Synthesis of Some 5-Aryl-2,2′-dipyrromethenes as Analogs of Prodigiosin (1)

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Three new dipyrromethenes have been synthesized as analogs of prodigiosin: 3-methoxy-5-phenyl-2,2′-dipyrromethene (**10a**), 3-methoxy-4′-pentyl-5-phenyl-5′-methyl-2,2′-dipyrromethene (**10b**), and 3-methoxy-4′-pentyl-5′-methyl-5-(2″-thienyl)-2,2′-dipyrromethene (**10c**). The Michael addition of ethyl glycinate to an appropriate arylidenemalonate, quenched with ethyl chloroformate and followed by a Dieckmann cyclization gave diethyl 1-ethoxycarbonyl-3-oxo-5-phenyl and thienylpyrrolidine-2,4-dicarboxylate, **2a** and **2b**. Methylation of the highly enolic keto-esters, followed by oxidation to *N*-ethoxycarbonylpyrroles led, after appropriate elaboration of the pyrrole nucleus, to 2-phenyl- and 2-thienyl-4-methoxypyrroles. The acid catalyzed condensation of these arylmethoxypyrroles with either pyrrole-2-carboxaldehyde or 5-methyl-4-pentylpyrrole-2-carboxaldehyde led to **10a, 10b** and **10c**.

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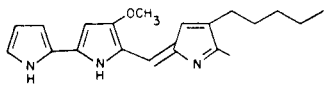
Prodigiosin, an antibiotic bacterial pigment, has been the subject of extensive investigation (*cf.*, 2a, 2b). The compound was first synthesized by Rapoport (3) and shown to be

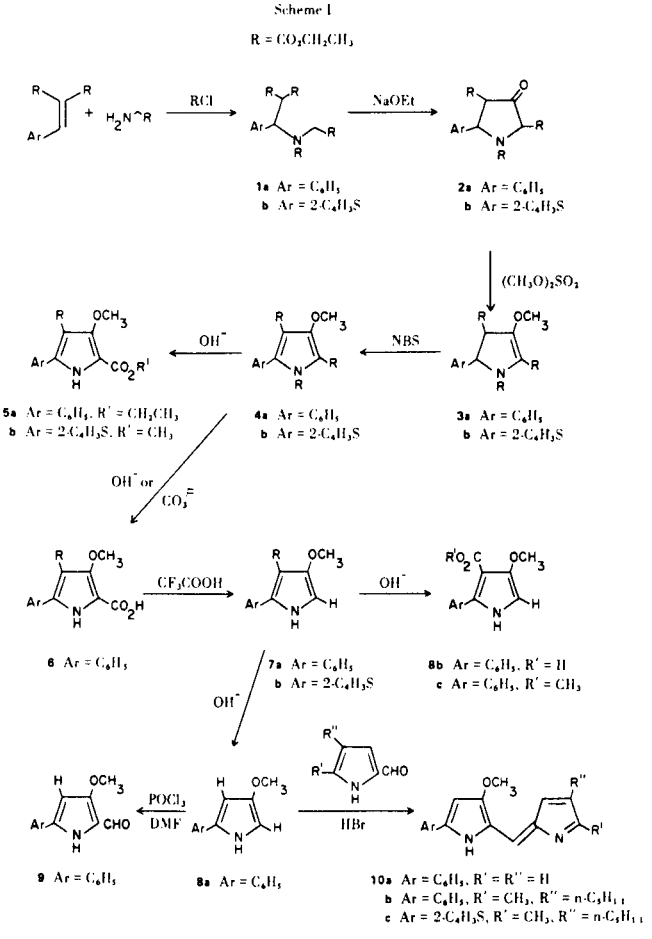


I

3-methoxy-4′-pentyl-5′-methyl-5-(2″-pyrryl)-2,2′-dipyrromethene (I). A number or synthetic analogs have been prepared and their antimicrobial properties investigated (4,5). The antimalarial properties of prodigiosin (6) and of some derivatives isolated by fermentation using selected organisms (7) have also been reported. In all of these analogs, the structural variations involved the alkyl and alkoxy groups on the dipyrromethene moiety. However, so far as we are aware, no one has reported the synthesis or biological activities of analogs of I in which the 5-(2″-pyrryl) group has been replaced by a different aryl group.

Accordingly, by an extension of our recent work on some 3-methoxy-5-arylpyrroles (8), we have synthesized the phenyl and 2-thienyl analogs of I, 3-methoxy-4′-pentyl-5-phenyl-5′-methyl-2,2′-dipyrromethene (**10b**) and 3-methoxy-4′-pentyl-5-(2″-thienyl)-5′-methyl-2,2′-dipyrromethene (**10c**).

Scheme I



Our approach to these compounds was to synthesize the appropriate 2-aryl-4-methoxypyrroles (**8**, Scheme I) and condense them with a pyrrole aldehyde in an acid catalyzed reaction, giving the dipyrromethenes **10**. The pyrroles **8** were obtained in a manner analogous to the method used to prepare various 1-methyl-3-methoxy-5-arylpyrroles (**8a,b**), *ie.*, the Michael addition of an amino acid ester to an arylidenemalonate, followed by Dieckmann cyclization to an oxopyrrolidine, oxidation to the pyrrole, and then appropriate elaboration of the pyrrole nucleus.

