Pyoluteorin Derivatives. II. Synthetic Approaches to Pyrrole Ring Substituted Pyoluteorins (1)

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A method for the regiospecific synthesis of 3-substituted 2-aroylpyrroles is described. These pyrroles, which are structurally related to the naturally occurring antibiotic pyoluteorin, are prepared by a Friedel-Crafts aroylation of 4-substituted pyrrole-3-carboxylic acid esters with 2,6-dimethoxybenzoyl chloride. The carboalkoxy group is then removed by hydrolysis and decarboxylation to produce isomerically pure 3-substituted-2-(2′,6′-dimethoxybenzoyl)pyrroles (**5** and **13**). Conversion of these pyrroles into pyoluteorin-like compounds led to some unexpected products which arise from facile cleavage of the dihydroxybenzoyl portion of the molecules during chlorination.

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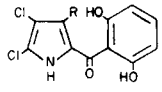
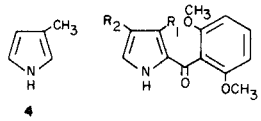
As part of our studies on the antibacterial activity of derivatives of pyoluteorin (**1**, R = H), we investigated the preparation of pyoluteorin analogs substituted at C-4 in the pyrrole ring with alkyl (**2**) and aryl (**3**) substituents. We now wish to report the results of this study, which include the preparation of 4-methylpyoluteorin *O,O*-diacetate (**18**) and its antibacterial activity.



1, R = H, pyoluteorin
2, R = CH_3
3, R = C_6H_5

We reasoned that compound **2** could be constructed by a Friedel-Crafts reaction between the known (2) 3-methylpyrrole (**4**) and 2,6-dimethoxybenzoyl chloride, especially since others have reported that electrophilic substitution of **4** occurs predominantly at C-2, with little reaction at C-5. However, we found that the above reaction between **4** and 2,6-dimethoxybenzoyl chloide afforded a 1:1 mixture (by nmr analysis) of the isomeric pyrroles **5** and **6** in 43% yield. By repeated fractional recrystallization of the mixture from benzene, pure **5** could be isolated in *ca.* 15% yield. We attribute this lack of selectivity to an unfavorable steric interaction between the C-3 methyl of **4** and the *ortho* substituents of the particular acid chloride used in our reaction.



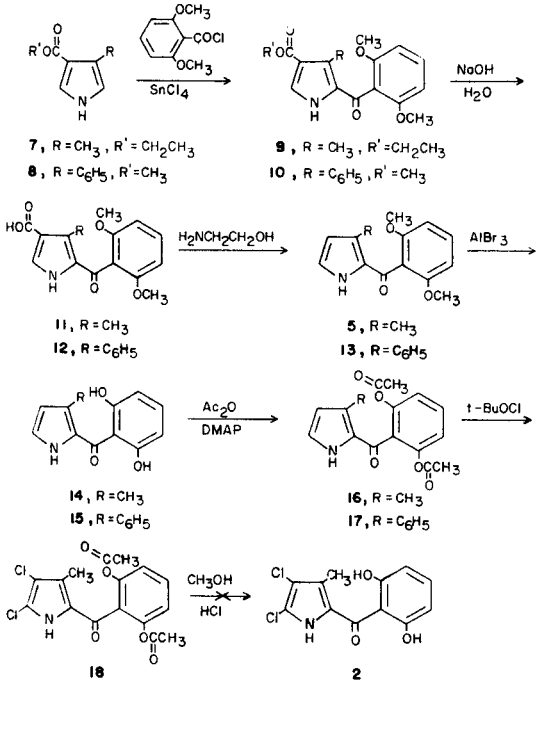
5, R_1 = CH_3, R_2 = H
6, R_1 = H, R_2 = CH_3

