxylate (XXII) and compounds A and B are compared in Table I.

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA OF DIETHYL PYRROLE-2,4-DICARBOXYLATES



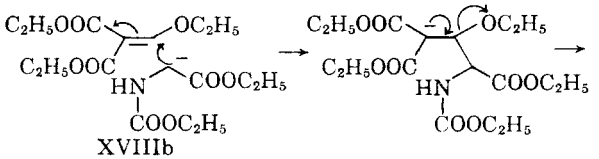
	R_1	R_3	R_5	λ_{max}, mμ	ϵ_{max}	λ_{max}, mμ	ϵ_{max}
XXIV[a]	H	CH_3	CH_3	221	27,500	273	16,700
XXV[a]	CH_3	CH_3	CH_3	226	29,100	274	14,400
XXII, C	H	CH_3O	H	220	30,000	258	13,800
XXIII, B	CH_3	CH_3O	H	223	33,900	259	12,800
XXVI, A	CH_3	H	CH_3O	212	26,000	273	16,200

[a] U. Eisner and P. H. Gore, *J. Chem. Soc.*, 922 (1958).

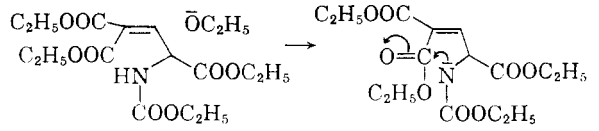
Thus the ultraviolet absorption spectrum of compound B is that expected for the N-methyl derivative of XXII, namely, XXIII. The spectrum of compound A suggests that it also is a diethyl pyrrole-2,4-dicarboxylate, but that it is certainly not XXIII. On this basis B is assigned structure XXIII. A is concluded to be diethyl 1-methyl-2-methoxypyrrole-3,5-dicarboxylate (XXVI) which must have arisen from diethyl 2-hydroxypyrrole-3,5-dicarboxylate (XXVII). Formation of the latter compound is easily rationalized by considering the initial step as involving Michael

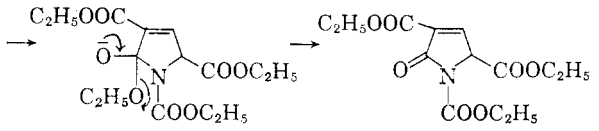
(19) R. Andrisano and G. Pappalardo, *Gazz. chim. ital.*, **85**, 1430 (1955).

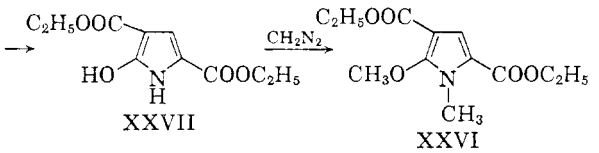
addition of the carbanion XVIIIb rather than of the amide ion XVIIIa



XVIIIb

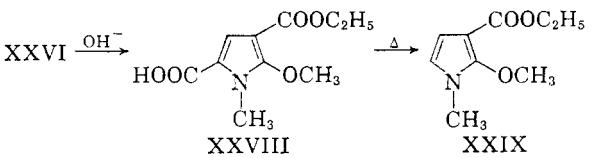




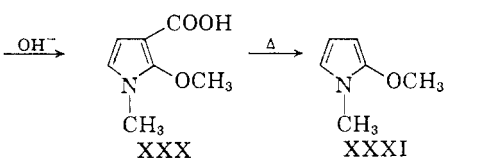


XXVII XXVI

Further support for the structural assignment of XXVI to A is provided by selective hydrolysis (see below) to 1-methyl-2-methoxy-3-ethoxycarbonylpyrrole-5-carboxylic acid (XXVIII). This was decarboxylated to ethyl 1-methyl-2-methoxypyrrole-3-carboxylate (XXIX), which in turn was hydrolyzed to 1-methyl-2-methoxypyrrole-3-carboxylic acid (XXX), and the latter was decarboxylated to 1-methyl-2-methoxypyrrole (XXXI). The various compounds in this sequence all have ultraviolet absorption consistent with the assigned structures,[15] and 1-methyl-2-methoxypyrrole gave an immediate rose-red color with Ehrlich reagent.



