Synthesis of Some 1-Methyl-3-Alkoxy-5-Arylpyrrolecarboxylic Acids and Derivatives (1)

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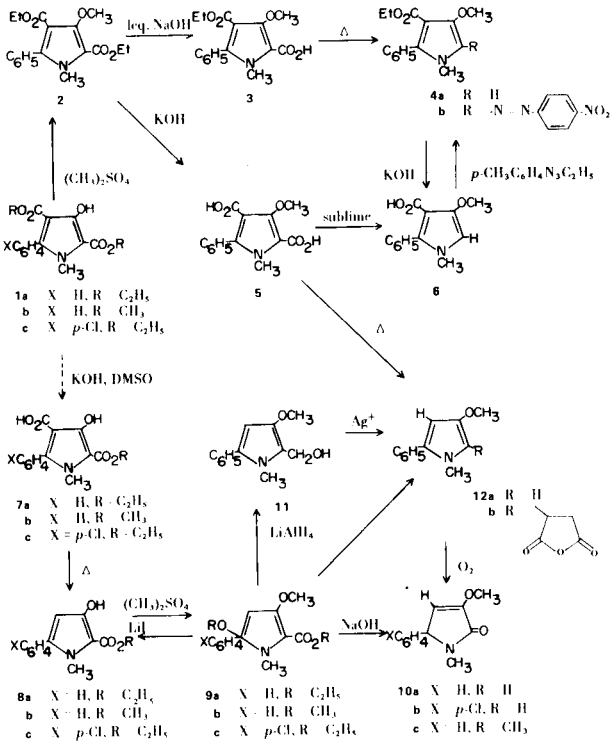
By a combination of hydrolysis, decarboxylation, and methylation diethyl 1-methyl-3-hydroxy-5-phenylpyrrole-2,4-dicarboxylate was converted into 1-methyl-3-methoxy-5-phenylpyrrole-2,4-dicarboxylic acid (**5**) and into the isomeric compounds ethyl 1-methyl-2-phenyl-4-methoxypyrrole-3-carboxylate (**4a**) and ethyl 1-methyl-3-methoxy-5-phenylpyrrole-2-carboxylate (**9a**). 1-Methyl-2-phenyl-4-methoxypyrrole-3-carboxylic acid was synthesized both by the selective decarboxylation of **5** and by the hydrolysis of **4a**. Hydrolysis of **9a**, however, did not give the corresponding acid, but rather an oxidation product, 1-methyl-3-methoxy-5-hydroxy-5-phenyl-3-pyrrolin-2-one (**10a**). Compound **10a** was shown to arise from the air oxidation of the completely decarboxylated product, 1-methyl-2-phenyl-4-methoxypyrrole. Reduction of **9a** with lithium aluminum hydride gave 1-methyl-3-methoxy-5-phenylpyrrole-2-methanol, which yielded **10a** upon oxidation with silver oxide.

We recently reported (3) the synthesis of compound **1a**, diethyl 1-methyl-3-hydroxy-5-phenylpyrrole-2,4-dicarboxylate. Because of continued interest in the wide spectrum of biological activity exhibited by the pyrrole acids (*e.g.* references 4-7) we undertook an investigation of the chemistry of **1a** and some of its derivatives. The compounds and synthetic routes discussed in this paper are illustrated in scheme I.

The treatment of **1a** wtih dimethyl sulfate according to the recommendations of Chong and Clezy (8) gave diethyl 1-methyl-3-methoxy-5-phenylpyrrole-2,4-dicarboxylate, **2**, in excellent yield. Hydrolysis of **2** according to established procedures (9) with exactly one equivalent of hydroxide gave 1-methyl-3-methoxy-4-ethoxycarbonyl-5-phenylpyrrole-2-carboxylic acid, **3**, again in good yield. This acid decarboxylated cleanly upon heating under vacuum, giving ethyl 1-methyl-2-phenyl-4-methoxypyrrole-3-carboxylate, **4a**. This ester proved to be somewhat unstable, darkening over several hours. However, it reacted rapidly and cleanly with *p*-nitrobenzenediazonium acetate (see Treibs and Ohorodnik (10) for other examples of this reaction) to give the stable, crystalline compound, ethyl 1-methyl-5-(*p*-nitrophenylazo)-4 methoxy-2-phenylpyrrole-3-carboxylate, **4b**.