4

To circumvent this problem we developed a method for preparing 2-aroyl-3-substituted pyrroles such as **5**, free from contamination with 5-aroyl compounds **6**, as shown in Scheme I. To accomplish this, ethyl 4-methylpyrrole-3-carboxylate (**7**) (4) was allowed to react with 2,6-dimethoxybenzoyl chloride under Friedel-Crafts conditions to afford ethyl 5-(2′,6′-dimethoxybenzoyl)-4-methyl-pyrrole-3-carboxylate (**9**) in 85% yield. Similarly, the reaction of methyl 4-phenylpyrrole-3-carboxylate (**8**) (5) with 2,6-dimethoxybenzoyl chloride gave **10** in 80% yield. Removal of the carboalkoxy directing group was accomplished by hydrolysis of **9** and **10** in aqueous sodium hydroxide followed by decarboxylation of the resulting acids (**11**, R = CH_3 and **12**, R = C_6H_5) in refluxing ethanolamine to produce 2-(2′,6′-dimethoxybenzoyl)-3-methylpyrrole (**5**) and 2-(2′,6′-dimethoxybenzoyl)-3-phenylpyrrole (**13**) in 37% and 66% yields, respectively.

The methoxy groups of **5** and **13** were cleaved by the action of three equivalents of aluminum bromide in benzene to give the corresponding dihydroxybenzoylpyrroles **14** and **15** in 78% and 85% yields, respectively. Acylation of **14** and **15** with an excess of acetic anhydride in benzene containing a catalytic amount of 4-dimethylaminopyridine (DMAP) gave **16** and **17** in 72% and 70%

Scheme I



7, R = CH_3, R′ = CH_2CH_3
8, R = C_6H_5, R′ = CH_3
9, R = CH_3, R′ = CH_2CH_3
10, R = C_6H_5, R′ = CH_3
11, R = CH_3
12, R = C_6H_5
5, R = CH_3
13, R = C_6H_5
14, R = CH_3
15, R = C_6H_5
16, R = CH_3
17, R = C_6H_5
18
2

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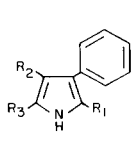
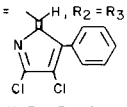
yields, respectively. The pyrroles **16** and **17** were now suitably protected so that chlorination would occur exclusively in the pyrrole ring.

Chlorination of **16** using slightly more than two equivalents of *t*-butylhypochlorite in methylene chloride afforded 4-methylpyoluteorin *O,O*-diacetate (**18**) in 60% yield. Using chlorine in acetic acid or *N*-chlorosuccinimide in refluxing carbon tetrachloride to chlorinate **16** resulted in much lower yields of **18**. On the other hand, chlorination of the 3-phenyl derivative **17** with any of the above reagents failed to give 4-phenylpyoluteorin *O,O*-diacetate (**19**). In each case, 3-phenyl-2,4,5-trichloropyrrole (**20**) was produced form **19** in moderate yield along with other unidentified products.

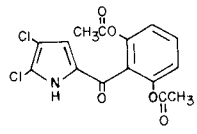
An alternate route to **3** was investigated, which involved the synthesis of 4,5-dichloro-3-phenylpyrrole-2-carboxaldehyde (**21**) as a crucial intermediate. The dihydroxybenzoyl moiety of **3** could then be elaborated by a series of reactions on the aldehyde functionality of **21**.



8, R_1 = H, R_2 = CO_2CH_3, R_3 = H
20, R_1 = R_2 = R_3 = Cl
21, R_1 = CHO, R_2 = R_3 = Cl
22, R_1 = CHO, R_2 = CO_2CH_3, R_3 = H
23, R_1 = CHO, R_2 = COOH, R_3 = H
24, R_1 = CHO, R_2 = R_3 = H
25, R_1 =  , R_2 = R_3 = Cl
26, R_1 = H, R_2 = R_3 = Cl

Vilsmeier formylation of the pyrrole ester **8** gave the aldehyde **22** in 70% yield; this aldehyde was converted to **24** by hydrolysis of **22** and decarboxylation of the resulting acid **23** in refluxing ethanolamine. The yield for this two step conversion was 43%. Chlorination of **24** with 2.2 equivalents of *t*-butylhypochlorite in methylene chloride failed to give the desired dichloroaldehyde **21**. Instead, a dipyrrylmethene **25** was isolated in low yield; compound **25** presumably arises by decarbonylation of **21** to produce **26** followed by condensation of **26** with **21** to give **25**.