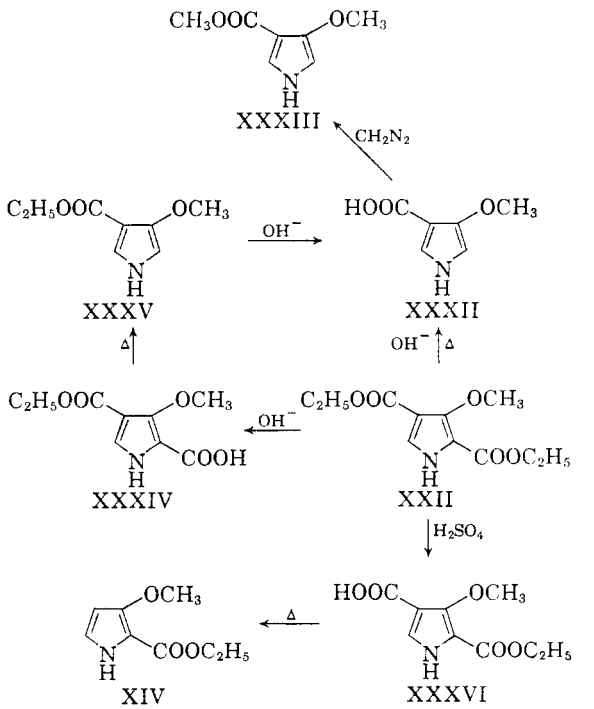
XXVIII XXIX



XXX XXXI

In order to obtain ethyl 3-methoxypyrrole-2-carboxylate (XIV), the 4-ethoxycarbonyl group had to be removed from diethyl 3-methoxypyrrole-2,4-dicarboxylate (XXII). Since it has been shown[20] that the 3-ethoxycarbonyl group is selectively removed from 3-ethoxycarbonyl-4-methylpyrrole-2-carboxylic acid to give 4-methylpyrrole-2-carboxylic acid on refluxing in concentrated alkali, similar treatment of diethyl 3-methoxypyrrole-2,4-dicarboxylate (XXII) was expected to give 3-methoxypyrrole-2-carboxylic acid. However, the acid obtained had an ultraviolet absorption spectrum identical with that of 4-methoxypyrrole-3-carboxylic acid (XXXII)[15] and on treatment with diazomethane gave methyl 4-methoxypyrrole-3-carboxylate (XXXIII) identical with an authentic sample of this material synthesized by an unambiguous route.[15]

To achieve the selective removal of the ethoxycarbonyl group necessary to complete the synthesis, recourse then was made to the remarkable specificity which has been realized in the hydrolysis of pyrrole polyesters.[21] Mild alkali hydrolyzed only the α-ester of diethyl 3-methoxypyrrole-2,4-dicarboxylate (XXII), giving 4-ethoxycarbonyl-3-methoxypyrrole-2-carboxylic acid (XXXIV) which could be decarboxylated on heating to ethyl 4-methoxypyrrole-3-carboxylate (XXXV).[15] However, on treatment with concentrated sulfuric acid, the β-ester of XXII was hydrolyzed, and the resulting 2-ethoxycarbonyl-3-methoxypyrrole-4-carboxylic acid (XXXVI) was decarboxylated to the desired ethyl 3-methoxypyrrole-2-carboxylate (XIV).



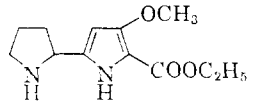
XXXIII XXXV XXXII XXXIV XXII XIV XXXVI

With the synthesis of the key intermediate XIV accomplished, the synthesis of 4-methoxy-2,2′-bipyrrole-5-carboxaldehyde (VIII) became quite straightforward, paralleling the synthesis of the isomeric bipyrrole aldehyde IX. Condensation of ethyl 3-methoxypyrrole-2-carboxylate (XIV) with Δ^1-pyrroline gave ethyl 3-methoxy-5-(2′-pyrrolidinyl)-pyrrole-2-carboxylate (XXXVII) which was dehydrogenated to ethyl 4-methoxy-2,2′-bipyrrole-5-carboxylate (XXXVIII). Using the previous aldehyde synthesis, 4-methoxy-2,2′-bipyrrole-5-carboxaldehyde (VIII) was produced. The ultraviolet spectrum (Fig. 1) and melting

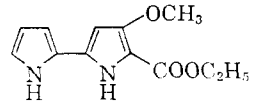
(20) R. A. Nicolaus, L. Mangoni and D. Misiti, *Ann. chim.* (Rome), **46**, 847 (1956); R. Oesterlin, this Laboratory.

(21) H. Fischer and H. Orth, "Die Chemie des Pyrrols," Band I, Akademische Verlagsgesellschaft, Leipzig, 1934; A. Treibs, R. Schmidt and R. Zinsmeister, *Ber.*, **90**, 79 (1957). These references contain various examples of the hydrolysis of pyrrole-2,4-dicarboxylates from which the generalization may be drawn that the α-ester is selectively hydrolyzed by mild alkali and the β-ester by concentrated sulfuric acid.

point of this compound [m.p. 265° dec.; λ_{max} 251 mμ (ϵ 14,700), 361 (40,300)] agreed quite well with the values reported[14] for the naturally occurring prodigiosin precursor [m.p. dec. above 250°; λ_{max} 254 mμ (ϵ 13,000), 363 (35,000)].



XXXVII

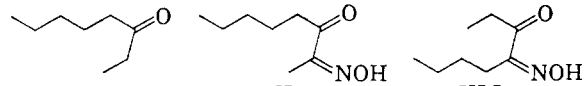


XXXVIII

Since the aldehyde VIII appeared to be identical with prodigiosin precursor, it only remained to condense it with 2-methyl-3-amylpyrrole in order to arrive at what seemed to be the structure of prodigiosin, I. Wrede and Rothhass[5d] had synthesized 2-methyl-3-amylpyrrole for comparison with the prodigiosin degradation product, and this synthesis plus the isolation of amylmaleimide from oxidation experiments left absolutely no doubt as to the nature of the third pyrrole ring. However, since their synthesis began with the oximation of 3-octanone, the presence of an isomeric impurity was distinctly possible. Lest such an impurity might possibly confuse the final comparison of synthetic and natural prodigiosin, this synthesis was examined in some detail.

Oximination of 3-octanone (XXXIX) gave a mixture of the two possible α-oximinoketones XL and XLI in a ratio of about 15:1 as shown by vapor phase chromatography. When this mixture was subjected to second-order Beckmann rearrangement conditions,[22] the acidic fraction was found to contain caproic acid and propionic acid in a ratio of about 15:1, while the neutral fraction contained acetonitrile and very little valeronitrile. Thus, 2-oximino-3-octanone (XL) is the predominant product, and use of this reaction mixture in continuing the synthesis gave 2-methyl-3-amylpyrrole (XLII) contaminated with a small amount of 2-butyl-3-ethylpyrrole (XLIII). The two alkylpyrroles were separated readily by vapor phase chromatography.

