urnished 18,19-dihydro-19-corynantheone[37] (31 mg.), m.p. 223–25°. Further elution with ether–methanol (9:1) gave ajmaliciol (32 mg.).

The ketone so obtained was exposed to a Wolff–Kishner reduction as described previously[17a] except that the reaction time was reduced from 4 to 3.25 hours resulting in a consistent 62% yield of dihydrocorynantheane.

N_a-Methylyohimbane.[38]—To yohimbane (60 mg.) in dry benzene (4 ml.) potassium (10 mg.) was added and the mixture was stirred under reflux in a nitrogen atmosphere for several hours, until the metal was consumed. The suspension was cooled to room temperature and treated with an excess of methyl iodide in benzene. The reaction mixture was stirred overnight and the precipitate (120 mg.) of potassium iodide and N_a-methylyohimbane methiodide was collected and dried. When this mixture (40 mg.) was heated at 280–300° *in vacuo*, it gave a sublimate which afforded N_a-methylylohimbane, m.p. 178–179° (lit. 179°) from methanol. The total yield after processing all the salt mixture was 38 mg.

N_a-Methylylohimbane with excess methyl iodide in benzene gave the methiodide, m.p. 287–288° (lit. 288–289°). Repetition of the above vacuum pyrolysis at 280–300° regenerated the tertiary base.

N_a-Methyldihydrocorynantheane.—Following the procedure described above, dihydrocorynantheane (10 mg.) in dry benzene (4 ml.) was treated with potassium (6 mg.). Two additions of methyl iodide (0.5 ml.) at 45-minute intervals to the resulting potassium salt gave after 15 hours a white precipitate (20 mg.). Pyrolysis of this *in vacuo* at 340° gave a crystalline sublimate (6 mg.) which afforded N_a-methyldihydrocorynantheane, m.p. 109–110.5°, $[\alpha]_D$ −22°, from aqueous methanol.

Anal. Calcd. for $C_{20}H_{28}N_2$: C, 81.03; H, 9.52; N, 9.45. Found: C, 79.71; H, 9.52; N, 9.24.

N_a-Methylcorynantheidane.—Corynantheidane (60 mg.) was converted by the procedure above into its potassium derivative in dry benzene and alkylated with excess methyl iodide. A portion (50 mg.) of the crude salt mixture (127 mg.) was vacuum pyrolyzed at 280–320° to furnish an oily sublimate. This was dissolved in 5% acetic acid and treated with a few drops of perchloric acid to give N_a-methylcorynantheidane perchlorate (25 mg.), m.p. 208–210° after recrystallization from methanol.

Anal. Calcd. for $C_{20}H_{28}N_2 \cdot ClO_4 \cdot CH_3OH$: C, 57.78; H, 7.89. Found: C, 57.54; H, 7.48.

N_a-Methyl-3,4,5,6-tetradehydroyohimbane Perchlorate. (a).—N_a-Methylyohimbane (20 mg.) was catalytically dehydrogenated in an aqueous solution on a steam-bath by palladium black (10 mg.) using maleic acid (40 mg.) as an acceptor. The hot reaction mixture was filtered and gave upon addition of perchloric acid N_a-methyl-3,4,5,6-tetradehydroyohimbane perchlorate, m.p. 250–251°.

(b).—3,4,5,6-Tetradehydroyohimbane perchlorate (20 mg.) was dissolved in a small volume of methanol and treated with a few drops of 10% sodium hydroxide. The deep yellow solution was diluted with water until a precipitate began to form and then was extracted with ether. The extract was dried, evaporated and the residue in dry benzene was treated with 2 drops of methyl *p*-toluenesulfonate. The resultant precipitate (9 mg.) had m.p. 205°. It was dissolved in a minimum of methanol and treated with perchloric acid to furnish N_a-methyl-3,4,5,6-tetradehydroyohimbane perchlorate, m.p. 250–251° after crystallization from methanol. The perchlorate could also be obtained by passing a solution of the *p*-toluenesulfonate through a column of Amberlite resin [CG45 (ClO_4)].

Anal. Calcd. for $C_{20}H_{23}N_2 \cdot ClO_4$: C, 59.64; H, 6.43; N, 6.62. Found: C, 59.37; H, 6.24; N, 6,58.

***d-trans*-2,3-Diethyl-1,2,3,4-tetrahydro-12-methylindolo-[2,3-a]quinolizinium Perchlorate (*trans*-X).** (a).—N_a-Methyldihydrocorynantheane (5 mg.), maleic acid (10 mg.) and palladium black (4 mg.) were heated in water on a steam-bath with stirring for 13 hours. Filtration and then addition of perchloric acid to the cooled solution gave the perchlorate (4 mg.), m.p. 198–200°, $[\alpha]_D$ +15°, after crystallization from aqueous methanol.

(b).—Dihydrocorynantheane (90 mg.) was heated in a sealed evacuated tube with palladium black (90 mg.), maleic acid (200 mg.) and water (4 ml.) for 36 hours, when the ultraviolet absorption spectrum indicated that conversion to the tetradehydro compound was complete. After filtration and basifying with 25% sodium hydroxide, the anhydro compound was extracted into methylene chloride which was dried and evaporated. The residue was heated with methyl bromide for 10 minutes in a sealed tube at 100°, then dissolved in water and a drop of perchloric acid was added. The perchlorate recrystallized from aqueous ethanol had m.p. 200°, $[\alpha]_D$ +5° (4MeOH–1$CHCl_3$).