Numerous attempts to remove the acetate protecting groups of **18** to produce **2**, using conditions which cleanly converted pyoluteorin *O,O*-diacetate (**27**) to pyoluteorin (**1**) (1), resulted in extensive decomposition of the molecule. Even heating **18** in methanol, conditions where **27** is inert, led to the production of methyl 2,6-dihydroxybenzoate (**28**), an expected cleavage product. We were unable to isolate any products derived from 2,3-dichloro-4-methylpyrrole (**29**), the other possible cleavage product (6) from this reaction. The instability of **18** and presumably **2** under these conditions is undoubtably due to the combined steric effect of the methyl group and the electronic effects of the chlorines since **14** is inert to cleavage. The decarbonylation reaction of **21** to ultimately give **25** is probably also a consequence of the dichloro substituents of **21**.



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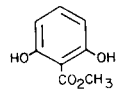

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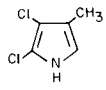

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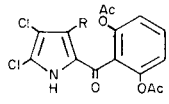
The *in vitro* antibacterial activities of 4-methylpyoluteorin *O,O*-diacetate (**18**) and pyoluteorin *O,O*-diacetate (**27**) against both Gram positive and Gram negative pathogens (Table I) are comparable, but neither **18** nor **27** was effective in controlling systemic infections in mice.

Table I

Antibacterial Activity of Pyoluteorin *O,O*-diacetates **18** and **27**



Compd.	R_1	(MIC, μ/ml.) *S. aureus*	*Strep. zoo.*	*E. Coli*	*Salm. chol-su.*	*Past. Mult.*
18	CH_3	3.12	50	50	25	1.56
27	H	3.12	50	50	200	25

In summary, we have developed a method for the regiospecific synthesis of pyrrole ring substituted analogs of pyoluteorin which utilizes the directing effect of a carboalkoxy group in the pyrrole ring which is subsequently removed by hydrolysis and decarboxylation. We have also shown that pyoluteorin analogs bearing alkyl or aryl substituents at C-4 in the pyrrole ring are extremely labile, and this instability is a consequence of a combination of factors including the steric effect of the C-4 substituent as well as the electronic effects of the chloro substituents at C-2 and C-3.

EXPERIMENTAL (8)

2-(2',6'-Dimethoxybenzoyl)-3-methylpyrrole (**5**) and 2-(2',6'-Dimethoxybenzoyl)-4-methylpyrrole (**6**).

To a vigorously stirred solution of stannic chloride (12 ml.) in dry methylene chloride (100 ml.) under a nitrogen atmosphere solutions of 3-methylpyrrole (2) (3.5 g., 0.042 mole) in methylene chloride (25 ml.) and 2,6-dimethoxybenzoyl chloride [prepared by the reaction of 2,6-dimethoxybenzoic acid (7.3 g., 0.04 mole) and thionyl chloride (25 ml.) in methylene chloride (25 ml.)] were added dropwise over a 30-minute period. Stirring was continued for 3 hours, then a 100 ml. portion of aqueous 5% sulfuric acid was added cautiously to the ice-cold reaction mixture to decompose the excess stannic chloride. The organic layer was separated and washed successively with water, aqueous 5% sodium bicarbonate solution and water, then dried over anhydrous magnesium sulfate. Evaporation of the solvent *in vacuo* gave a solid (4.2 g., 43%) which consisted of an equal amount of **5** and **6** by nmr analysis. Two recrystallizations of this solid from benzene afforded pure **5** (1.5 g., 15%); m.p. 189-191°: nmr (deuteriochloroform): δ 9.30 (br s, 1H, NH,

exchanges with deuterium oxide), 7.33 (d of d, 1H, H_4', J = 8.0 Hz), 7.00 (d, 1H, H_5, $J_{4,5}$ = 3.5 Hz), 6.70 (d, 2H, J = 8.0 Hz, H_3' and H_5'), 6.10 (d, 1H, H_4, $J_{4,5}$ = 3.5 Hz), 3.75 (s, 6H, OCH_3's) and 1.90 (s, 3H, 3-CH_3); ir (potassium bromide): 3.05 (NH) and 6.25 μ (C=O); ms: (70 eV) m/e 245 (M^+).