Compound **4a** proved to be somewhat resistant to hydrolysis (see Experimental) but upon treatment with excess hydroxide 1-methyl-2-phenyl-4-methoxypyrrole-3-carboxylic acid, **6**, was obtained in moderate yield. The ester, **4a**, could be regenerated from the acid, **6**, by treatment with 1-ethyl-3-*p*-tolytriazene in ether and alcohol, although this reaction required several days to go to completion. This reaction is reported to proceed much

Scheme I



faster in non-polar solvents (11) but the use of alcohol was necessary in this case because of solubility problems.

If **2** was treated with excess hydroxide, 1-methyl-3-methoxy-5-phenylpyrrole-2,4-dicarboxylic acid, **5**, was obtained cleanly. Upon sublimination, this diacid was selectively decarboxylated to the 3-acid, **6**. It has been demonstrated with derivatives of Knorr's pyrrole (reference 9, p. 304-305) that a pyrrole α-carboxylic acid decarboxylates at a lower temperature than the isomeric β-acid, mirroring the greater reactivity of the α-position. Thus, this selective decarboxylation of **5** is another manifestation of the enhanced basisity of the 2-position.

The classical method for the selective hydrolysis of a pyrrole 2,4-diester at the 4-position is treatment with concentrated sulfuric acid (12). This procedure, when applied to the diester **1a**, gave 1-methyl-5-ethoxycarbonyl-4-hydroxy-2-phenylpyrrole-3-carboxylic acid, **7a**, in moderate yield. We have found, however, that **7a** can be obtained in much better yield by the treatment of **1a** under the conditions used by Taub *et. al.*, (13) for the hydrolytic cleavage of the lactone group of zearolenone, *i.e.* excess potassium hydroxide in hot, aqueous DMSO. This hydrolysis is presumably selective because of the protection of the pyrrole-2-ester by a 3-hydroxy group as described by Chong and Clezy (8). Like **3**, the 3-acid **7a** decarboxylated smoothly to give ethyl 1-methyl-3-hydroxy-5-phenylpyrrole-2-carboxylate, **8a**, which provided ethyl 1-methyl-3-methoxy-5-phenylpyrrole-2-carboxylate, **9a**, upon treatment with dimethyl sulfate.

In 1953, Davoll (14) discussed a compound, $C_{13}H_{13}NO_3$, m.p. 182-183° to which he attributed the structure of methyl 1-methyl-3-hydroxy-5-phenylpyrrole-2-carboxylate, **8b**. Since this compound was available unambiguously from our work, the methyl esters **1b** and **7b** were synthesized in an identical manner to the ethyl esters **1a** and **7a**. Compound **7b** was decarboxylated by treatment with hot trifluoroacetic acid, giving **8b**, m.p. 61-62°. It is unlikely that Davoll's compound was **8b** because of the discrepancy in melting points.

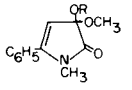
Hot trifluoroacetic acid was employed for the transformation of **7b** to **8b** since the decarboxylation temperature of **7b** in a melting point capillary was determined to be quite high. Furthermore, since **8b** proved to be a crystalline compound it was convenient to work it up from a solvent.

In order to demonstrate that it was possible to vary the aryl group in these pyrroles, the reaction to give compound **1a** and the subsequent reactions to give compound **9a** were duplicated on the *p*-chloro analogs, giving compounds **1c** and **7c-9c**, all in good yield. The decarboxylation with hot trifluoroacetic acid was employed for the transformation of **7c** to **8c**.