In the present case the Michael adduct formed from ethyl glycinate and the arylidenemalonate was quenched in ethyl chloroformate to give the urethanes I. These were cyclized in fair yield in ethanolic sodium ethoxide to give the oxopyrrolidines **2**. In contrast to the *N*-methyl cases (8a) these oxopyrrolidines were shown by their ir and nmr spectra to be highly enolic. Treatment of compounds **2** with dimethyl sulfate and potassium carbonate in refluxing acetone, then, gave pyrrolines **3** as a mixture of diastereomers. The double bond was assigned to the 2,3-position because of the multiplicity of the nmr absorptions assigned to H-4 and H-5. These protons must be somewhat coupled in each of the diastereomeric forms of **3** to give rise to the complex multiplets observed for H-4 and H-5.

Although *N*-bromosuccinimide in refluxing carbon tetrachloride, followed by triethylamine, worked well for the oxidation of **3a** to **4a** (see reference 9 for other instances of the use of these conditions), the concomitant bromination of the thiophene ring made these conditions impractical for synthesizing **4b**. However, treatment of the sodium enolate of **3b** with NBS at room temperature in ethanol allowed **4b** to be synthesized cleanly. An attempt was made to distill **4a** for purification but considerable thermal *N*-decarboethoxylation occurred, giving **5a**, presumably through a six-centered transition state, with elimination of ethylene and carbon dioxide, as observed by Bailey, *et. al.* (10).

The pyrrole carbamate diesters **4** showed the typical (11) carbonyl infrared absorption between 5.65 and 5.70 microns. They also demonstrated the reported (11) rapid rate of hydrolysis so that the pyrrolediesters **5** could be isolated if desired. Interestingly, if the hydrolysis of **4b** was run in aqueous methanol, a facile transesterification occurred at the 2-position, giving the mixed ester **5b**. Castro (9b) noted a similar transesterification in the hydrolysis of ethyl 1-ethoxycarbonyl-4-methoxypyrrole-2-carboxylate, giving methyl 4-methoxypyrrole-2-carboxylate, although he attributed it to alcoholysis during the reaction of ethyl 1-ethoxycarbonyl-4-oxopyrroldidine-2-carboxylate with methyl sulfite and hydrogen chloride in methanol.

More vigorous hydrolysis permitted the isolation, in the phenyl series, of the 2-acid **6**, which decarboxylated in trifluoroacetic acid to give **7a**. Generally esters of pyrrole-2-carboxylic acids are hydrolyzed more readily than pyrrole-3-carboxylates (11) and this holds true in the present case. Comparison of the nmr spectra of **5a** and **6** shows that the ester shielded by the phenyl group (methyl group absorption δ 1.15) survives the hydrolysis (12).

The ease of hydrolysis of these pyrrole-2-carboxylic esters was demonstrated in the thienyl case, in which potassium carbonate in aqueous ethanol was employed. Compound **6** (Ar = 2-C_4H_3S) could not be crystallized, but rather, the crude hydrolysate was treated with trifluoroacetic acid and then purified by column chromatography to give **7b** directly.

Treatment of **7a** with hydroxide gave a little of the acid **8b**, characterized as its methyl ester **8c**, but the principle product was the desired 2-phenyl-4-methoxypyrrole, **8a**. The aldehyde **9** could be synthesized in good yield under Vilsmeier conditions, but the *meso* carbon was introduced into the dipyrromethenes as the aldehyde of the simple pyrrole. The condensation of **8a** with pyrrole-2-carboxaldehyde and 5-methyl-4-pentylpyrrole-2-carboxaldehyde gave **10a** and **10b**, respectively. The thienyl analog of **8a** was not isolated, but rather the crude hydrolysate was treated with 5-methyl-4-pentylpyrrole-2-carboxaldehyde to give, after chromatography, **10c**.

The ultraviolet and nmr spectral characterization of prodigiosin and compounds **10a-c** is given in Tables I and II. The ultraviolet spectra of **10b** and **10c** are in quite

Table I

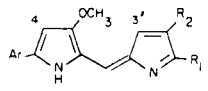
Ultraviolet Absorption of Some Dipyrromethenes

Compound	λ max, nm (Ethanol, Sodium Hydroxide)	ϵ	λ max, nm (Ethanol, Hydrogen Chloride)	ϵ
Prodigiosin (a)	470	45,000	535	138,000
10a	436	29,000	484	64,000
10b	476	(b)	508	(b)
10c	495	26,000	530	93,000

(a) A. Treibs and R. Zimmer-Galler, *Z. Physiol. Chem.*, 318, 12 (1960). (b) Insufficiently pure for an accurate determination.