Anal. Calcd. for $C_{20}H_{25}N_2 \cdot ClO_4$: C, 61.14; H, 6.41. Found: C, 61.4; H, 6.5.

Both synthetic samples had infrared spectra identical with the degradation product of isoajmaline and the mixed m.p.'s showed no depression.

1-*cis*-2,3-Diethyl-1,2,3,4-tetrahydro-12-methylindolo[2,3-a]quinolizinium Perchlorate (X).—A portion (30 mg.) of the salt mixture obtained above from the methylation of corynantheidane was vacuum pyrolyzed at 300–340°. The oily sublimate was dissolved in alcohol and added to an aqueous solution of maleic acid (60 mg.) and suspended palladium black (20 mg.). The whole was heated on a steam-bath for 16 hours. The solution was filtered hot and the filtrate plus hot water washings were concentrated to remove most of the ethanol. The cooled solution was treated with perchloric acid to yield the β-carbolinium perchlorate (13 mg.). Recrystallization from aqueous methanol gave the pure salt, m.p. 212–214°, $[\alpha]_D$ −27° ($CHCl_3$). The infrared spectrum was identical with the degradation product derived from ajmaline and the mixed m.p. showed no depression.

(37) This ketone was refluxed in methanolic sodium methoxide and recovered unchanged. As a consequence, its previously assumed stereochemistry (*vide* iii) has been corroborated.

(38) Similar to a procedure described by B. Witkop [*J. Am. Chem. Soc.*, **75**, 3361 (1953)] for the same compound.

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

The Preparation and Properties of Some Methoxypyrroles

BY HENRY RAPOPORT AND CLYDE D. WILLSON[1]

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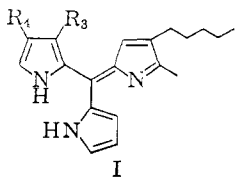
Using ethyl glycinate-1-^{14}C derivatives, a series of cyclizations by which these compounds yield 3-pyrrolidones has been shown to involve the carbonyl and not the methylene group of the glycine residue. Dimethyl ketals or methoxypyrrolines derived from these pyrrolidones give methoxypyrrolecarboxylic acids on catalytic dehydrogenation. From these acids and others, several unsymmetrical dipyrryl ketones also have been prepared. A comparison of the spectral properties of these compounds with those of the prodigiosin precursor showed that the prodigiosin precursor could not be a methoxydipyrryl ketone.

At one stage prior to the synthesis of prodigiosin,[2] we had considered various approaches to the synthesis of the then postulated tripyrrylmethene structure I, for prodigiosin. The key substance

(1) Public Health Service Predoctoral Research Fellow of the National Institute of Mental Health, 1958–1960.

(2) H. Rapoport and K. G. Holden, *J. Am. Chem. Soc.*, **84**, 635 (1962).

in our consideration was the compound $C_{10}H_{10}N_2O_2$, which had been clearly established as a prodigiosin precursor[3] and differed from prodigiosin by the elements of methylamylpyrrole. This precursor of necessity would have a pyrryl methoxypyrryl ketone structure, II, if the tripyrrylmethene structure were correct. The published properties of this precursor did not appear inconsistent with such a structure, although no methoxypyrryl ketones were known at that time. For these reasons we undertook and here report the preparation of some methoxypyrroles and related ketones.



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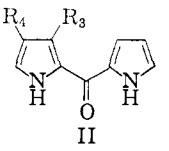


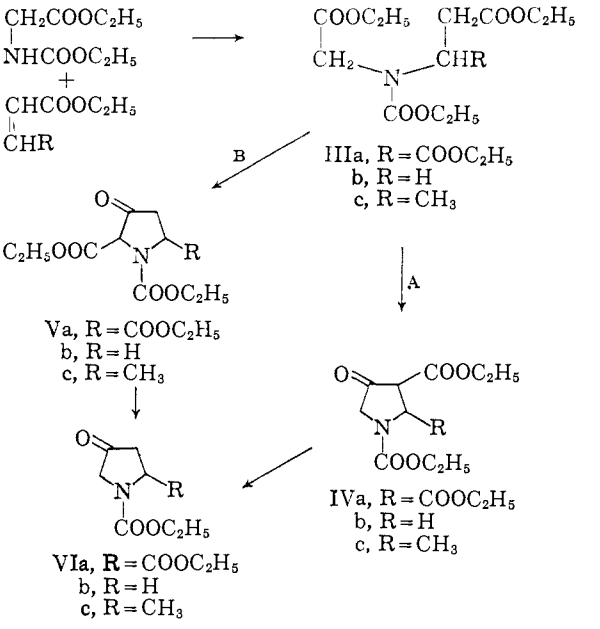
II

a, R_3 = OCH_3, R_4 = H
b, R_3 = H, R_4 = OCH_3

Two methods are available for the preparation of unsymmetrical dipyrryl ketones, both involving the reaction of a pyrrolecarboxylic acid chloride with a second pyrrole, either under Friedel–Crafts conditions[4,5] or with the pyrryl Grignard reagent.[6,7] Thus the corresponding methoxypyrrolecarboxylic acids were needed, and a promising approach appeared to be present in suitable modifications of the method of Kuhn and Osswald[8] who had reported the synthesis of 4-ethoxypyrrole-2-carboxylic acid.