Of the hydroxypyrroles **1a, b, c, 7a, b, c,** and **8a, b, c** the evidence given by ir is that **1** and **7** are indeed hydroxypyrroles (no ketone absorption below 5.95 μ). Compounds **8**, however, exhibit absorption at 5.90 μ as well as at 6.10 μ in chloroform solution, indicating that they exist at least to a certain extent as 3-oxo-4-pyrrolines (8, 15).

The ester **9a** is isomeric with compound **4a** and their structures are clearly defined by nmr (see Table I). Of particular significance is the shielding of the 3-ester of **4a**, presumably by the phenyl group orthogonal to the plane of the pyrrole ring. This shielding clearly distinguishes between the two ester groups of compounds **1a** and **2** and clearly indicates that the structures of the isomers **4a** and **9a** are as indicated (Scheme I).

All attempts to hydrolyze **9a** to the 2-acid which would be isomeric with compound **6** met with failure. Like ester **4a**, ester **9a** proved to be resistant to mild hydrolysis. When more drastic conditions were employed (large excesses of hydroxide in a variety of co-solvents), dark tars were obtained along with a small amount of an oxidized product, identified as 1-methyl-3-methoxy-5-hydroxy-5-phenyl-3-pyrroline-2-one, **10a**. Spectral data did not conclusively rule out the methyl hemiketal of 1-methyl-5-phenyl-4-pyrroline-2,3-dione, **A**, as the structure for **10a**, although the stability of the compound to acid made structure **A** unlikely. Indeed, nmr of the methylated compound, **10c**, confirmed the indicated (Scheme I) 3-methoxy-3-pyrroline structure for **10a** since the chemical shifts of the two methoxy groups were very different, even at 160°. This high temperature nmr was run to rule out the possibility that the structure of the methylated product was the dimethyl ketal, **B**, and that the methoxy groups had different chemical shifts due to some distortion of the pyrrolidone ring.



A. R = H
B. R = CH_3

Drawing on a knowledge of some of the oxidations observed with various pyrroles (see reference (3) and references contained therein) it seemed to us that **10a** might be arising by the rapid decarboxylation of the initially formed 2-acid to give compound **12a**, 1-methyl-2-phenyl-4-methoxypyrrole, which reacted with oxygen in the manner shown in Scheme II. To test this theory,

Scheme II

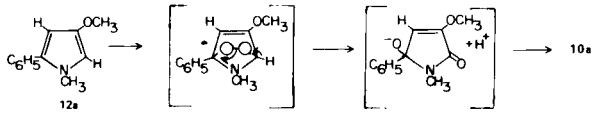


Table 1

Nmr Chemical Shifts of Pyrrole Esters and Derivatives (a)

Compound	α-$CO_2CH_2CH_3$		β-$CO_2CH_2CH_3$		α-H	β-H	NCH_3 (b)	OCH_3
	CH_2	CH_3	CH_2	CH_3				
1a (c)	4.30	1.38	4.02	0.96			3.58	
1c	4.22	1.33	4.00	1.00			3.52	
2	4.33	1.38	4.05	1.01			3.58	3.92
3			4.00	0.95			3.60	4.08
4a			3.90	0.98	6.03		3.60	3.22
4b			4.01	1.00			3.64	4.16
5							3.53	3.90
6					6.36		3.68	3.28
7a	4.35	1.38					3.56	
7c	4.30	1.37					3.54	
8a	4.28	1.35				5.65	3.60	
8c	4.35	1.38				5.76	3.60	
9a	4.18	1.28				5.70	3.66	3.66
9c	4.30	1.36				5.82	3.70	3.80
11						6.00	3.57	3.65
12a					6.02	5.68	3.56	3.44
12b						5.88	3.64	3.49

(a) Chemical shifts are given in ppm downfield from TMS. (b) Since the chemical shift of the *N*-methyl group was relatively constant in the range 3.60-3.70 ppm for compounds **1**, **7**, **8**, and **9**, the three proton singlet nearest 3.60 ppm was assigned to the *N*-methyl absorption for all compounds having both *N*-methyl and *O*-methyl groups. The methyl group of *N*-methylpyrrole itself appears at 3.50 ppm (J. C. N. Ma and E. W. Warnhoff, *Can. J. Chem.*, **43**, 1849 (1965)). (c) This compound is reported in reference 3.