Table II

Nmr Chemical Shifts (ppm) of Some Dipyrromethenes in Deuteriochloroform



Compound	R_1	R_2	H-3′	*meso*	OCH_3	H-4	Ar
Prodigiosin (a)	1.67 (s)	0.82 (t, 3) 1.18-1.48 (m, 6) 2.16 (t, 2)	6.26 (s)	6.75 (s)	3.90 (s)	6.01 (s)	6.02-6.08 (m, 1. H-4″) 6.50-6.62 (m, 2. H-3″, 5″)
10a	7.10-7.25 (m)	6.60-6.70 (m)	6.25-6.35 (m)	7.00 (s)	3.90 (s)	6.05 (s)	7.40-7.58 (m, 3, *m* and *p*) 7.92-8.11 (m, 2, *o*)
10b	2.32 (s)	0.88 (t, 3) 1.20-1.50 (m, 6) 2.34 (t, 2)	6.40 (s)	6.80 (s)	3.86 (s)	6.02 (s)	7.30-7.40 (m, 3, *m* and *p*) 7.86-7.96 (m, 2, *o*)
10c	2.28 (s)	0.86 (t,,3) 1.22-1.58 (m, 6) 2.32 (t, 2)	6.36 (s)	6.72 (s)	3.80 (s)	5.86 (s)	6.96-7.04 (m, 1. H-4″) 7.24-7.40 (m, 2. H-3″. 5″)

(a) H. H. Wasserman, *et al.*, *Tetrahedron*, Suppl. 8, Part II, p. 647 (1966). The numbers given are from the authors' own spectrum, taken on a sample graciously provided by Dr. E. A. Steck of the Walter Reed Army Institute of Research. These values are in agreement with those published by Wasserman.

close agreement with that of prodigiosin itself. The assignment of nmr chemical shift values for H-3′ and H-4 in **10b** and **10c** was not immediately obvious, but it became clear upon examination of the spectrum of **10a**. Since the absorption in the 6.25-6.40 p.p.m. range in **10a** was a multiplet and the absorption in the 5.86-6.05 p.p.m. range was still a singlet, the assignments must be as indicated. The *meso* protons were in the general range of 6.8-6.9 p.p.m. observed for some other dipyrromethenes (13).

One of the most striking features of Table II is the low value for the chemical shift of the 5′-methyl group of prodigiosin (1.67 δ) as opposed to the values for compounds **10b**, **10c**, 2-methyl-3-pentylpyrrole, and 5-methyl-4-pentylpyrrole-2-carboxaldehyde (*ca.*, 2.3 δ). This must be a long-range manifestation of the electron donating ability of pyrrole as opposed to benzene or thiophene.

Finally, there was initially some uncertainty about the hydrogen tautomerism of substituted pyrromethene free bases (3). We would refer the reader to an excellent nmr study which has examined this question (14).

EXPERIMENTAL

Melting points were obtained on a Mel-Temp capillary melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer model 137 infrared spectrometer. Nmr spectra were taken either on a Varian Associates' HA-100 or EM-360 instrument using tetramethysilane as an internal standard. Mass spectra were determined on a Varian MAT CH-7 spectrometer or an Associated Electrical Industries' MS-9 spectrometer at 70 eV.

Ultraviolet spectra were measured on a Bausch and Lomb Spectronic 505. Solutions of the dipyrromethenes for ultraviolet spectra were prepared initially by dissolving 3-5 mg. of sample in absolute ethanol and then diluting with either 0.1*N* hydrochloric acid or 0.1*N* sodium hydroxide to give convenient concentrations.

Thin layer chromatography was done on glass slides, coated with silica gel GF-254 (Brinkmann). The slides were eluted with 10% tetrahydrofuran in benzene and visualization was by ultraviolet light. Vapor phase chromatography was performed on a Hewlett-Packard HP5110A gas chromatograph equipped with a thermal conductivity detector and temperature programmer. Samples were run on a 0.125 in. x 20 in. column of 10% UC-W98 on 80-100 mesh chromosorb, with the temperature programmed between 130° and 270° at 8°/min.

Magnesium sulfate was used for drying solutions in organic solvents, and analyses were performed by Galbraith Laboratories, Knoxville, Tennessee, and Midwest Microlab, Indianapolis, Indiana.

5-Methyl-4-pentylpyrrole-2-carboxaldehyde.

This aldehyde was prepared by the following route, employed by Castro, *et al.*, (9b), who converted pyrrole-2-carboxaldehyde *via* 2-methylpyrrole, ethyl 5-methylpyrrole-2-carboxylate, ethyl 5-methyl-4-valeroylpyrrole-2-carboxylate, 2-methyl-3-pentylpyrrole to 5-methyl-4-pentylpyrrole-2-carboxaldehyde. We found it more convenient, however, to use the method of Triebs and Ott (15) for the preparation of ethyl 5-methylpyrrole-2-carboxylate from 2-methylpyrrole. Our yields, melting points, and boiling points were in good agreement with the literature, and the nmr spectrum of the 2-methyl-3-pentylpyrrole so obtained was identical to the published spectrum (16). 5-Methyl-4-pentylpyrrole-2-car-

boxaldehyde has the following nmr in deuteriochloroform: δ 0.91 (t, 3H, $CH_2(CH_2)_3CH_3$), 1.25-1.70 (m, 6H, $CH_2(CH_2)_3CH_3$), 2.30-2.55 (m, 5H, $CH_2(CH_2)_3CH_3$ and $-CH_3$ (s at 2.30)), 6.75 (d, 1H, J = 3 Hz, H-3), 9.30 (s, 1H, CHO).

Ethyl Glycinate.

Ethyl glycinate hydrochloride was synthesized by the method of Holly and Stammer (17) and had m.p. 143-145° after recrystallization from ethanol (Lit. (18) m.p. 145°). The free base could not be stored so it was released from the hydrochloride shortly before use by the method previously described for ethyl sarcosinate (8a). The best results were obtained when the free base was distilled immediately before use, b.p. 70-72° at 25 mm. (Lit. (19) b.p. 61° at 20 mm.).