In methanolic hydrochloric acid 4-methoxy-2,2′-bipyrrole-5-carboxaldehyde (VIII) condensed with 2-methyl-3-amylpyrrole (XLII) to give the pyrryldipyrrylmethene. Chromatography on alumina gave synthetic prodigiosin, I, whose infrared as well as ultraviolet and visible spectra, in both acidic and alkaline solution, were identical with those of natural prodigiosin.[23,24]



XXXIX XL XLI

XLII XLIII

(22) M. Levitz, D. Perlman and M. T. Bogert, *J. Org. Chem.*, **6**, 105 (1941).

(23) We are indebted to Dr. M. C. Bachman of Commercial Solvents Corporation for a sample of natural prodigiosin.

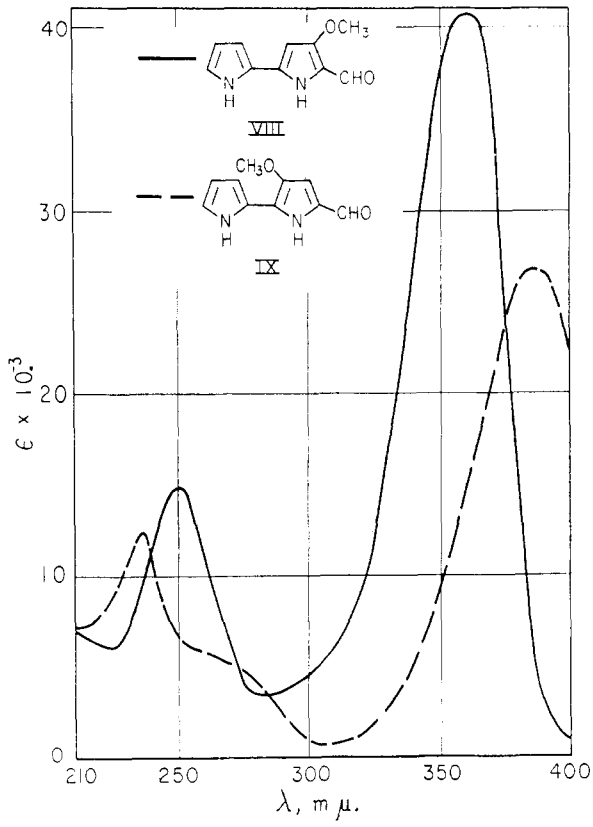
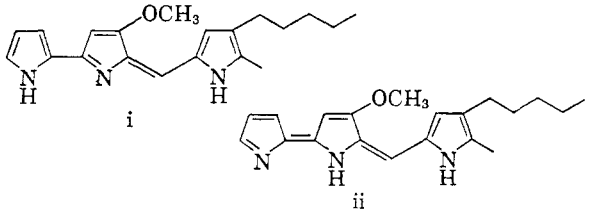


Fig. 1.—Ultraviolet absorption spectra in methanol of 4-methoxy-2,2′-bipyrrole-5-carboxaldehyde (VIII) (———) and 3-methoxy-2,2′-bipyrrole-5-carboxaldehyde (IX) (- - - -).

The interesting pyrryldipyrrylmethene structure established for prodigiosin by this synthesis[25] has as its closest, and that quite distant, analogy a similar, partially hydrogenated skeleton within the ring structure of vitamin B_{12}.[26] This synthesis also eliminates the one presumed natural occurrence of a tripyrrylmethene.[27]

(24) Of course the tautomer i and the less likely ii, are also possibilities, and prodigiosin may be a mixture of tautomers. However



i

ii

when prodigiosin is protonated, as it occurs naturally and as it is formed synthetically above, any tautomers become indistinguishable.

(25) Similar prodigiosin-like pigments with the composition $C_{15}H_{25}N_3O$ and appearing to be identical have been isolated from other microorganisms [E. Dietzel, *Z. physiol. Chem.*, **284**, 262 (1949); F. Arcamone, A. DiMarco, M. Ghione and T. Scotti, *Giorn. Microbiol.*, **4**, 77 (1957); R. A. Nicolaus, R. Nicoletti and F. Arcamone, *Ricerca sci.*, **28**, 2314 (1958)]. Since this pigment can be reconstituted [H. H. Wasserman, J. Keggi, F. Bohlmann and W. Luders, *Angew. Chem.*, **72**, 779 (1960)] from prodigiosin precursor (VIII) and a C_{15}-pyrrole, the pyrryldipyrrylmethene structure now can be assigned to it.

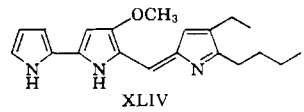
(26) R. Bonnett, J. R. Cannon, V. M. Clark, A. W. Johnson, L. F. J. Parker, E. L. Smith and A. Todd, *J. Chem. Soc.*, 1158 (1957).

(27) Tripyrrylmethenes have been postulated as intermediates in porphyrin biosynthesis [D. Shemin, C. S. Russel and T. Abramsky, *J. Biol. Chem.*, **215**, 613 (1955)], with prodigiosin being pointed to as

Prodigiosin and the other pyrryldipyrrylmethenes which have been synthesized are listed in Table II with their characteristic visible absorption

TABLE II

VISIBLE ABSORPTION SPECTRA OF PYRRYLDIPYRRYLMETHENES

Compound	λ_{max} (base), mμ	λ_{max} (acid salt), mμ
I	470, 532	535
 XLIV	475	535
II	480, 570	585, 556(sh)

peaks. As expected, the isomer XLIV obtained from 2-butyl-3-ethylpyrrole (XLIII) has visible spectra very similar to those of prodigiosin (I); however, the small shift of the main peak in the free base form and the absence of the low extinction peak at 532 mμ, present in the spectrum of prodigiosin, serve to differentiate them. The isomeric prodigiosin, II, obtained from condensation of 2-methyl-3-amylpyrrole (XLII) with the isomeric precursor IX, shows a 50 mμ shift from prodigiosin (I) in acid solution; thus, an acidic solution of prodigiosin is red-violet while that of the isomer II is blue-violet.