the diacid, **5**, was heated strongly under vacuum and a pale yellow oil was isolated by distillation. By carefully handling this oil under nitrogen, spectroscopy (nmr) proved it to be the completely decarboxylated pyrrole, **12a**. Immediately upon contact with oxygen this oil began to darken and to precipitate a white solid, **10a**. It seemed that since compound **12a** reacted with oxygen in this manner it might condense with maleic anhydride. Indeed, it reacted to give compound **12b**, α-(1-methyl-3-methoxy-5-phenyl-2-pyrryl)succinic anhydride, in the manner found for other pyrroles (16).

Reduction of the 2-ester, **9a**, with lithium aluminum hydride gave the very unstable 1-methyl-3-methoxy-5-phenylpyrrole-2-methanol, **11**. Sonnet (17) reported the synthesis of a pyrrole-2-methanol with lithium aluminum hydride but offered no proof of structure. Since **11** was stable as a dilute solution in certain solvents we were able to demonstrate its existence by nmr in pyridine-d_5. It was hoped that oxidation of **11** with silver oxide/pyridine complex (18) might yield the 2-acid, since silver oxide has proved useful in heterocyclic work (19). However, the only product of this reaction, obtained in good yield, was **10a**. It may be that the 2-acid is indeed produced by oxidation with silver and then decarboxylates to **12a** which reacts with atmospheric oxygen to give **10a**. On the other hand, the direct oxidation of **11** to **10a** by silver oxide, bypassing **12a**, cannot be ruled out.

In one attempt to hydrolyze the ester **9a** to the corresponding 2-acid, **9a** was subjected to conditions of nucleophilic ester cleavage, anhydrous lithium iodide in refluxing pyridine (20a). It was very surprising to find that the major product of this reaction was the hydroxyester, **8a**, resulting from the preferential cleavage of the methyl ether rather than the ethyl ester. Since the methyl ester **9b** was available by the transesterification of **9a** in sodium methoxide it also was subjected to lithium iodide in pyridine. The results of this experiment were less well defined, however. A number of products were obtained, along with a good deal of dark tars. Analysis of the reaction mixture by tlc showed that starting material was still present, but neither the hydroxyester **9b** nor the hydroxylactam **10a** had been formed. The former would have arisen from cleavage at the methyl ether and the latter from cleavage at the methyl ester. Thus, it must be that this reagent is cleaving both the methyl ether and methyl ester in the same molecule. It was not surprising that the ethyl ester **9a** was cleaved cleanly to the hydroxyester while the methyl ester **9b** was not, in view of the fact that ethyl esters are cleaved by this nucleophilic reagent only with difficulty (20b). It is interesting to note that the methyl ether in this compound behaves like a vinylogous methyl ester, behavior which is consistent with other characteristics of these 3-methoxypyrroles.

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 on a Varian Associates' HA-100 instrument operating in the frequency sweep mode and using tetramethylsilane as the standard. Mass spectra were determined on a Varian MAT CH-7 spectrometer at 70eV. Magnesium sulfate was used as a drying agent except where otherwise indicated.

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. Analyses were obtained courtsey of Galbraith Laboratories, Knoxville, Tennessee.

Dimethyl 1-Methyl-3-hydroxy-5-phenylpyrrole-2,4-dicarboxylate (**1b**).