Ethyl *N*-Ethoxycarbonyl-*N*-[2,2-bis(ethoxycarbonyl)-1-arylethyl]-glycinate (**1a,b**).

Ethyl benzylidenemalonate (8a) (25 g., 0.1 mole) was warmed slightly and poured into a 250 ml. 3-neck flask containing an efficient mechanical stirrer. The liquid was stirred vigorously while it was chilled with an ice-water bath, giving a thick paste. To this paste was added ethyl glycinate (21 g., 0.2 mole) and then the ice bath was removed and stirring continued. The mixture was allowed to warm to room temperature over 1 hour, giving a colorless, homogeneous liquid. The ice bath was then reapplied and, after about 20 minutes, this cold mixture was added as rapidly as possible to vigorously stirring, chilled (ice bath) ethyl chloroformate (21.7 g., 0.2 mole). After the initial vigorous reaction subsided, the ice bath was removed and stirring was continued an additional 30 minutes. At the end of this time, 100 ml. of 10% aqueous sodium carbonate was added to the stirring mixture and, after another 15 minutes, the suspension was extracted three times with 75 ml. of chloroform. The combined, dried organic phase was then distilled, first at 25 mm and then at 0.3 mm. At 0.3 mm ethyl *N*-ethoxycarbonylglycinate was collected at 90-92° (Lit. (20) b.p. 126° at 12 mm) and ethyl benzylidenemalonate was collected from 135-145° (Lit. (21) b.p. 140-142° at 4 mm). A little *N,N'*-bis(ethoxycarbonyl)piperazine-2,5-dione, m.p. 146.5-147° (methanol/ethyl acetate) (Lit. (22) m.p. 142-143°) codistilled below 140° also; nmr (deuteriochloroform-DMSO-d_6) δ 1.28 (t, 3H, $CO_2CH_2CH_3$), 3.72 (s, 2H, $COCH_2N$), 4.22 (q, 2H, $CO_2CH_2CH_3$). When the distillate reached 150°, heating was stopped, leaving 37 g. of the phenyl ester **1a** (87%) remaining in the distilling flask as a yellow oil. Glpc analysis of this oil revealed that it contained about 12% of ethyl benzylidenemalonate. This material was used in its crude state for further reactions but was purified for characterization by distillation through a short path apparatus, b.p. 200°/0.05 mm; ir (sodium chloride, neat) 5.75-5.85 (C=O, broad, esters), 5.90 μ (C=O, urethane); nmr (deuteriochloroform): δ 1.00-1.42 (m, 12H, $CO_2CH_2CH_3$), 3.74-4.36 (m, 11H, $CO_2CH_2CH_3$, NCH_2, $COCHCO$), 5.80 (s, broad, H/2, ArCH), 5.92 (s, broad, H/2, ArCH), 7.16-7.32 (m, 5H, aryl H).

Anal. Calcd. for $C_{21}H_{29}NO_2$: C, 59.56; H, 6.90; N, 3.31; m.w. 423. Found: C, 59.39; H, 6.96; N, 3.41; M^+ 423.

In like manner, the thienyl ester **1b** was obtained from diethyl 2-thienylmethylidenemalonate (23), ethyl glycinate and ethyl chloroformate. Its purity was comparable to **1a** but the yield was considerably lower, 32%. The infrared spectra of **1a** and **1b** were congruent in the carbonyl region and the nmr spectra differed only in the region of the aromatic and benzylic protons: δ 5.90 (d, J = 1 Hz, H/2, ArCH), 6.12 (d, J = 1 Hz, H/2, ArCH), 6.85-7.40 (m, 3H, thienyl H's).

Anal. Calcd. for $C_{19}H_{27}NO_8S$: C, 53.13; H, 6.34; N, 3.26; S, 7.47; m.w. 429. Found: C, 53.45; H, 6.33; N, 3.13; S, 8.38; M^+ 429.

Diethyl 1-Ethoxycarbonyl-3-oxo-5-arylpyrrolidine-2,4-dicarboxylate (**2a,b**).

To a solution of freshly cut sodium (1.78 g., 0.077 mole) in 150 ml. of anhydrous ethanol (Commercial Solvents Corp.) under a nitrogen atmosphere was added 37 g. of crude **1a** (0.077 mole, based on 88% pure **1a**) dissolved in 30 ml. of anhydrous ethanol. The reaction was warmed at 45° overnight, then poured into 300 ml. of benzene containing 4.6 g. of glacial acetic acid (0.077 mole). This solution was extracted five times with 100 ml. of 0.2*N* sodium hydroxide solution and then the combined aqueous phase was acidified to *p*H 2-3 with concentrated hydrochloric acid. Extraction of the aqueous phase with four 75 ml. portions of chloroform followed by drying of the organic phase and concentration under reduced pressure gave 22.7 g. of the phenylpyrrolidine **2a** (78%) that was homogeneous to tlc. This material was used in this state for further reactions, but a little was distilled in a short path apparatus for characterization, b.p. *ca.* 200°/0.05 mm; ir (sodium chloride, neat) 3.10 (broad, OH, enol), 5.73 (C=O, ketone), 5.90 (C=O, broad, esters), 6.03 (C=O, urethane), 6.13 μ (strong, enol); nmr (carbon tetrachloride) δ 0.80-1.34 (m, 9H, $CO_2CH_2CH_3$), 3.80-4.30 (m, 6H, $CO_2CH_2CH_3$), 4.94-5.10 (m, 1H, H-4), 5.38-5.60 (m, 1H, H-5), 7.10-7.45 (m, 5H, aryl H), 8.50 (s, broad, 1H, OH, exchanges with deuterium oxide). This material gave a positive test with ferric chloride.