Experimental[28]

2,2'-Bipyrrole (XIII).—A mixture of 2,2'-pyrrolidinylpyrrole (XII)[16] (1 g., 7.35 mmoles) and 500 mg. of 5% palladium-on-carbon in 25 ml. of dry xylene was boiled with vigorous stirring under a carbon dioxide sweep. Measurement of the hydrogen evolution showed that over 30% of the theoretical amount of hydrogen was evolved during the first 30 minutes; during the next 3 hours an additional 30% was evolved. The cooled reaction mixture was diluted with benzene and chromatographed on 30 g. of activity III neutral alumina. Elution with benzene and benzene–chloroform (3:1) gave 593 mg. (4.50 mmoles, 60%) of 2,2'-bipyrrole (XIII), which after two recrystallizations from benzene–hexane and sublimation at 100° (200 μ), melted at 187°; ultraviolet absorption: λ_{max} 297 mμ sh. (ε 8,200), 283 (16,700), 277 (17,300), 273sh. (16,700).

Anal. Calcd. for $C_8H_8N_2$: C, 72.7; H, 6.1; N, 21.2; mol. wt., 132. Found: C, 72.5; H, 6.1; N, 21.4; mol. wt. (Rast), 128.

Methyl 4-Methoxy-5-(2'-pyrrolidinyl)-pyrrole-2-carboxylate (XVI).—A solution of 2.73 g. (17.7 mmoles) of methyl 4-methoxypyrrole-2-carboxylate (XV)[15] in methanolic Δ^1-pyrroline[16,29] (from 0.1 mole of pyrrolidine) was heated under reflux under nitrogen for 3 days. Most of the methanol was evaporated under reduced pressure, and the residue was distributed between water (75 ml.) and ether (50 ml.), the *p*H of the aqueous phase being adjusted to 11–12 with sodium hydroxide. The aqueous phase was extracted with additional portions of ether (3 × 50 ml.) and the combined ethereal extracts were dried over anhydrous magnesium sulfate. Evaporation of the ether gave 4.21 g. of material which was chromatographed on 60 g. of activity III alumina. Elution with benzene–hexane (1:1) gave starting material (0.16 g., 1 mmole, 6%) while elution with benzene–chloroform (3:1) gave 3.23 g. (14.4 mmoles, 81%) of crude product. Recrystallization from hexane followed by sublimation at 80° (30 μ) gave pure methyl 4-methoxy-5-(2'-pyrrolidinyl)-pyrrole-2-carboxylate (XVI), m.p. 77°; ultraviolet absorption: λ_{max} 238 mμ (ε 7,300), 292 (13,800); in methanol 0.1 *M* in hydrochloric acid: λ_{max} 238 mμ (ε 8,700), 287 (12,700).

Anal. Calcd. for $C_{11}H_{16}O_3N_2$: C, 58.9; H, 7.2; N, 12.5; OCH_3, 27.7 Found: C, 59.1; H, 7.4; N, 12.5; OCH_3, 27.4.

Methyl 3-Methoxy-2,2'-bipyrrole-5-carboxylate (XVII).—A mixture of methyl 4-methoxy-5-(2'-pyrrolidinyl)-pyrrole-2-carboxylate (XVI) (293 mg., 1.31 mmoles), 300 mg. of 5% palladium-on-carbon and 3 ml. of *p*-cymene was boiled, with magnetic stirring, for 20 minutes under a nitrogen sweep. The cooled reaction mixture was filtered and the catalyst was washed with chloroform (3 × 5 ml.). The chloroform and *p*-cymene were evaporated from the combined filtrates under reduced pressure and the residue was taken up in benzene–hexane (1:1) and chromatographed on 8 g. of activity III alumina. Elution with benzene gave 114 mg. (0.52 mmole, 40%) of crude product which, after recrystallization from benzene–hexane and from ethanol, was sublimed at 120° (30 μ) to give pure methyl 3-methoxy-2,2'-bipyrrole-5-carboxylate (XVII), m.p. 178°; ultraviolet absorption: λ_{max} 224 mμ (ε 11,900), 346 (25,200).

Anal. Calcd. for $C_{11}H_{12}O_3N_2$: C, 60.0; H, 5.5; N, 12.7; OCH_3, 28.2. Found: C, 60.2; H, 5.5; N, 12.8; OCH_3, 28.0.