Their procedure involved as the first step condensation of ethyl N-ethoxycarbonylglycinate and diethyl fumarate to give the reported diethyl 1-ethoxycarbonyl-4-oxopyrrolidine-2,3-dicarboxylate (IVa) directly. This condensation is capable of yielding either of two isomers (IVa and Va), or a mixture of both. Since their subsequent objective was the decarboxylated ketone VIa, it was not necessary to prove the structure of the intermediate pyrrolidone. However, in order to extend this method to the synthesis of other alkoxypyrrole acids, it was essential to know the direction of ring closure in this type of reaction.

We therefore utilized ethyl N-ethoxycarbonylglycinate-1-^{14}C in these syntheses with three different α,β-unsaturated esters, going directly to the ring-closed product and decarbethoxylating the resulting β-ketoesters. The carbon dioxide evolved, and the pyrrolidones resulting from these decarbethoxylations were then analyzed for radioactivity. In every case the carbon dioxide was inactive and essentially all of the activity remained in the pyrrolidones. Therefore, with each compound, the direction of ring closure was the same and exclusively that shown by arrow A, rather than the alternative direction B. Similarly, ring closure of the isolated ^{14}C-labeled triester IIIb in sodium ethoxide–ethanol solution yielded only the pyrrolidone IVb. Thus this method, although applicable for the ultimate synthesis of 4-alkoxypyrrole-2-carboxylic acids (derivable from IVa) and 4-alkoxypyrrole-3-carboxylic acids (derivable from IVb, c), was not adaptable for the synthesis of 3-alkoxypyrrole-2-carboxylic acids, for which the unrealized isomer V would be needed.

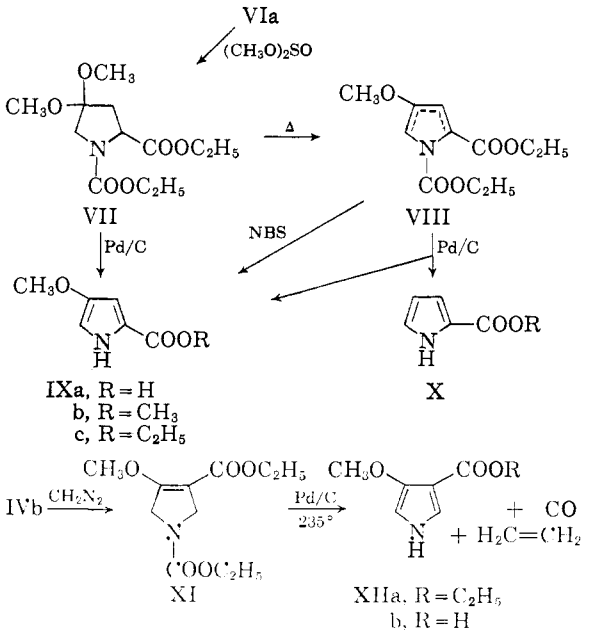


Conversion of the ethyl 1-ethoxycarbonyl-4-oxopyrrolidine-2-carboxylate (VIa) to the corresponding pyrrole paralleled the known procedure[8] through the dimethyl ketal VII, which could be thermally converted to a mixture of the various possible methyl enol ethers VIII. The final aromatization to the 4-methoxypyrrole-2-carboxylic acid (IXa), using the recommended N-bromosuccinimide, however, proceeded in much poorer yield than was reported[8] for the homologous 4-ethoxy compound. Direct catalytic dehydrogenation of the mixed enol ethers VIII in various solvents also gave low yields of a mixture of methoxy methyl ester IXb and the demethoxylated methyl ester X, isolated by hydrolysis and re-esterification with diazomethane.

However, catalytic dehydrogenation of the ketal VII resulted in the direct formation of ethyl 4-methoxypyrrole-2-carboxylate (IXc), probably arising by cracking of the 1-ethoxycarbonyl group (see below). Hydrolysis and esterification with diazomethane gave pure methyl 4-methoxypyrrole-2-carboxylate (IXb) in reasonable yield.

The same type of pyrrolidone intermediate was utilized for the synthesis of 4-methoxypyrrole-3-carboxylic acid (XIIb). For this purpose, the β-ketoester IVb was treated with diazomethane to form the methyl enol ether XI, and this was dehydrogenated directly to ethyl 4-methoxypyrrole-3-carboxylate (XIIa) by heating at 235° with palladium-on-carbon. During the dehydrogenation ethylene and carbon monoxide were evolved, undoubtedly arising by cracking of the 1-ethoxycarbonyl group.

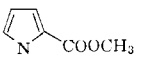
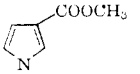
(3) U. V. Santer and H. J. Vogel, *Federation Proc.*, **15**, 1131 (1956); *Biochem. Biophys. Acta*, **19**, 578 (1956).
(4) H. Fischer and H. Orth, *Ann.*, **502**, 237 (1933).
(5) R. Huisgen and E. Laschtuvka, *Ber.*, **93**, 65 (1960).
(6) V. V. Chelintsev and D. K. Skvortzov, *J. Russ. Phys. Chem. Soc.*, **47**, 170 (1915).
(7) B. Oddo, *Gass. chim. ital.*, **50**, 267 (1920).
(8) R. Kuhn and G. Osswald, *Ber.*, **89**, 1423 (1956).