Following the procedure reported for the preparation of **1a** (3) diethyl benzylidenemalonate and ethyl sarcosinate were condensed in methanolic sodium methoxide to give dimethyl 1-methyl-3-oxo-5-phenylpyrrolidine-2,4-dicarboxylate in 36% crude yield; ir: 5.61 (C=O, 5-membered ring ketone), 5.75 μ (c=O, broad, esters). This crude material was treated without further purification, as reported for the synthesis of **1a**, to give **1b** in 50% yield, m.p. 122-123° (methanol); ir (potassium bromide): 3.25 (-OH, broad), 5.95 (C=O, ester), 6.00 μ (C=O, ester); nmr (deuteriochloroform): δ 3.56 (s, 6H, $-NCH_3$, 4-CO_2CH_3) 3.85 (s, 3H, 2-CO_2CH_3), 7.16-7.40 (m, 5H aromatics), 9.24 (s, 1H, exchanges with deuterium oxide -OH).

Anal. Calcd. for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84; m.w. 289. Found: C, 62.24; H, 5.13; N, 4.75; M^+ 289.

Diethyl 1-Methyl-3-hydroxy-5-(*p*-chlorophenyl)pyrrole-2,4-dicarboxylate (**1c**).

Following the procedure reported for the preparation of **1a** (3) diethyl *p*-chlorobenzylidenemalonate and ethyl sarcosinate were condensed to give diethyl 1-methyl-3-oxo-5(*p*-chlorophenyl)-pyrrolidine-2,4-dicarboxylate in 60% crude yield; ir: 5.65 (C=O, 5-membered ring ketone), 5.75 μ (C=O, broad, esters). This crude material was treated without further purification, as reported for the synthesis of **1a**, to give **1c** in 55% yield, m.p. 106-107° (methanol/water, *ca* 5:1); ir (potassium bromide): 3.0 (-OH, broad), 5.95 (C=O, ester), 6.00 μ (C=O, ester); nmr (carbon tetrachloride): δ 1.00 (t, 3H, J = 7 Hz, 4-$CO_2CH_2CH_3$), 1.33 (t, 3H, J = 7 Hz, 2-$CO_2CH_2CH_3$), 3.52 (s, 3H, $-NCH_3$), 4.00 (q, 2H, J = 7 Hz 4-$CO_2CH_2CH_3$), 4.22 (q, 2H, J = 7 Hz, 2-$CO_2CH_2CH_3$), 7.16 (d, 2H, J_{ortho} = 8 Hz (21)) 7.30 (d, 2H, J_{ortho} = 8 Hz), 8.88 (s, 1H, exchanges with deuterium oxide, -OH).

Anal. Calcd. for $C_{17}H_{18}ClNO_5$: C, 58.03; H, 5.18; N, 3.99; Cl, 10.10; m.w. 351.5. Found: C, 58.21; H, 5.36; N, 4.05; Cl, 9.91; M^+ 351, 353 (^{37}Cl).

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

The hydroxypyrrole **1a** (5.0 g.; 15.7 mmoles) was refluxed overnight in 500 ml. of anhydrous acetone containing 6 g. (47.6 mmoles) dimethyl sulfate and 20 g. (145 mmoles) of anhydrous potassium carbonate. Vigorous stirring was applied to maintain a suspension of the inorganic salts. At the end of the reflux period the salts were filtered off and most of the acetone removed under reduced pressure. The residue was shaken for five minutes with 50 ml. of concentrated ammonium hydroxide to destroy the excess dimethyl sulfate, diluted with 25 ml. of water, and then extracted with two 50 ml. portions of chloroform. The chloroform was dried and removed under reduced pressure to give tan crystals which, after one recrystallization from ethanol/water (*ca* 5:1), yielded 4.6 g. (89%) of **2** as white crystals, m.p. 58-60°; ir (potassium bromide): 5.95 μ (C=O, broad, aryl esters); nmr (deuteriochloroform): δ 1.01 (t, 3H, J = 7 Hz, 4-$CO_2CH_2CH_3$, 1.38 (t, 3H, J = 7 Hz, 2-$CO_2CH_2CH_3$), 3.58 (s, 3H, $-NCH_3$), 3.92 (s, 3H, $-OCH_3$), 4.05 (q, 2H, J = 7 Hz, 4-$CH_2CH_2CH_3$), 4.33 (q, 2H, J = 7 Hz, 2-$CH_2CH_2CH_3$), 7.15-7.45 (m, 5H, aromatics).