3-Methoxy-2,2'-bipyrrole-5-carboxaldehyde (IX).—A solution of 259 mg. (1.18 mmoles) of methyl 3-methoxy-2,2'-bipyrrole-5-carboxylate (XVII) in 3 ml. of anhydrous hydrazine was heated under reflux in a nitrogen atmosphere for 2 hours. The warm reaction mixture was poured into 15 ml. of ice-water and the precipitate was collected and dried to give 243 mg. (1.10 mmoles, 94%) of **3-methoxy-2,2'-bipyrrole-5-carboxhydrazide.** To 214 mg. (0.98 mmole) of the hydrazide in 2 ml. of dry pyridine was added 210 mg. (1.1 mmoles) of *p*-toluenesulfonyl chloride in 1 ml. of pyridine. After stirring for 15 minutes the reaction mixture was poured into 15 ml. of ice-water. Filtration and drying of the precipitate gave 360 mg. (0.96 mmole, 98%) of **3-methoxy-2,2'-bipyrrole-5-carbox-*p*-toluenesulfonylhydrazide.** A mixture of 360 mg. (0.96 mmole) of the *p*-toluenesulfonylhydrazide, 360 mg. of anhydrous sodium carbonate and 5 ml. of dry diethylene glycol was stirred under nitrogen at 170° for 5 minutes. The warm reaction mixture was distributed between ice-water (20 ml.) and chloroform (25 ml.). The emulsion which formed was broken by filtration through filter-aid and the filter cake was washed with several portions of chloroform, which subsequently were used to extract the aqueous phase. The combined chloroform extracts were dried over anhydrous magnesium sulfate and evaporated to dryness. Chromatography of the residue on 8 g. of activity III alumina gave, on elution with benzene, 62 mg. (0.33 mmole, 34%) of 3-methoxy-2,2'-bipyrrole-5-carboxaldehyde (IX), which was recrystallized from benzene and sublimed at 110° (30 μ), m.p. 186°; ultraviolet absorption: λ_{max} 236 mμ (ε 12,400), 386 (26,800).

Anal. Calcd. for $C_{10}H_{10}O_2N_2$: C, 63.2; H, 5.3. Found: C, 63.3; H, 5.5.

Diethyl 3-Hydroxypyrrole-2,4-dicarboxylate (XXI).—To a suspension of sodium sand (9.65 g., 0.42 mole) in 35 ml. of xylene was added 200 ml. of benzene followed by 33.8 g. (0.21 mole) of ethyl N-ethoxycarbonylglycinate. The mixture was stirred under nitrogen for 2 hours and then allowed to stand for 14 hours. To this mixture of sodium sand and the sodium salt of ethyl N-ethoxycarbonylglycinate was added 45.4 g. (0.21 mole) of diethyl ethoxymethylenemalonate. The addition was carried out over a 1.5-hour period with stirring, maintaining the reaction mixture at reflux. After 3 hours the mixture had become so viscous that stirring was no longer possible. The cooled reaction mixture was dissolved in a minimum amount of absolute ethanol and poured into 1 l. of ice-water and 500 ml. of ether in a separatory funnel. After being shaken, the aqueous layer was drawn off and washed with 250 ml. of ether. The ethereal

an example of such a structure in nature. Except as it removes the prop of a naturally occurring example, prodigiosin not being a tripyrrylmethene in no way influences this postulate, since prodigiosin has been shown to be biosynthesized by a path quite distinct from porphyrins [G. S. Marks and L. Bogorad, *Proc. Natl. Acad. Sci.*, **46**, 25 (1960)].

(28) All melting points are corrected and those above 200° were taken in evacuated capillaries; microanalyses were performed by V. Tashinian, Microchemical Laboratory, University of California, Berkeley. Infrared spectra were taken in chloroform and ultraviolet spectra were taken in methanol.

(29) We experienced difficulty in preparing solutions of Δ^1-pyrroline of consistently good quality. By using calcium hypochlorite for the formation of the intermediate 1-chloropyrrolidine, this difficulty was overcome.

phases were extracted successively with cold 1 *N* sodium hydroxide (2 × 200 ml.). The combined aqueous extracts were acidified with concd. phosphoric acid to *p*H 3–4 and extracted with chloroform (3 × 300 ml.). The combined chloroform extracts were then washed with 2 *M* sodium bicarbonate solution (2 × 200 ml.), the aqueous extracts being washed with a 200-ml. portion of chloroform. The combined chloroform extracts, after drying, were evaporated to dryness to give 14.5 g. (0.064 mole, 30%) of crude die hyl 3-hydroxypyrrole-2,4-dicarboxylate (XXI), which, after recrystallization from benzene–hexane and methanol–water followed by sublimation at 100° (50 μ), melted at 121°; ultraviolet absorption: λ_{max} 224 mμ (ϵ 25,400), 258 (14,200), 328 (2,800); in methanol 0.1 *M* in sodium hydroxide; λ_{max} 236 mμ (ϵ 25,400), 285 (8,200), 316 (9,500); in methanol 0.1 *M* in hydrochloric acid: λ_{max} 224 mμ (ϵ 25,000), 258 (14,200), 290sh. (4,700).

Anal. Calcd. for $C_{10}H_{13}O_5N$: C, 52.9; H, 5.8; N, 6.2; OC_2H_5, 39.6. Found: C, 52.9; H, 5.7; N, 6.0; OC_2H_5, 39.3.

Diethyl 3-Methoxypyrrole-2,4-dicarboxylate (XXII).—A solution of 6.90 g. (34 mmoles) of crude diethyl 3-hydroxypyrrole-2,4-dicarboxylate (XXI) in 50 ml. of methanol and 150 ml. of ether was treated with diazomethane generated from 0.1 mole of N-methyl-N-nitroso-*p*-toluenesulfonamide. After standing for 5 hours the ethereal solution was extracted with 75 ml. of 2 *M* sodium bicarbonate solution. From the organic phase was obtained 7.31 g. of material which, by chromatography on 125 g. of activity III alumina, was separated into three distinct bands, A, B and C.

Elution with benzene–hexane (1:1) gave an oil, A (3.79 g., 14.9 mmoles, 44%), which, after rechromatography followed by short path distillation at 100° (300 μ), crystallized on standing and was found to be **diethyl 2-methoxypyrrole-3,5-dicarboxylate (XXVI)**, m.p. 43°; ultraviolet absorption: λ_{max} 212 mμ (ϵ 26,000), 255sh. (11,600), 274 (16,200); in the infrared there was no N–H or OH absorption.