Since the direction of pyrrolidone formation precluded the preparation of any other isomeric methoxypyrrole acids by this procedure, the further compounds desired for comparison were prepared by the reaction of ethyl N-ethoxycarbonylglycinate with diethyl ethoxymethylenemalonate.[2] These were a 2-methoxy pyrrole-3-carboxylic ester, and 3-methoxy- and 5-methoxypyrrole-2-carboxylic esters. The position of longest wave length absorption for the various methoxypyrrole esters is presented in Table I along with the corresponding values for the methyl analog. It can be seen that in practically every instance the effect of the methyl and methoxyl substituent is quite similar. In those cases (eight of the thirteen compounds) where the acid was also measured, it was found to show a hypsochromic shift of 2–5 mμ.

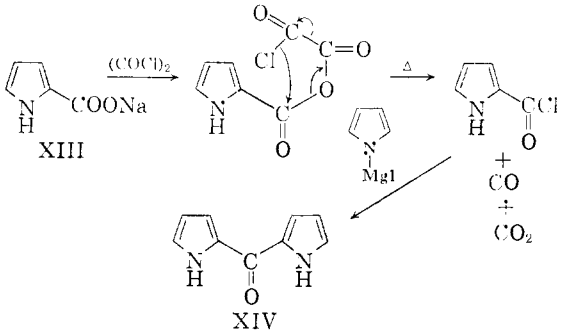
TABLE I

ULTRAVIOLET ABSORPTION[a] OF SOME PYRROLE CARBOXYLIC ESTERS: COMPARISON OF THE EFFECT OF METHYL AND METHOXYL SUBSTITUENTS

Compound	λ_{max}, mμ	Compound	λ_{max}, mμ
	264		247[e]
3-CH_3	268[b]	2-CH_3	255[a]
3-OCH_3	264[c]	2-OCH_3, 1-CH_3	257[c]
4-CH_3	272[d]	4-CH_3	227[d]
4-OCH_3	286	4-OCH_3	234
5-CH_3	278[b]	5-CH_3	262[b]
5-OCH_3, 1-CH_3	286[c]		

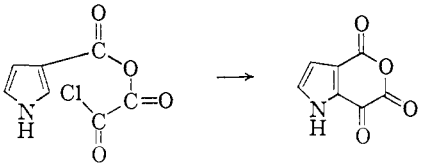
[a] In methanol. [b] M. Scrocco and R. A. Nicolaus, *Atti accad. naz. Lincei, Rend., Classe sci. fis., mat. e. nat.*, **22**, 311 (1957). [c] Ref. 3. [d] R. Oesterlin, unpublished observations, this Laboratory. [e] Ref. 13.

We next turned our efforts to the synthesis of some methoxypyrryl pyrryl ketones. For this purpose, the corresponding acid chlorides were needed, and in the past these have been prepared from the acids by the action of thionyl chloride or phosphorus pentachloride. It was immediately clear that the methoxypyrroles would not withstand such vigorous treatment. A feasible alternative was found in the use of oxalyl chloride.[9] Formation of acid chloride may be followed conveniently by carbon dioxide evolution as the sodium salt of the acid is warmed with oxalyl chloride. Without isolation of the acid chloride, the solution is then treated with the pyrryl Grignard reagent to form the resultant dipyrryl ketone. When applied to the sodium salt of pyrrole-2-carboxylic acid (XIII), 100 mole per cent. of carbon dioxide was evolved and a 95% yield of 2,2′-dipyrryl ketone (XIV) was obtained. However,



with pyrrole-3-carboxylic acid and 4-methoxypyrrole-2-carboxylic acid only about 50 mole per cent. of carbon dioxide was evolved and the yields of 2,3′-dipyrryl ketone (XV) and 4-methoxy-2,2′-dipyrryl ketone (IIb) were correspondingly lower.

We have attempted to explain these differences, and particularly the decreased carbon dioxide evolution, by postulating an intramolecular cyclization to the easily substituted α-position in the case of the β-acid

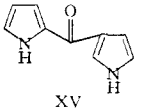


Such a cyclization might also occur to the β-position in the more nucleophilic methoxypyrrole.

We have summarized the physical properties of the dipyrryl ketones and prodigiosin precursor in Table II. Obviously, the methoxydipyrryl ketone

TABLE II

PROPERTIES OF SOME DIPYRRYL KETONES

Ketone	M.p., °C.	λ_{max}, mμ[a] (ε)	Carbonyl absorption, mμ[b]
XIV	160–161	257 (5,350) 334 (25,000)	6.26
 XV	99–100	249 (7,500) 312 (16,680)	6.22
IIb	130–131	260 (6,140) 347 (20,730)	6.27
Prodigiosin precursor[c]	>250 dec.	254 (13,000) 363 (35,000)	Amide (?)

[a] In methanol. [b] In chloroform. [c] Ref. 3.

(9) A. L. Wilds and C. H. Shunk, *J. Am. Chem. Soc.*, **70**, 2427 (1948)

IIb is quite different from prodigiosin precursor, and by interpreting the data of Table II in conjunction with those of Table I it is possible to predict that the isomeric ketone, 3-methoxy-2,2′-dipyrryl ketone (IIa) will also be quite different from prodigiosin precursor.