Anal. Calcd. for $C_{14}H_{15}NO_3$ (245.27): C, 68.55; H, 6.16; N, 5.71. Found: C, 68.43; H, 6.12; N, 5.70.

Ethyl 5-(2',6'-Dimethoxybenzoyl)-4-methylpyrrole-3-carboxylate (**9**).

In a manner similar to the preparation of **5**, ethyl 4-methylpyrrole-3-carboxylate (**7**) (4) (4.0 g., 0.026 mole) and 2,6-dimethoxybenzoyl chloride (6.0 g., 0.03 mole) gave **9** (7.0 g., 85%); m.p. 150-152°C; nmr [deuteriochloroform/DMSO-d_6 (1:1)]: δ 11.40 (br s, 1H, NH), 7.50-7.20 (m, 2H, H_5 and H_4'), 6.65 (d, 2H, H_3' and H_5') 4.27 (q, 2H, $CO_2CH_2CH_3$), 3.80 (s, 6H, OCH_3's), 2.07 (s, 3H, 4-CH_3) and 1.30 (t, 3H, ester CH_3); ir (KBr) 3.10 (NH), 5.80 and 6.20 (C=O); ms: (70 eV) m/e 317 (M^+).

Anal. Calcd. for $C_{17}H_{19}NO_5$ (317.33): C, 64.34; H, 6.03; N, 4.41. Found: C, 63.86; H, 5.75; N, 4.15.

Methyl 5-(2',6'-Dimethoxybenzoyl)-4-phenylpyrrole-3-carboxylate (**10**).

In the same manner, the Friedel-Crafts reaction of methyl 4-phenylpyrrole-3-carboxylate (**8**) (5) (6.80 g., 0.033 mole) and 2,6-dimethoxybenzoyl chloride (6.60 g., 0.033 mole) gave **10** (9.80 g., 80%); m.p. 173-174°; nmr (deuteriochloroform): δ 9.60 (br s, 1H, NH), 7.70 (s, 1H, H_5), 7.37 (m, 1H, H_4'), 7.03 (s, 5H, phenyl H), 6.35 (d, 2H, H_3' and H_5'), and 3.70 (s, 6H, OCH_3's); ir (potassium bromide): 3.05 (NH), 5.80 and 6.20 μ (C=O); ms: (70 eV) m/e 365 (M^+).

Anal. Calcd. for $C_{21}H_{19}NO_5$ (365.35): C, 69.03; H, 5.24; N, 3.83. Found: C, 68.62; H, 5.30; N, 3.77.

5-(2',6'-Dimethoxybenzoyl)-4-methylpyrrole-3-carboxylic Acid (**11**).

Heating a solution of **9** (11.0 g., 0.035 mole) in 300 ml. of 2.5 *N* aqueous sodium hydroxide for 8 hours, followed by acidification with 6*N* hydrochloric acid, gave **11** (6.5 g., 65%); m.p. 230° dec; nmr (DMSO-d_6): δ 12.10 (br s, 2H, NH and COOH), 7.43 (m, 2H, H_5 and H_4'), 6.72 (d, 2H, H_3' and H_5'), 3.73 (s, 6H, OCH_3's) and 2.00 (s, 3H, 4-CH_3); ms: (70 eV) m/e 289 (M^+).

Anal. Calcd. for $C_{15}H_{15}NO_5$ (289.28): C, 62.27; H, 5.23; N, 4.84; Found: C, 62.40; H, 5.23; N, 4.86.

5-(2',6'-Dimethoxybenzoyl)-4-phenylpyrrole-3-carboxylic Acid (**12**).