Anal. Calcd. for $C_{12}H_{17}O_5N$: C, 56.5; H, 6.7; N, 5.5; OR, 3.00/255. Found: C, 56.5; H, 6.6; N, 5.4; OR, 3.09/255.

Further elution with the same solvent gave crystalline *B* (0.27 g., 1.06 mmoles, 3%) which, after two crystallizations from hexane followed by sublimation at 100° (50 μ), melted at 50° and was found to be **diethyl 1-methyl-3-methoxypyrrole-2,4-dicarboxylate (XXIII)**; ultraviolet absorption: λ_{max} 223 mμ (ϵ 33,900), 259 (12,800); in the infrared there was no N–H or O–H absorption.

Anal. Calcd. for $C_{12}H_{17}O_5N$: C, 56.5; H, 6.7; N, 5.5; OR, 3.00/255. Found: C, 56.6; H, 6.7; N, 5.2; OR, 3.06/255.

Elution with benzene–chloroform (1:1) gave C, 2.83 g. (11.8 mmoles, 35%) of **diethyl 3-methoxypyrrole-2,4-dicarboxylate (XXII)**, which, after two recrystallizations from benzene–hexane and sublimation at 80° (50 μ), melted at 83°; ultraviolet absorption: λ_{max} 202 mμ (ϵ 30,000), 258 (13,800).

Anal. Calcd. for $C_{11}H_{15}O_5N$: C, 54.8; H, 6.3; N, 5.8; OR, 3.00/241. Found: C, 55.0; H, 6.3; N, 5.9; OR, 3.03/241.

1-Methyl-2-methoxy-3-ethoxycarbonylpyrrole-5-carboxylic Acid (XXVIII).—A solution of 4.08 g. (16.0 mmoles) of diethyl 2-methoxypyrrole-3,5-dicarboxylate (XXVI), in 10 ml. of ethanol and 17.6 ml. of 1 *M* aqueous sodium hydroxide was allowed to stand at room temperature for 12 hours. Dilution with 50 ml. of water followed by extraction with chloroform (2 × 10 ml.) removed neutral and basic material. The aqueous phase then was acidified with concd. phosphoric acid and extracted with ether (3 × 60 ml.) to give 2.77 g. (12.2 mmoles, 76%) of crystalline 1-methyl-2-methoxy-3-ethoxycarbonylpyrrole-5-carboxylic acid (XXVIII). After two recrystallizations from methanol and sublimation at 150° (30 μ) it melted at 199–200° dec.; ultraviolet absorption: λ_{max} 269 mμ (ϵ 13,400), 257sh. (11,000); in methanol 0.1 *M* in sodium hydroxide: λ_{max} 264 mμ sh. (ϵ 12,100), 253 (13,300).

Anal. Calcd. for $C_{10}H_{13}O_5N$: C, 52.9; H, 5.8. Found: C, 53.2; H, 6.0.

Ethyl 1-Methyl-2-methoxypyrrole-3-carboxylate (XXIX).—In a sublimation apparatus was placed 476 mg. (2.10 mmoles) of 1-methyl-2-methoxy-3-ethoxycarbonylpyrrole-5-carboxylic acid (XXVIII). Heating with a free flame at 50 mm. caused decarboxylation and distillation of the product to the cold finger. The residue and distillate were taken up in 20 ml. of chloroform and washed with 20 ml. of sodium carbonate solution. Drying and evaporation of the organic phase gave 359 mg. (2.01 mmoles, 96%) of ethyl 1-methyl-2-methoxypyrrole-3-carboxylate (XXIX), which was distilled at 100° (3 mm.); ultraviolet absorption: λ_{max} 257 mμ (ϵ 6,200), 225 (8,100).

Anal. Calcd. for $C_9H_{13}O_3N$: C, 59.0; H, 7.2. Found: C, 58.7; H, 7.2.

1-Methyl-2-methoxypyrrole-3-carboxylic Acid (XXX).—A solution of 1.63 g. (8.90 mmoles) of ethyl 1-methyl-2-methoxypyrrole-3-carboxylate (XXIX) in 10 ml. of 8 *M* sodium hydroxide, diluted with 15 ml. of ethanol, was heated on the steam-bath for 30 minutes. The resulting solution was diluted with 50 ml. of water and extracted with chloroform (2 × 25 ml.). The aqueous phase was acidified with phosphoric acid and extracted with ether (4 × 30 ml.) to give 0.86 g. (5.56 mmoles, 65%) of 1-methyl-2-methoxypyrrole-3-carboxylic acid (XXX) which was sublimed at 70° (70 μ) and crystallized from benzene–hexane; m.p. 111–112° dec.; ultraviolet absorption: λ_{max} 255 mμ (ϵ 5,800), 224 (8,000); in methanol 0.1 *M* in sodium hydroxide: λ_{max} 244 mμ sh. (ϵ 5,500).

Anal. Calcd. for $C_7H_9O_3N$: C, 54.2; H, 5.9. Found: C, 54.6; H, 6.1.

1-Methyl-2-methoxypyrrole (XXXI).—In a small distillation flask was placed 292 mg. (1.88 mmoles) of 1-methyl-2-methoxypyrrole-3-carboxylic acid (XXX). Careful heating with an open flame caused decarboxylation and distillation. The distillate of 1-methyl-2-methoxypyrrole (XXXI) (147 mg., 1.33 mmoles, 70%) was distilled at 120°; ultraviolet absorption: λ_{max} 222 mμ (ϵ 6,714); immediate rose-red color with Ehrlich reagent.