Thus, the effect of the 4-methoxy substituent on the ultraviolet absorption of methyl pyrrole-2-carboxylate (Table I) is a bathochromic shift in the long wave length maximum of 22 mμ. Correspondingly, the effect of a 4-methoxy group on the spectrum of 2,2′-dipyrryl ketone is a bathochromic shift of 13 mμ. In the isomeric series, there was no effect on the position of maximum absorption of methyl pyrrole-2-carboxylate when substituted with a 3-methoxy group, both compounds absorbing at 264 mμ. Correspondingly, the long wave length maximum of 3-methoxy-2,2-dipyrryl ketone would be expected to differ only slightly if at all from that of 2,2′-dipyrryl ketone itself, which differs considerably from the reported[3] values for prodigiosin precursor (Table II).

From these considerations, we concluded that prodigiosin precursor could not be either methoxydipyrryl ketone II, and that the tripyrrylmethene structure (I) for prodigiosin was untenable.

Experimental[10]

Diethyl 1-Ethoxycarbonyl-4-oxopyrrolidine-2,3-dicarboxylate (IVa).—The procedure of Kuhn and Osswald[8] was modified as follows: To a suspension of 8.6 g. (0.38 mole) of freshly prepared sodium sand in 1 l. of benzene was added slowly, with stirring, 66 g. (0.38 mole) of ethyl N-ethoxycarbonyl-glycinate and, after 6 hours, 65.0 g. (0.38 mole) of diethyl fumarate, dissolved in about 100 ml. of benzene, was added. The addition was completed in 15 minutes, and the suspension was allowed to stir at room temperature for 3 hours and then boiled for 30 min.

The reaction mixture then was cooled to 0°, 200 ml. of ether was added followed by 600 ml. of ice-water, and the organic phase then was removed and washed with two 200-ml. portions of ice-water. The combined aqueous solutions were washed with 250 ml. of ether and poured over a mixture of 12 ml. of concd. sulfuric acid and 150 g. of cracked ice. This mixture was extracted five times with 200-ml. portions of chloroform, and the combined chloroform extracts were washed with 100 ml. of aqueous bicarbonate, dried, and distilled to yield 70 g. (61%) of diethyl 1-ethoxycarbonyl-4-oxopyrrolidine-2,3-dicarboxylate, b.p. 175–177° (1.0 mm.) (reported[8] b.p. 175–177° (1.0 mm.)). The semicarbazone was crystallized from ethanol; m.p. 188–189° (reported[8] m.p. 183–185°).

Ethyl 1-Ethoxycarbonyl-4,4-dimethoxypyrrolidine-2-carboxylate (VII).—Ethyl 1-ethoxycarbonyl-4-oxopyrrolidine-2-carboxylate (VIa)[8] (37 g., 0.16 mole), 19.2 g. (0.175 mole) of dimethyl sulfite,[11] 100 ml. of abs. methanol and 2 drops of a satd. solution of methanolic hydrochloric acid were heated under reflux for 6 hours, then cooled and distributed between 1500 ml. of chloroform and 500 ml. of satd. aqueous bicarbonate. The aqueous portion was washed with 150 ml. of chloroform, and the chloroform extracts were combined, dried and fractionally distilled. After a small fore-run appeared at 110–120° (0.8 mm.), the main product was collected at 124–125° (0.8 mm.), yielding 41 g. (93%) of ethyl 1-ethoxycarbonyl-4,4-dimethoxypyrrolidine-2-carboxylate (VII); infrared absorption, λ_{max} 5.74(s), 5.90(s) μ.

Anal. Calcd. for $C_{12}H_{21}O_6N$: C, 52.3; H, 7.7; N, 5.1; OR, 4.00/275. Found: C, 52.3; H, 7.6; N, 5.1; OR, 3.95/275.

Methyl 4-Methoxypyrrole-2-carboxylate (IXb).—In a dehydrogenation vessel equipped with a carbon dioxide sweep inlet, reflux condenser and magnetic stirrer were placed 20.0 g. (0.073 mole) of ethyl 1-ethoxycarbonyl-4,4-dimethoxypyrrolidine-2-carboxylate (VII), 15 g. of 5% palladium-on-carbon and 50 ml. of diisopropylbenzene. This mixture was vigorously stirred and boiled (220°) for 8 hours, after which gas evolution had virtually ceased. The reaction mixture was filtered, the catalyst was washed with chloroform several times, and the combined chloroform washes and filtrates were then fractionally distilled. The mixture, boiling from 120–135° (1.5 mm.), crystallized in the receiver and was recrystallized from benzene to yield ethyl 4-methoxypyrrole-2-carboxylate (IXc), m.p. 55–58°; ultraviolet absorption, λ_{max} 238 mμ (ε 8100), 288 (10,100).

Anal. Calcd. for $C_8H_{11}O_3N$: C, 56.8; H, 6.6; N, 8.3; OR, 2.00/169. Found: C, 56.6; H, 6.6; N, 8.2; OR, 1.95/169.