Anal. Calcd. for $C_{19}H_{23}NO_6$: C, 60.47; H, 6.14; N, 3.71; m.w. 377. Found: C, 60.26; H, 6.38; N, 4.01; M^+ 377.

In similar fashion the thienylpyrrolidine **2b** was obtained in 52% yield from **1b**. The infrared spectra of **2a** and **2b** were congruent in the carbonyl region and the nmr spectra differed only in the chemical shift of H-5 (δ 5.75-6.05, m) and the thienyl H's (δ 6.85-7.40, m, 3H). This pyrrolidine was considerably less stable than **2a**, turning dark green overnight. M.w. Calcd. for $C_{17}H_{21}NO_7S$: 383. Found, M^+ 383.

Diethyl 1-Ethoxycarbonyl-3-methoxy-5-aryl-2-pyrroline-2,4-dicarboxylate (**3a,b**).

The crude oxopyrrolidine (**2a**) (22.7 g., 0.06 mole) was dissolved in 2300 ml. of dry acetone and refluxed 3 hours with 34 ml. of dimethyl sulfate (44.2 g., 0.35 mole) and 90 g. of anhydrous potassium carbonate (0.65 mole). At the end of this time, the inorganic salts were filtered from the reaction and the solvent removed under reduced pressure. The residue was chilled and the excess dimethyl sulfate was carefully hydrolyzed with concentrated aqueous ammonia. Then an additional 100 ml. of water was added and the suspension was extracted several times with chloroform. The combined, dried, organic phase was distilled, first at 25 mm and then at 0.3 mm. At 0.3 mm, **3a** was collected at 190-195° and amounted to 18 g. (76%). This material, while homogeneous to tlc, was shown by glpc analysis to contain approximately equal amounts of two diastereomers. These components were never separated but were characterized as a mixture; ir (sodium chloride, neat) 5.75 (C=O, ester), 5.88 (broad, C=O, α-β-unsaturated ester and urethane), 6.10 μ (enol ether); nmr (carbon tetrachloride); δ 0.85-1.45 (m, 9H, $CO_2CH_2CH_3$), 4.15 (s, 3H, OCH_3), 3.80-4.35 (m, 6H, $CO_2CH_2CH_3$), 5.0-5.25 (m, 1H, H-4), 5.55-5.85 (m, 1H, H-5), 7.40-7.60 (m, 5H, aryl H's).

Anal. Calcd. for $C_{20}H_{25}NO_7$: C, 61.37; H, 6.44; N, 3.58; m.w. 391. Found: C, 61.12; H, 6.48; N, 3.41; M^+ 391.

The methoxypyrroline **3b**, obtained as above from **2b**, proved

to be much more sensitive to heat than **3a**, suffering considerable decomposition upon distillation. Therefore a little **3b** was distilled for characterization but the bulk of the material was used in its crude state for the next reaction. The infrared spectra of **3a** and **3b** were congruent in the carbonyl region and the nmr spectra, again, differed in the chemical shift of H-5 (δ 5.80-6.15, m) and the thienyl H's (δ 6.80-7.00, m, 1H, H-4′; 7.10-7.35, m, 2H, H-3′, H-5′.

Anal. Calcd. for $C_{18}H_{23}NO_7S$: C, 54.39; H, 5.83; N, 3.52; S, 8.07; m.w. 397. Found: C, 54.32; H, 5.89; N, 3.62; S, 8.39; M^+ 397.

Diethyl 1-Ethoxycarbonyl-3-methoxy-5-phenylpyrrole-2,4-dicarboxylate (**4a**).

The methoxypyrroline **3a** (5.0 g., 12.8 mmoles) was dissolved in 90 ml. of carbon tetrachloride, *N*-bromosuccinimide (3.4 g., 19.0 mmoles) was added, and the mixture was refluxed for 2 hours. At the end of this time 1.5 g. of triethylamine (14.8 mmoles) in 5 ml. of carbon tetrachloride was added and refluxing was continued for an additional 10 minutes. After allowing the reaction to cool, it was filtered through a pad of filter aid and then washed once with 40 ml. of 1*N* hydrochloric acid. Drying and concentration of the organic phase under reduced pressure gave **4a** as an oil that was homogeneous to tlc and glpc but which could not be distilled.

One attempt to distill this oil gave a mixture of **4a** and another material which crystallized from the distillate and was identified by tlc, glpc, and ir as diethyl 3-methoxy-5-phenylpyrrole-2,4-dicarboxylate (**5a**, see below). The crude oil was therefore characterized; ir (sodium chloride, neat): 5.65 (C=O, N-ester), 5.85 μ (C=O, broad, esters); nmr (carbon tetrachloride): δ 0.90-1.55 (m, 9H, $CO_2CH_2CH_3$), 3.95 (s, 3H, OCH_3), 4.00-4.45 (m, 6H, $CO_2CH_2CH_3$), 7.30 (s, 5H, aryl H's).