Anal. Calcd. for C_6H_9ON: C, 64.8; H, 8.2; OCH_3, 27.9. Found: C, 64.9; H, 8.0; OCH_3, 27.6.

Methyl 4-Methoxypyrrole-3-carboxylate (XXXIII).—A mixture of 294 mg. (1.22 mmoles) of diethyl 3-methoxypyrrole-2,4-dicarboxylate (XXII) and 4 g. of potassium hydroxide in 12 ml. of water was boiled under nitrogen for 4 hours. The cooled reaction mixture was acidified to *p*H 3 with concd. phosphoric acid and extracted with ether (4 × 35 ml.). After drying and evaporating the ether, the white crystalline residue (m.p. 203–204°) was found to be identical with **4-methoxypyrrole-3-carboxylic acid (XXXII)**.[15] On treatment of this material with diazomethane, 49 mg. (0.316 mmole, 36%) of methyl 4-methoxypyrrole-3-carboxylate (XXXIII) was formed, which, after sublimation at 110° (500 μ) and recrystallization from benzene–hexane, melted at 122° (reported[15] m.p. 115–117°) and had ultraviolet and infrared absorption spectra identical with those of an authentic sample.[15]

Ethyl 4-Methoxypyrrole-3-carboxylate (XXXV).—A solution of 133 mg. (0.55 mmole) of diethyl 3-methoxypyrrole-2,4-dicarboxylate (XXII) in 5.80 ml. (0.58 mmole) of 0.1 *N* sodium hydroxide and 5 ml. of ethanol, after standing at room temperature for 12 hours, was diluted with 30 ml. of water and extracted with ether (3 × 20 ml.) to give 53 mg. (40%) of recovered starting material. The aqueous phase was acidified with concd. phosphoric acid and extracted with ether (3 × 20 ml.) to give 52 mg. (0.244 mmole, 44%) of **4-ethoxycarbonyl-3-methoxypyrrole-2-carboxylic acid (XXXIV)**, m.p. 143–145° dec.; ultraviolet absorption: λ_{max} 258 mμ (ϵ 11,100), 219 (27,900); in methanol 0.1 *M* in sodium hydroxide: λ_{max} 261 mμ (ϵ 11,100). On heating above its melting point this material decarboxylated to ethyl 4-methoxypyrrole-3-carboxylate (XXXV), which was identical with the same material prepared by an alternate route.[15]

2-Ethoxycarbonyl-3-methoxypyrrole-4-carboxylic Acid (XXXVI).—A solution of 6.7 g. (25.2 mmoles) of diethyl 3-methoxypyrrole-2,4-dicarboxylate (XXII) in 20 ml. of concd. sulfuric acid was maintained at 35° for 12 hours. The acid solution then was poured into 250 ml. of ice and water and basified with sodium hydroxide. Extraction with ether (3 × 75 ml.) gave 1.46 g. (6.05 mmoles, 24%) of recovered starting material. When the aqueous phase was acidified to *p*H 3 with concd. phosphoric acid and extracted with ether (3 × 75 ml.), 3.16 g. (14.8 mmoles, 59%) of 2-ethoxycarbonyl-3-methoxypyrrole-4-carboxylic acid (XXXVI) was obtained. Continuous extraction with ether yielded an additional 0.79 g. to give a total of 3.95 g. (18.5 mmoles,

74%) of the acid, m.p. 178° dec.; ultraviolet absorption: λ_{max} 218 mμ (ε 27,400), 260 (13,700); in methanol 0.1 *M* in sodium hydroxide: λ_{max} 265 mμ (ε 16,900).

Anal. Calcd. for $C_9H_{11}O_5N$: C, 50.7; H, 5.2; equiv. wt., 213. Found: C, 50.9; H, 5.2; equiv. wt., 214.

Ethyl 3-Methoxypyrrole-2-carboxylate (XIV).—Crude 2-ethoxycarbonyl-3-methoxypyrrole-4-carboxylic acid (XXXVI) (3.95 g., 18.5 mmoles) was heated at 200° for 3 hours in a sublimation apparatus at 50 mm. The sublimate was recrystallized from benzene–hexane and resublimed at 80° (1 mm.) to give 2.24 g. (13.2 mmoles, 72%) of ethyl 3-methoxypyrrole-2-carboxylate (XIV), m.p. 94°; ultraviolet absorption: λ_{max} 264 mμ (ε 17,600).

Anal. Calcd. for $C_8H_{11}O_3N$: C, 56.8; H, 6.6. Found: C, 56.7; H, 6.8.

Ethyl 4-Methoxy-2,2′-bipyrrole-5-carboxylate (XXXVIII).—A solution of 2.24 g. (13.2 mmoles) of ethyl 3-methoxypyrrole-2-carboxylate (XIV) in 50 ml. of ethanolic Δ^1-pyrroline[16] (prepared from 0.1 mole of pyrrolidine) was heated at 150° in a sealed tube for 36 hours. The ethanol then was distilled under reduced pressure and the residue was distributed between water (75 ml.) and ether (50 ml.). The aqueous phase was extracted with additional portions of ether (3 × 50 ml.) and the combined ethereal extracts were dried and evaporated to give 3.66 g. of oily material. Chromatography on 60 g. of activity III alumina gave recovered starting material (1.09 g., 6.5 mmoles, 49%), eluted with benzene–hexane (1:1), and **ethyl 3-methoxy-5-(2′-pyrrolidinyl)-pyrrole-2-carboxylate (XXXVII)** (0.407 g., 1.71 mmoles, 13%), eluted with benzene–chloroform (3:1), m.p. 117–120°; ultraviolet absorption in methanol: λ_{max} 272 mμ (ε 25,200); in methanol 0.1 *M* in hydrochloric acid: λ_{max} 266 mμ (ε 21,700). A mixture of 200 mg. (0.84 mmole) of this material, 300 mg. of 5% palladium-on-carbon and 5 ml. of *p*-cymene was heated at reflux, with stirring under a nitrogen sweep for 30 minutes. The cooled reaction mixture was filtered and the catalyst was washed with several portions of warm chloroform. The chloroform was evaporated from the combined filtrates under reduced pressure causing the product to crystallize from the residual *p*-cymene. Recrystallization from benzene–hexene and ethanol–water followed by sublimation at 140° (20 μ) gave 162 mg. (0.69 mmole, 82%) of pure ethyl 4-methoxy-2,2′-bipyrrole-5-carboxylate (XXXVIII), m.p. 214°; ultraviolet absorption: λ_{max} 241 mμ (ε 12,600), 322 (31,700).