In a parallel experiment only the diisopropylbenzene was distilled off from the dehydrogenation reaction mixture, the crude residue then being dissolved in a solution of 30 g. of potassium hydroxide in 250 ml. of methanol which was boiled for 1 hour. The methanol then was removed under reduced pressure and the residue was diluted with 100 ml. of water and boiled for an additional 15 minutes. The aqueous solution was then washed with two 100-ml. portions of chloroform, acidified at 5–10° to *p*H 2.5 with phosphoric acid, and extracted with five 100-ml. portions of ether. A large excess of ethereal diazomethane was added to the combined ether extracts; after standing for 5 hours, the yellow-orange solution was washed with 50 ml. of satd. aqueous bicarbonate, dried, and evaporated to a residue which was placed on a column of 120 g. of neutral alumina (activity I). Benzene and benzene–chloroform (4:1) eluted 2.6 g. of a yellow crystalline material which was sublimed at 40° (0.5 mm.) and recrystallized from methanol to yield 2.3 g. (20%) of methyl 4-methoxypyrrole-2-carboxylate (IXb), m.p. 85–86°, infrared absorption, λ_{max} 2.92(m), 5.84(m), 5.90(s), 6.31(s), 7.47(s), 9.01(s), 10.03(m), 10.39(m)μ; ultraviolet absorption, λ_{max} 237 mμ (ε 8080), 286 (10,020).

Anal. Calcd. for $C_7H_9O_3N$: C, 54.2; H, 5.9; N, 9.0; CH_3O, 40.0. Found: C, 54.1; H, 5.9; N, 9.0; CH_3O, 39.9.

Methyl Enol Ethers (VIII) of Ethyl 1-Ethoxycarbonyl-4-oxopyrrolidine-2-carboxylate (VIa).—Ethyl 1-ethoxycarbonyl-4-oxopyrrolidine-2-carboxylate (VIa)[8] (74 g., 0.32 mole), 38.5 g. (0.35 mole) of dimethyl sulfite,[11] 50 ml. of abs. methanol and 3 ml. of a satd. solution of hydrochloric acid in methanol were boiled for 6 hours, then the contents of the flask were distilled until drops of methanol ceased to distil (bath temp. 200° for 1 hour). The residue was dissolved in 400 ml. of ether, the ether solution was washed with 100 ml. of 1 *N* sodium hydroxide and 50 ml. of water, then dried and distilled at 137–142° (1.0 mm.), yielding 71 g. (93%) of a slightly yellow liquid, characterized as a mixture of the three possible methyl enol ethers VIII; infrared absorption: λ_{max} 5.73(s), 5.87(s), 6.04(m)μ; ultraviolet absorption: λ_{max} 223 mμ (ε 3500), which did not shift in 1 *N* HCl or in KOH–methanol. Gas phase chromatography on a silicone column at 183° separated this material into three peaks.

Anal. Calcd. for $C_{11}H_{17}O_5N$: C, 54.3; H, 7.0; N, 5.8; OR, 3.00/243. Found: C, 54.1; H, 7.2; N, 5.7; OR, 2.95/243.

4-Methoxypyrrole-2-carboxylic Acid (IXa).—To a solution of 5.6 g. of potassium hydroxide in 25 ml. of 50% aqueous methanol was added 3.1 g (0.02 mole) of methyl 4-methoxypyrrole-2-carboxylate (IXb), and the mixture was boiled for 1 hour. It was then distributed between 250 ml. of water and 100 ml. of ether. The aqueous phase was separated and acidified with phosphoric acid at 5–10° to *p*H 2.5, and then extracted with five 100-ml. portions of ether. The combined ether extracts were dried and evaporated to a volume of about 50 ml. and then diluted slowly with 100 ml. of chloroform. On cooling, a crystalline precipitate formed which was sublimed at 100° (0.1 mm.), yielding 2.45 g. (80%) of 4-methoxypyrrole-2-carboxylic acid (IXa), m.p.

(10) All melting points were taken on a Kofler block and are corrected; boiling points are uncorrected. Infrared spectra were taken in chloroform and ultraviolet spectra were taken in methanol. Microanalyses and pK_a determinations were performed by V. Tashinian, Microchemical Laboratory, University of California, Berkeley. Radioactivity was determined by wet combustion as barium carbonate and specific activities are reported as disintegrations/minute/millimole (d.p.m./mmole). Unless otherwise specified, a nitrogen atmosphere was maintained during all reactions.

(11) C. M. Suter and H. L. Gerhart, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, New York, 1943, p. 112.

179–180°, pK_a 4.2; infrared absorption: λ_{max} 2.97(w), 6.00(s), 632(s) μ; ultraviolet absorption: λ_{max} 235 mμ (ϵ 7970), 281 (8300), and in 0.1 *N* methanolic potassium hydroxide, 232 (7830), 270 (7970).

Anal. Calcd. for $C_6H_7O_3N$: C, 51.1; H, 5.0; N, 9.9; OCH_3, 22.0; equiv. wt., 141. Found: C, 51.3; H, 5.2; N, 10.0; OCH_3, 21.9; equiv. wt., 143.

Ethyl 1-ethoxycarbonyl-4-oxopyrrolidine-3-carboxylate (IVb) was prepared by exactly the same procedure as above for the 2,3-dicarboxylate IVa, using an equivalent amount of ethyl acrylate in place of diethyl fumarate. The product was distilled at 125–130° (0.8 mm.) and melted at 60–62° (reported[8] m.p. 59–62°); infrared absorption: λ_{max} 2.96(w), 5.69(s), 5.84–6.00(s), 6.12(s) μ, ultraviolet absorption: λ_{max} 246 mμ (ϵ 6200), in 1 *N* methanolic potassium hydroxide, 275 (14,300).