M.w. Calcd. for $C_{20}H_{23}NO_7$: 389.1475. Found: M^+ 389.1457.

Diethyl 1-Ethoxycarbonyl-3-methoxy-5-(2′-thienyl)pyrrole-2,4-dicarboxylate (**4b**).

The methoxypyrrole **3b** (3.0 g., 7.45 mmoles) was added to 120 ml. of absolute ethanol under nitrogen in which was dissolved 0.19 g. of freshly cut sodium (8.26 mmoles). After 30 minutes, *N*-bromosuccinimide was added (1.5 g., 8.43 mmoles) and after another 40 minutes, the reaction was poured into 300 ml. of water and extracted with one 100 ml. and one 50 ml. portion of chloroform. The combined, dried organic phase was concentrated under reduced pressure to give an essentially quantitative yield of crude **4b**. Its infrared spectrum displayed the same characteristic carbonyl absorptions as **4a** and their nmr spectra were essentially identical except in the aromatic region (δ 6.80-7.32, m, 3H).

M.w. Calcd. for $C_{18}H_{21}NO_7S$: 395. Found: M^+ 395.

Diethyl 3-Methoxy-5-phenylpyrrole-2,4-dicarboxylate (**5a**).

The pyrrole **4a** (0.5 g., 1.29 mmoles) was suspended in 12.9 ml. 0.1*N* sodium hydroxide (1.29 mmoles), sufficient ethanol was added to dissolve the organic material, and the solution was refluxed for 30 minutes. At the end of this time the reaction mixture was chilled and acidified to *p*H 1-2, then extracted with two 10 ml. portions of chloroform. The combined, dried organic phase was concentrated under reduced pressure and a portion of the residue chromatographed on a preparative tlc plate (10% tetrahydrofuran in benzene), separating the major reaction product from dark and highly polar materials. This material crystallized from cyclohexane overnight to give crystals of m.p. 68-70°; ir (sodium chloride, chloroform) 3.10 (NH), 5.90 μ (C=O, broad, esters); nmr (deuteriochloroform): δ 1.15 (t, 3H, 4-$CO_2CH_2CH_3$), 1.35 (t, 3H, 2-$CO_2CH_2CH_3$), 4.00 (s, 3H, OCH_3), 4.25 (q, 4H, $CO_2CH_2CH_3$), 7.10-7.35 (m, 5H, aryl H's), 9.30 (s, broad, 1H, NH).

M.w. Calcd. for $C_{17}H_{19}NO_5$: 317.1263. Found: 317.1259.

Methyl 3-Methoxy-4-ethoxycarbonyl-5-(2′-thienyl)pyrrole-2-carboxylate (**5b**).

The crude product **4b** (1.5 g., 3.80 mmoles) was refluxed for 30 minutes in a mixture of 15 ml. of methanol and 5 ml. of water containing 0.6 g. of 85% potassium hydroxide. At the end of this time, the basic solution was chilled and extracted several times with chloroform. The dried, concentrated organic extracts crystallized to give, after one recrystallization from benzene/cyclohexane, 200 mg. (17%) of analytically pure **5b**, m.p. 134-136°; ir (potassium bromide): 3.10 (NH), 5.90 (C=O, ester), 6.00 μ (C=O, ester); nmr (deuteriochloroform): δ 1.29 (t, 3H, 4-$CO_2CH_2CH_3$), 3.81 (s, 3H, OCH_3 or $COOCH_3$), 3.92 (s, 3H, OCH_3 or $COOCH_3$), 4.28 (q, 2H, 4-$CO_2CH_2CH_3$), 6.98, 7.03 (d of d, J = 4 Hz, H-4′), 7.30-7.44 (m, 2H, H-3′, H-5′), 9.10 (s, broad, 1H, NH).

Anal. Calcd. for $C_{14}H_{15}NO_5S$: C, 54.35; H, 4.89; N, 4.53; S, 10.37; m.w. 309. Found: C, 54.30; H, 4.90; N, 4.43; S, 10.45; M^+ 309.

3-Methoxy-5-ethoxycarbonyl-5-phenylpyrrole-2-carboxylic Acid (**6**).

The crude pyrrole **4a** (from 4.0 g. of **3**, 12.8 mmoles) was dissolved in 75 ml. of methanol and a solution of 3 g. of 85% potassium hydroxide in 20 ml. of water was added. This solution was refluxed for 4 hours, then cooled. An additional 200 ml. of water was added and the dark solution was extracted with four 75 ml. portions of chloroform or until the organic phase was no longer dark. The aqueous phase was then made strongly acidic with concentrated hydrochloric acid and extracted again with four 75 ml. portions of chloroform. These last extracts were combined, dried, and concentrated under reduced pressure, leaving a dark viscous residue. This residue was dissolved in hot ethyl acetate and cyclohexane was added to cloudiness. Tan crystals of **6** separated as this solution cooled, amounting to 1.7 g. (46%), m.p. 150-152° dec. The analytical sample was recrystallized once more from ethyl acetate/cyclohexane, m.p. 154° dec.; ir (potassium bromide): 3.10-4.00 (broad, NH and COOH), 5.90 (C=O, aryl ester), 6.05 μ (C=O, aryl acid); nmr (deuteriochloroform): δ 1.20 (t, 3H, 4-$CO_2CH_2CH_3$), 3.95-4.30 (m, 5H, 4-$CO_2CH_2CH_3$ and OCH_3 (s, at 4.00)), 7.30 (s, broad, 5H, aryl H's), 10.00 (s, broad, 2H, NH and COOH).