Anal. Calcd. for $C_{12}H_{14}O_3N_2$: C, 61.5; H, 6.0. Found: C, 61.2; H, 6.2.

4-Methoxy-2,2′-bipyrrole-5-carboxaldehyde (VIII) was prepared by the same method used to prepared 3-methoxy-2,2′-bipyrrole-5-carboxaldehyde (IX). Starting with 171 mg. (0.73 mmole) of ethyl 4-methoxy-2,2′-bipyrrole-5-carboxylate (XXXVIII) there was obtained 140 mg. (0.64 mmole, 87%) of the **hydrazide**, whose ***p*-toluenesulfonyl derivative** (216 mg., 0.58 mmole, 91%) yielded 35 mg. (0.18 mmole, 32%) of 4-methoxy-2,2′-bipyrrole-5-carboxaldehyde (VIII). The latter, after sublimation at 130° (30 μ) and recrystallization from ethanol–water, melted at 265° dec.; ultraviolet absorption: λ_{max} 251 mμ (ε 14,700), 361 (40,300).

Anal. Calcd. for $C_{10}H_{10}O_2N_2$: C, 63.2; H, 5.3. Found: C, 63.5; H, 5.6.

2-Methyl-3-amylpyrrole (XLII) and 2-Butyl-3-ethylpyrrole (XLIII).—A sample of pure 3-octanone was oximinated by the procedure described[5d] to give the oximinoketone, b.p. 105° (5 mm.) (reported[5d] b.p. 130° (10 mm.)). Vapor phase chromatography (200°, silicone) separated this product into two oximinoketones present in the ratio of about 15:1,[30] and both of these compounds were cleaved to acid and nitrile.[22] The major product, 2-oximino-3-octanone (XL), gave acetonitrile and caproic acid; the minor product XLI gave propionic acid and valeronitrile; and the original mixture of oximinoketones by this procedure gave a mixture of caproic acid and propionic acid (15:1) and acetonitrile and valeronitrile. In each case identity was established by comparison with authentic samples.

Reduction of the mixture of oximinoketones and condensation with diethyl oxaloacetate[5d] gave the 3-carbethoxypyrrole-2-carboxylic acids, from which the β-carbethoxyl group was removed by boiling in 30% aqueous potassium hydroxide for 12 hr. The α-acids ($\lambda_{max}^{CH_3OH}$ 283 mμ) were decarboxylated by sublimation at 180° (10 mm.) to give a mixture of 2-methyl-3-amylpyrrole (XLII) and 2-butyl-3-ethylpyrrole (XLIII), b.p. 110–115° (10 mm.) (reported b.p. 120–125° (10 mm.)[5d] and 119° (15 mm.)[6] for 2-methyl-3-amylpyrrole). This mixture was separated by vapor phase chromatography (160°, 50 ml./min. flow rate, silicone column) into a minor fraction XLIII, retention time 5.3 min., and a major fraction XLII, retention time 7.9 min. Both compounds gave positive Ehrlich tests and showed end-absorption typical of alkylpyrroles in the ultraviolet.

Prodigiosin (I).—A solution of 9.6 mg. (0.0505 mmole) of 4-methoxy-2,2′-bipyrrole-5-carboxaldehyde (VIII) and 1 drop of 2-methyl-3-amylpyrrole (XLII) in 20 ml. of methanol was treated with 1 drop of concd. hydrochloric acid. The reddish-purple solution that formed was allowed to stand for 2 days. After most of the solvent was removed *in vacuo*, the residue was distributed between dilute aqueous ammonium hydroxide and ether. The aqueous phase was extracted with a few additional portions of ether, and the combined organic extracts, after drying, were evaporated to dryness under reduced pressure. The residue was taken up in hexane and applied to 2 g. of activity III alumina. Elution with benzene–hexane (1:1) gave 9.0 mg. (0.0275 mmole, 55%) of the pyrryldipyrrylmethene (I) which was identical in all respects on direct comparison with a sample of natural prodigiosin.[11,23] Similarly, condensation of 4-methoxy-2,2′-bipyrrole-5-carboxaldehyde (VIII) with 2-butyl-3-ethylpyrrole (XLIII) gave the isomer **XLIV**, while 3-methoxy-2,2′-bipyrrole-5-carboxaldehyde (IX) and 2-methyl-3-amylpyrrole (XLII) condensed to give **II**, also isomeric with prodigiosin; ultraviolet absorption, see Table II.

(30) Wrede and Rothhass[5d] identified their product as 2-oximino-3-octanone by preparation of the known 2,3-dioxime. However, it is conceivable that in the purification by recrystallization, the small amount of 3,4-isomer could have been lost.