Ethyl 1-Ethoxycarbonyl-4-methoxy-Δ^3-pyrroline-3-carboxylate (XI).—A large excess of ethereal diazomethane was added to a solution of 69.0 g. (0.3 mole) of ethyl 1-ethoxycarbonyl-4-oxopyrrolidine-3-carboxylate (IVb) in 500 ml. of ether. After standing for 3 hours the reaction mixture was evaporated under reduced pressure, and the residue was dissolved in 500 ml. of ether, washed with 200 ml. of 1 *N* sodium hydroxide, dried, and fractionally distilled. Ethyl 1-ethoxycarbonyl-4-methoxy-Δ^3-pyrroline-3-carboxylate (XI) was obtained in 60 g. (83%) yield at 160–162° (2.0 mm.) and rapidly crystallized, m.p. 65–66°; infrared absorption: λ_{max} 5.85–5.95(s), 6.08(s)μ; ultraviolet absorption: λ_{max} 248 mμ (ϵ 7400).

Anal. Calcd. for $C_{11}H_{17}O_5N$: C, 54.3; H, 7.0; N, 5.8; OR, 3.00/243. Found: C, 54.0; H, 7.2; N, 5.9; OR, 3.02/243.

Ethyl 4-Methoxypyrrole-3-carboxylate (XIIa).—In a dehydrogenation vessel fitted with a stirrer, reflux condenser and carbon dioxide sweep were placed 5.0 g. (0.02 mole) of ethyl 1-ethoxycarbonyl-4-methoxy-Δ^3-pyrroline-3-carboxylate (XI), 3.0 g. of 5% palladium-on-carbon and 40 ml. of di-*n*-hexyl ether. The system was heated at 235° for 3 hours after which gas evolution had practically ceased. The reaction mixture was filtered, the catalyst was washed several times with chloroform, and the combined filtrate and washings were dried and distilled from a short-path still. The product was a viscous liquid, boiling at 130–145° (0.7 mm.), which crystallized and was recrystallized from benzene and sublimed at 103° (0.1 mm.), yielding 700 mg. (21%) of ethyl 4-methoxypyrrole-3-carboxylate (XIIa), m.p. 107–109°; infrared absorption: λ_{max} 2.91(m), 3.06(w), 5.88–5.95(s), 6.36(s) μ; ultraviolet absorption: λ_{max} 233 mμ (ϵ 12,500), 265sh (2185).

Anal. Calcd. for $C_8H_{11}O_3N$: C, 56.8; H, 6.6; N, 8.3; OR, 2.00/169. Found: C, 57.3; H, 6.4; N, 8.5; OR, 2.01/169.

The gas collected over potassium hydroxide in the eudiometer was transferred to an infrared gas cell and its infrared absorption spectrum examined; it was found to contain ethylene and carbon monoxide.

4-Methoxypyrrole-3-carboxylic Acid (XIIb).—The ester XIIa was hydrolyzed exactly as described above for the 2-carboxylate IXb. Methoxypyrrole-3-carboxylic acid (IXb) was crystallized from methanol–benzene; m.p. 203–204° dec., pK_a 5.6; ultraviolet absorption: λ_{max} 231 mμ (ϵ 10,876), 265sh (2060), in 0.1 *N* methanolic potassium hydroxide, 220sh (8230).

Anal. Calcd. for $C_6H_7O_3N$: C, 51.1; H, 5.0; equiv. wt., 141. Found: C, 51.0; H, 5.0; equiv. wt., 141.

Methyl 4-Methoxypyrrole-3-carboxylate (XIIc).—Esterification of the acid XIIb with diazomethane and crystallization of the product from ether–hexane, yielded methyl 4-methoxypyrrole-3-carboxylate (XIIc), m.p. 115–117° after sublimation at 60° (0.1 mm.); infrared absorption: λ_{max} 2.94(m), 5.88–5.94(s), 6.35(s) μ; ultraviolet absorption: λ_{max} 234 mμ (ϵ 12,070), 265sh (2240).

Anal. Calcd. for $C_7H_9O_3N$: C, 54.2; H, 5.9. Found: C, 54.4; H, 6.0.

2,2'-Dipyrryl Ketone (XIV).—A solution of 1.11 g. (10 mmoles) of pyrrole-2-carboxylic acid in a minimum quantity of water was titrated to *p*H 8.0 with 0.1 *N* sodium hydroxide and the solution was evaporated to dryness under reduced pressure and dried overnight at 100° (0.01 mm.). The anhydrous powder was suspended in 25 ml. of benzene and to this suspension immersed in an oil-bath at 50° was added 1.22 g. (9.5 millimoles) of oxalyl chloride dissolved in 25 ml. of benzene. Evolution of carbon dioxide began immediately and 97 mole per cent. was evolved in 45 minutes. At this point, 10 mmoles of pyrryl Grignard reagent (freshly prepared from pyrrole and ethylmagnesium iodide) in ether was added, the mixture was stirred for an additional 30 min. at 50°, and 30 ml. of a satd. aqueous ammonium chloride solution was added. The aqueous phase was separated and extracted with five 20-ml. portions of chloroform, these chloroform extracts were combined with the original benzene extract, the combined extracts were washed with 30 ml. of aqueous bicarbonate solution, dried and evaporated to a residue, which was recrystallized from methanol and sublimed at 120° (0.5 mm.), yielding 1.2 g. (75%) of 2,2'-dipyrryl ketone (XIV), m.p. 160–161° (reported[12] m.p. 160–161°); infrared absorption: λ_{max} 2.94(s), 6.26(s), 6.35(s), 6.45(s) μ; ultraviolet absorption: λ_{max} 257 mμ (ϵ 5350), 291sh (6630), 334 (25,000).