Heating a solution of **10** (6.50 g., 0.018 mole) in aqueous 2.5 *N* sodium hydroxide (200 ml.) at refluxing for 4 hours followed by cooling to 0° and acidification with 6*N* hydrochloric acid gave **12** (6.15 g., 100%); m.p. 242-243°C (recrystallized from chloroform); nmr (DSMO-d_6): δ 12.00 (br s, 2H, NH and COOH); 7.67 (s, 1H, H_5), 7.00 (s, 5H, phenyl H), 7.27 (m, 1H, H_4'), 6.30 (d, 2H, H_3' and H_5') and 3.60 (s, 6H, OCH_3's); ms: (70 eV) m/e 351 (M^+).

Anal. Calcd. for $C_{20}H_{17}NO_5$ (351.35): C, 68.36; H, 4.88; N, 3.99. Found: C, 68.20; H, 4.63; N, 4.02.

2-(2',6'-Dimethoxybenzoyl)-3-methylpyrrole (**5**) and 2-(2',6'-Dimethoxybenzoyl)-3-phenylpyrrole (**13**).

A solution of **11** (7.0 g., 0.024 mole) in 50 ml. of freshly distilled ethanolamine was heated at reflux for 2 hours, cooled and poured into ice water. The precipitate was collected by filtration and was recrystallized from benzene to give **5** (3.4 g., 75%); m.p. 189-191°; identical in all respects with the product obtained from the reaction of 3-methylpyrrole and 2,6-dimethoxybenzoyl chloride. Similarly, **12** (6.15 g., 0.018 mole) gave **13** (3.56 g., 66%); m.p. 221-222° (recrystallized from ethanol); nmr (deuteriochloroform): δ 7.00 (m, 7H, H_4', H_5' and phenyl H), 6.20 (m, 3H, H_3', H_4 and H_5') and 3.67 (s, 6H, OCH_3); ir (potassium bromide): 2.95 and 6.20 μ; (70 eV) m/e 307 (M^+).

Anal. Calcd. for $C_{19}H_{17}NO_3$ (307.34): C, 74.25; H, 5.58; N, 4.56. Found: C, 73.96; H, 5.72; N, 4.58.

2-(2',6'-Dihydroxybenzoyl)-3-methylpyrrole (**14**) and 2-(2',6'-Dihydroxybenzoyl-3-phenylpyrrole (**15**).

To a vigorously stirred solution of **5** (3.13 g., 0.013 mole) in benzene (300 ml.) aluminum bromide (10.2 g., 0.038 mole) was added portionwise over a 30 minute period. After stirring at room temperature for 4 hours, the reaction mixture was poured into ice water, ethyl acetate (300 ml.) was added and the organic layer was separated, dried over anhydrous sodium sulfate, filtered and evaporated. The resulting residue was recrystallized from chloroform to give **14** (2.15 g., 78%); m.p. 145-146°; nmr (DMSO-d_6-deuterium oxide): δ 7.10 (m, 2H, H_2' and H_5), 6.43 (d, 2H, H_3' and H_5'), 6.10 (d, 1H, H_4) and 1.90 (s, 3H, 3-CH_3); ir (potassium bromide): 2.95 (NH), 3.30 (br, OH), 6.15 and 6.40 μ (C=O); ms: (70 eV) m/e 217(M^+).

Anal. Calcd. for $C_{21}H_{11}NO_3$ (217.22): C, 66.35; H, 5.11; N, 6.45. Found: C, 66.48; H, 5.03; N, 6.12.

In the same manner, the reaction of **13** (3.00 g., 0.01 mole) and aluminum bromide (7.80 g., 0.03 mole) in benzene (300 ml.) afforded **15** (2.30 g., 85%); m.p. 162-162° (recrystallized from ether/hexanes); nmr (deuteriochloroform): δ 9.64 (br s, 1H, NH), 7.67 (br s, 2H, OH), 7.15 (m, 6H, H_5 and phenyl H), 7.00 (m, 1H, H_4'), 6.35 (m, 1H, H_4) and 6.10 (d, 2H, H_3' and H_4'); ms: (70 eV) m/e 279(M^+).