Anal. Calcd. for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84; m.w. 289. Found: C, 62.08; H, 5.20; N, 4.60; M^+ 289.

Ethyl 2-Phenyl-4-methoxypyrrole-3-carboxylate (**7a**).

The acid **6** (1.25 g., 4.33 mmoles) was blanketed with nitrogen in a flask and treated with 10 ml. of trifluoroacetic acid. Carbon dioxide evolution was immediate and ceased after about two minutes. The dark solution was warmed briefly on a steam bath and then poured into 50 ml. of chloroform. This solution was washed with two 30 ml. portions of water and one 30 ml. portion of 10% sodium bicarbonate, then dried. Upon concentration of the organic phase under reduced pressure, **7a** crystallized as a dark mass. One recrystallization from benzene/cyclohexane (Norite) gave 0.80 g. (75%) of analytically pure material, m.p. 124-125°; ir (potassium bromide): 3.05 (NH), 5.95 μ (C=O); nmr (deuteriochloroform): δ 1.15 (t, 3H, 3-$CO_2CH_2CH_3$), 3.70 (s, 3H, OCH_3), 4.20 (q, 2H, 3-$CO_2CH_2CH_3$), 6.30 (d, J = 3 Hz, 1H, H-5), 7.30-7.50 (m, 5H, aryl. H's), 8.60 (s, broad, 1H, NH).

Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.16; N, 5.71; m.w. 245. Found: C, 68.42; H, 6.22; N, 5.72; M^+ 245.

Ethyl-2-(2′-Thienyl)-4-methoxypyrrole-3-carboxylate (**7b**).

The crude pyrrole **4b** (3.0 g., 7.60 mmoles) was refluxed overnight under a nitrogen atmosphere in 120 ml. of 60% aqueous ethanol containing 6 g. of potassium carbonate. At the end of this time the mixture was poured into 200 ml. of water and extracted with two 100 ml. portions of chloroform. The organic phase was discarded and the aqueous phase was then acidified with concentrated hydrochloric acid and extracted again with chloroform. This combined organic phase was then itself extracted two times with 10% sodium bicarbonate solution. Acidification of this aqueous phase followed by extraction, drying, and concentration of the final organic phase gave a dark viscous mass that was treated with 10 ml. of trifluoroacetic acid and worked up as in the preparation of **7a** above. The dark oil that resulted from this operation was chromatographed on 120 g. of alumina (activity I, Woelm), eluting first with 10% tetrahydrofuran in benzene, then ethyl acetate. A fraction was collected that contained material identical to **7a** by tlc. Concentration of this fraction gave a viscous oil that crystallized from benzene/cyclohexane to give 150 mg. of analytically pure **7b** (8%), m.p. 90-92°; ir (potassium bromide): 3.10 (NH), 6.00 μ (C=O, ester); nmr (deuteriochloroform): δ 1.22 (t, 3H, 3-$CO_2CH_2CH_3$), 3.70 (s, 3H, OCH_3), 4.19 (q, 2H, 3-$CO_2CH_2CH_3$), 6.20 (d, 1H, J = 2 Hz, H-5), 6.91, 6.96 (d of d, 1H, J = 4 Hz, H-4′), 7.16-7.28 (m, 2H, H-3′, H-5′), 8.20 (s, broad, 1H, NH).

Anal. Calcd. for $C_{12}H_{13}NO_3S$: C, 57.35; H, 5.21; N, 5.58; S, 12.76. Found: C, 57.45; H, 5.38; N, 5.57; S, 12.59.

2-Phenyl-4-methoxypyrrole (**8a**).

The ester **7a** (0.80 g., 3.27 mmoles) was refluxed for 1 hour under a nitrogen atmosphere in a solution of 25 ml. of methanol and 25 ml. of 5*N* potassium hydroxide solution. At the end of this time the solution was chilled in an ice bath and 100 ml. of water was added. The crystals that precipitated were filtered and recrystallized from cyclohexane to give 0.35 g. (62%) of slightly pink crystals of **8a**, m.p. 60-61°; nmr (deuteriochloroform): δ 3.75 (s, 3H, OCH_3), 6.20 (m, 1H, H-3), 6.40 (m, 1H, H-5), 7.20-7.50 (m, 5H, aryl H's). This material proved to be too unstable for analysis.

M.w. Calcd. for $C_{11}H_{11}NO$: 173.0843. Found: M^+ 173.0841.