2,3'-Dipyrryl ketone (XV) was prepared in the same way as the 2,2'-isomer described above, starting with pyrrole-3-carboxylic acid.[13] Carbon dioxide evolution reached only 35 mole per cent. The product was purified by chromatography on alumina (neutral, activity I), eluting with benzene–chloroform, and crystallization from chloroform, from which it crystallized as the solvate. Sublimation at 50° (0.1 mm.) yielded 2,3'-dipyrryl ketone (XV), m.p. 99–100°; infrared absorption: λ_{max} 2.97(s), 6.22(s), 6.30(s); ultraviolet absorption: λ_{max} 249mμ (ϵ 7500), 312 (16,680).

Anal. Calcd. for $C_9H_8ON_2$: C, 67.5; H, 5.0; N, 17.5. Found: C, 67.4; H. 4.9; N, 17.5.

4-Methoxy-2,2'-dipyrryl ketone (IIb) was prepared in the same way as the two dipyrryl ketones above, starting with 4-methoxypyrrole-2-carboxylic acid (IXa). Carbon dioxide evolution reached 55 mole per cent. Purification on alumina (neutral, activity I), eluting with chloroform, sublimation at 100° (0.02 mm.), and crystallization from abs. ethanol gave 4-methoxy-2,2'-dipyrryl ketone (IIb), m.p. 130–131°; infrared absorption: λ_{max} 2.96(m), 6.27(s), 6.36(s)μ; ultraviolet absorption: λ_{max} 260mμ (ϵ 6140), 347 (30,730).

Anal. Calcd. for $C_{10}H_{10}O_2N_2$: C, 63.1; H. 5.3; N, 14.7; OCH_3, 16.3. Found: C, 62.7; H, 5.2; N, 14.8; OCH_3, 16.1.

Experiments with Glycine-1-^{14}C. Ethyl N-ethoxycarbonylglycinate-1-^{14}C was prepared by standard procedures[14] from glycine-1-^{14}C.

Condensations of **ethyl N-ethoxycarbonylglycinate-1-^{14}C with ethyl fumarate, ethyl acrylate and ethyl crotonate** to yield the radioactive **pyrrolidones IVa, IVb and IVc**, respectively, were carried out in benzene and in abs. ethanol.

A. Condensations in benzene have been described above with ethyl fumarate and ethyl acrylate for the preparation of IVa and IVb. In exactly the same manner, ethyl crotonate gave **ethyl 1-ethoxycarbonyl-2-methyl-4-oxopyrrolidine-3-carboxylate (IVc)**, b.p. 121–123° (1.0 mm.) (reported[8] b.p. 105–106° (0.02 mm.)).

B. Condensations in absolute ethanol were carried out by adding ethyl N-ethoxycarbonylglycinate-1-^{14}C to an equimolar solution of sodium ethoxide in ethanol. A solution of a molar equivalent of the corresponding α,β-unsaturated ester in ethanol then was added and the solution was boiled for 2 hours. Most of the ethanol was removed *in vacuo*, the residue was distributed between benzene and ice-water, the benzene phase was washed with two additional portions of water, and the combined aqueous phase acidified to *p*H 1.0. Extraction with chloroform and fractional distillation of the chloroform extracts yielded the pyrrolidones IVa, IVb and IVc in substantially the same yield as when the condensation was performed in benzene.

Alternative Preparation of Ethyl 1-Ethoxycarbonyl-4-oxo-pyrrolidine-3-carboxylate (IVb).—To a solution of 50 g. (0.36 mole) of ethyl glycinate-1-^{14}C hydrochloride in 100 ml. of ice-water was added 36 ml. of cold 1 *N* sodium hydroxide solution and then 60 g. of ethyl β-bromopropionate, 210 ml. of methanol and a solution of 24 g. of potassium carbonate in 275 ml. of water. After being stirred at room temperature for 24 hours, the solution was concentrated *in vacuo* to 400 ml., diluted with 100 ml. of water, and extracted with three 100-ml. portions of chloroform. Distillation of the chloro-

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(13) H. Rapoport and C. D. Willson, *J. Org. Chem.*, **26**, 1102 (1961).
(14) E. Fischer and E. Otto, *Ber.*, **36**, 2106 (1903).

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]

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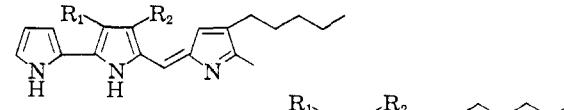
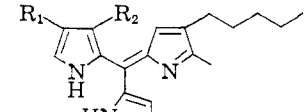
Prodigiosin, the red pigment of *S. marcescens*, has been synthesized. The pyrryldipyrrylmethene structure thus established for this pigment was built up through the following stages: (1) condensation of ethyl N-ethoxycarbonylglycinate with diethyl ethoxymethylenemalonate followed by treatment with diazomethane 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.

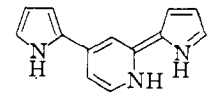
The first degradative work reported[5] on prodigiosin, $C_{20}H_{25}N_3O$, indicated the presence of three pyrrole nuclei (pyrrole, 3-methoxypyrrole and 2-methyl-3-amylpyrrole) joined in some manner by means of the remaining carbon atom required by the empirical formula. On the basis of his work Wrede, 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

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