Anal. Calcd. for $C_{17}H_{13}O_3N$: C, 73.11; H, 4.69; N, 5.02. Found: C, 72.87; H, 4.45; N, 4.86.

2-(2',6'-Dihydroxybenzoyl)-3-methylpyrrole *O,O*-Diacetate (**16**) and 2-(2',6'-Dihydroxybenzoyl)-3-phenylpyrrole *O,O*-Diacetate (**17**).

A solution of **14** (2.15 g., 0.01 mole) and acetic anhydride (10 ml.) (0.1 mole) in benzene (40 ml.) containing 4-dimethylaminopyridine (10 mg.) was heated at reflux for 30 minutes, allowed to cool and then poured into ice water. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layers were washed with water, dried over anhydrous sodium sulfate and evaporated *in vacuo* to give **16** (2.15 g., 72%); m.p. 111-113°C (recrystallized from ether/hexanes); nmr (deuteriochloroform): δ 9.60 (br s, 1H, NH), 7.30 (d of d, 1H, J = 8.0 H_2, H_4'); 7.00 (d, 1H, $J_{4,5}$ = 3.5 Hz, H_5), 6.70 (d, 2H, J = 8.0 Hz, H_3' and H_5'), 6.10 (d, 1H, $J_{4,5}$ = 3.5 Hz) 2.07 (s, 6H, $OCOCH_3$) and 1.90 (s, 3H, 3-CH_3); ms: 70 eV) m/e 301 (M^+).

Anal. Calcd. for $C_{16}H_{15}NO_5$ (301.29): C, 63.78; H, 5.02; N, 4.65. Found: C, 63.45; H, 4.81; N, 4.90.

Using the same method, **15** (2.20 g., 0.008 mole) was converted to **17** (2.00 g., 70%); m.p. 116-118° (recrystallized from hexanes); nmr (deuteriochloroform): δ 9.80 (br s, 1H, NH), 7.40-7.00 (m, 7H, H_5, H_4' and phenyl H), 6.83 (d, 2H, H_3' and H_5'), 6.33 (d, 1H, H_4) and 2.07 (s, 6H, $OCOCH_3$); ir (potassium bromide): 3.05 (NH), 5.75 and 6.20 μ (C=O); ms: (70 eV) m/e 363(M^+).

Anal. Calcd. for $C_{21}H_{17}NO_5$ (363.36): C, 69.41; H, 4.72; N, 3.86. Found: C, 69.26; H, 4.75; N, 3.95.

4-Methylpyoluteorin *O,O*-Diacetate (**18**).

In the dark, a stirred solution of **16** (2.15 g., 0.007 mole) in methylene chloride (50 ml.) at 5° under a nitrogen atmosphere was treated dropwise with a solution of *t*-butylhypochlorite (1.54 g., 0.0143 mole) in methylene chloride (25 ml.). After stirred at room temperature for 18 hours, the solvent was evaporated *in vacuo* without heating and the residue recrystallized from ether to give **18** (1.60 g., 60%); m.p. 149-150°; nmr (deuteriochloroform): δ 9.40 (br s, 1H, NH), 7.50-7.00 (m, 3H, H_3', H_4' and H_5'), 2.10 (s, 6H, $OCOCH_3$) and 2.00 (s, 3H, CH_3); ms: (70 eV) 370, 372, 374(M^+).

Anal. Calcd. for $C_{16}H_{13}Cl_2NO_5$ (370.18): C, 51.91; H, 3.54; N, 3.78. Found: C, 52.07; H, 3.37; N, 3.79.

4-Phenyl-2,3,5-trichloropyrrole (**20**).