If, after the precipitated **8a** was filtered, the basic filtrate was acidified and extracted with chloroform, a small amount of 2-phenyl-4-methoxypyrrole-3-carboxylic acid (**8b**) was obtained from the concentrated organic phase, m.p. 139-140° dec., (benzene/cyclohexane): ir (potassium bromide): 3.05-4.30 (broad, NH and COOH), 6.10 μ (C=O, aryl acid); nmr (deuteriochloroform-DMSO-d_6): δ 3.85 (s, 3H, OCH_3), 6.35 (m, 1H, H-5), 7.30-7.65 (m, 5H, aryl H's); M.w. Calcd. for $C_{12}H_{11}NO_8$: 217. Found: M^+ 217. Treatment of this acid with excess sodium bicarbonate and dimethyl sulfate in refluxing acetone (see preparation of **3a**) gave the methyl ester, **8c**, m.p. 128-129° (benzene/cyclohexane); nmr (deuteriochloroform): δ 3.65 (s, 3H, $COOCH_3$), 3.75 (s, 3H, OCH_3), 6.25 (d, J = 3 Hz, 1H, H-5), 7.30-7.40 (m, 5H, aryl H's);

M.w. Calcd. for $C_{13}H_{13}NO_3$: 231.0896. Found: M^+ 231.0882.

3-Methoxy-5-phenylpyrrole-2-carboxaldehyde (**9**).

2-Phenyl-4-methoxypyrrole (**8a**) (0.90 g., 5.20 mmoles) was dissolved in 8 ml. of dry DMF and added to an ice cold solution of phosphorus oxychloride (0.7 ml., 1.13 g., 7.37 mmoles) in 15 ml. of dry DMF. This solution was allowed to warm to room temperature over 30 minutes and then poured over ice and made basic with saturated aqueous sodium acetate. Then it was warmed on a hot plate and boiled for ten minutes. Upon cooling, **9** crystallized, yielding 0.88 g. of crude material (84%), m.p. 136-138°. One recrystallization from benzene/cyclohexane gave analytically pure material, m.p. 141-142°; ir (potassium bromide): 3.10 (NH), 6.15 μ (C=O, vinylogous formamide); nmr (deuteriochloroform): δ 3.90 (s, 3H, OCH_3), 6.14 (s, 1H, H-4), 7.20-7.64 (m, 5H, aryl H's), 9.48 (s, 1H, CHO), 9.70 (s, broad, 1H, NH).

Anal. Calcd. for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.60; H, 5.58; N, 6.91.

3-Methoxy-5-phenyl-2,2′-dipyrromethene (**10a**).

To a solution of **8a** (1.20 g., 6.95 mmoles) and pyrrole-2-carboxaldehyde (Aldrich) (0.66 g., 6.95 mmoles) in 50 ml. of absolute ethanol was added 1 ml. of 48% hydrobromic acid. After 30 minutes the hydrobromide (**10a**) was filtered off and recrystallized from 2-propanol, yielding 1.90 g. of red-orange needles (82%), m.p. 165-167° dec. The free base was obtained by neutralizing a chloroform suspension of the hydrobromide with concentrated aqueous ammonia. The organic phase was dried and concentrated, then the residue was dissolved in hot hexane and allowed to crystallize slowly. In this way long deep orange needles of **10a** were obtained, m.p. 89-90°. See Tables I and II for the spectral characterization of this compound.

Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.77; H, 5.67; N, 11.20; m.w. 250. Found: C, 77.00; H, 5.68; N, 11.45; M^+ 250.

3-Methoxy-4′-pentyl-5-phenyl-5′-methyl-2,2′-dipyrromethene (**10b**).

The methoxypyrrole **8** (0.15 g., 0.87 mmoles) and 5-methyl-4′-pentylpyrrole-2-carboxaldehyde (0.15 g., 0.84 mmole) were dissolved in 5 ml. of absolute ethanol and treated with 5 drops of concentrated hydrochloric acid. The solution turned dark but no precipitate was observed so the solution was neutralized with concentrated aqueous ammonia and extracted with chloroform. The dried organic phase was chromatographed first on activity I neutral alumina (Woelm), eluting with 10% tetrahydrofuran in benzene, and then on acitivity IV neutral alumina eluting with cyclohexane. In this way a small amount of the free base **10b** was obtained as a glass when all the orange fractions were combined and concentrated. See Tables I and II for the spectral characterization of this compound.

3-Methoxy-4′-pentyl-5′-methyl-5-(2″-thienyl)-2,2′-dipyrromethene (**10c**).

The ester **7b** (0.30 g., 1.20 mmoles) was refluxed 1 hour in a mixture of 10 ml. of methanol and 10 ml. of 5*N* potassium hydroxide. At the end of this time the volume of the reaction was doubled with water and it was extracted with two 25 ml. portions of chloroform. These extracts were combined, dried, and concentrated. This crude hydrolysate was dissolved in 5 ml. of absolute ethanol containing 250 mg. (1.40 mmoles) of 5-methyl-4-pentylpyrrole-2-carboxyaldehyde. Upon the addition of 5 drops of 48% hydrobromic acid the solution turned deep red, but no crystalline hydrobromide precipitated. Therefore the reaction mixture was neutralized with concentrated aqueous ammonia and chromatographed twice over 20 g. of activity I neutral alumina, collecting the orange band. Concentration of the combined orange fractions gave 260 mg. of **10c** (63%) as a glass. It was crystallized by dissolving it in a minimum of hexane at room temperature and chilling to -15°. Obtained in this way were deep orange dichroic crystals with a green reflex, m.p. 72-74°. See Tables I and II for

the spectral characterization of this compound.

Anal. Calcd. for $C_{20}H_{24}N_2OS$: C, 70.55; H, 7.10; N, 8.23; S, 9.42; M.w. 340. Found: C, 70.57; H, 7.13; N, 8.06; S, 9.70; M^+ 340.

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