A stirred solution of **17** (1.35 g., 3.7 mmoles) in glacial acetic acid (25 ml.) at 10° was treated dropwise with a solution of chlorine (600 mg.) in acetic acid (10 ml.), stirred at room temperature for 20 hours, then poured into ice water (500 ml.) and extracted with methylene chloride to give a yellow oil. Column chromatography of this oil on silica gel with benzene as the eluent gave **20** (290 mg., 32%); nmr (deuteriochloroform): δ 9.50 (br s, 1H, NH) and 7.28 (s, 5H phenyl H); ir (potassium bromide): 3.00 μ (NH); ms: (70 eV) m/e 247, 245, 243(M^+).

Anal. Calcd. for $C_{10}H_6Cl_3N$ (246.42): C, 48.72; H, 2.45; N, 5.68. Found: C, 48.61; H, 2.40; N, 5.57.

Further elution with chloroform gave unreacted **17** (300 mg., 22%) m.p. 115-117° (recrystallized from hexanes). Similar results were obtained when *t*-butylhypochlorite was used.

Methyl 5-Formyl-4-phenylpyrrole-3-carboxylate (**22**).

Following the procedure of Silverstein, Ryskiewicz and Chaikin (9) for the formylation of pyrrole, **8** (13.6 g., 0.068 mole) was converted to **22** (12.0 g., 70%); m.p. 162-164° (recrystallized from ethanol); nmr (DMSO-d_6): δ 11.60 (br s, 1H, NH), 9.35 (s, 1H, C*H*O), 7.87 (s, 1H, H_5), 7.50 (s, 5H, phenyl H) and 3.63 (s, 3H, CO_2CH_3); ir (potassium bromide): 3.00 (NH), 5.80, 5.95 μ (C=O); ms: (70 eV) m/e 229(M^+).

Anal. Calcd. for $C_{13}H_{11}NO_3$ (229.23): C, 68.11; H, 4.80; N, 6.11. Found: C, 68.10; H, 4.76; N, 6.07.

3-Phenylpyrrole-2-carboxaldehyde (**24**).

A solution of **22** (12.0 g., 0.052 mole) in aqueous 10% sodium hydroxide (200 ml.) was heated at reflux for 2 hours, cooled to 0° and acidified with 6*N* hydrochloric acid. After 1 hour, the precipitate was collected by filtration and air-dried to give **23** (9.00 g., 77%), m.p. 212-214° dec., which was used without further purification. A solution of **23** (3.75 g., 0.017 mole) in ethanolamine (50 ml.) was heated at reflux for 2 hours, cooled and then poured into 500 ml. of ice water. Extraction of the aqueous solution with chloroform followed by evaporation gave an oil which was chromatographed on silica gel. Elution with chloroform gave **24** (1.30 g., 43%); m.p. 156-158° (recrystallized from benzene); nmr (deuteriochloroform): δ 10.37 (br s, 1H, NH), 9.70 (s, 1H, CHO), 7.50 (m, 5H, aryl H); 7.30 (m, 1H, H_5) and 6.50 (m, 1H, H_4); ms: (70 eV) m/e 171(M^+).

Anal. Calcd. for $C_{11}H_9NO$: C, 77.17; H, 5.30; N, 8.18. Found: C, 76.93; H, 5.21; N, 8.02.

Chlorination of **24**.

In the dark, a stirred solution of **24** (670 mg., 3.9 mmoles) in methylene chloride (50 ml.) was treated dropwise with a solution of *tert*-butylhypochlorite (930 mg., 8.6 mmoles) in methylene chloride (15 ml.) over a 15 minute period. After stirring at room temperature overnight, the solvent was evaporated *in vacuo* and the dark red residue was chromatographed on a silica gel column. Elution with chloroform/benzene (1:1) gave the dipyrrylmethene **25** (150 mg., 18%); m.p. 161-164° dec.; nmr (deuteriochloroform): δ 9.60 (br S, 1H, NH), 7.50 (m, 10H, phenyl H) and 6.83 (s, 1H, -C*H*=C); ms: (70 eV) m/e 435, 433, 431(M^+).

Anal. Calcd. for $C_{21}H_{12}Cl_4N_2$ (434.15): C, 57.96; H, 2.79; N, 6.45. Found: C, 57.86; H, 2.71; N, 6.40.

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