Anal. Calcd. for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23; m.w. 331. Found: C, 65.13; H, 6.20; N, 4.42; M^+ 331.

1-Methyl-3-methoxy-4-ethoxycarbonyl-5-phenylpyrrole-2-carboxylic Acid (**3**).

The methoxydiester, **2**, (2.0 g., 6.05 mmoles) was dissolved in 120 ml. of 95% ethanol, 0.1 *N* sodium hydroxide added (60.5 ml., 6.05 mmoles), and this solution refluxed 30 minutes. At the end of this time the reaction was cooled, poured into 50 ml. of water and extracted with one 50 ml. portion of chloroform. The aqueous phase was made strongly acidic with concentrated hydrochloric acid and extracted with two 50 ml. portions of chloroform. Upon drying and concentrating this final organic phase under reduced pressure, white crystals of **3** were formed, which after one recrystallization from carbon tetrachloride amounted to 1.21 g. (66%) m.p. 134-136° dec.; ir (potassium bromide): 3.00-4.50 (-OH, acid) 5.84 (C=O, aryl ester), 6.01 μ (C=O, aryl acid); nmr (deuteriochloroform): δ 0.95 (t, 3H, J = 7 Hz, 4-$CO_2CH_2CH_3$), 3.60 (s, 3H, $-NCH_3$), 4.00 (q, 2H, J = 7 Hz, 4-$CO_2CH_2CH_3$), 4.08 (s, 3H, $-OCH_3$), 7.15-7.45 (m, 5H, aromatics), 9.50-10.10 (broad, 1H, exchanges with deuterium oxide, -COOH).

Anal. Calcd. for $C_{16}H_{17}NO_5$: C, 63.35; H, 5.65; N, 4.62; m.w. 303. Found: C, 63.24; H, 5.58; N, 4.60; M^+ 303.

Ethyl 1-Methyl-2-phenyl-4-methoxypyrrole-3-carboxylate (**4a**).

The acid **3** (2.0 g., 6.6 mmoles) was heated under vacuum (0.1 mm) in a 190° oil bath. It decarboxylated rapidly and **4a** distilled from the foaming melt, b.p. 153-155°, yielding 1.6 g. (94%); ir (CCl_4, AgCl) 5.85 μ (C=O, aryl ester); nmr (carbon tetrachloride): δ 0.98 (t, 3H, J = 7 Hz, 3-$CO_2CH_2CH_3$), 3.22 (s, 3H, $-OCH_3$), 3.60 (s, 3H, $-NCH_3$), 3.90 (q, 2H, J = 7 Hz, 3-$CO_2CH_2CH_3$); 6.03 (s, 1H, H-5), 7.20 (s, 5H, aromatics); m.w. Calcd. for $C_{15}H_{17}NO_3$, 259. Found: M^+ 259.

This compound proved to be too unstable for analysis so the azo derivative, **4b**, was synthesized as follows: *p*-nitroaniline (0.27 g., 1.95 mmoles) was dissolved in 5 ml. of glacial acetic acid and chilled in ice. A few chips of ice were added and then a solution of sodium nitrite (0.15 g., 2.17 mmoles) in 5 ml. of chilled water was added. This mixture was neutralized to *p*H 6.0-6.5 with solid potassium carbonate and to it was added 0.5 g. (1.93 mmoles) of the ester, **4a**, in 5 ml. of glacial acetic acid. A red precipitate formed immediately and coagulated into a large sticky mass. The liquid was decanted and this material crystallized from 95% ethanol, giving red needles of **4b** (0.5 g., 63%) m.p. 132-133°; ir (potassium bromide): 5.95 (C=O, ester), 6.65, 7.55 μ ($-NO_2$); nmr (deuteriochloroform): δ 1.00 (t, 3H, J = 7 Hz, 4-$CO_2CH_2CH_3$), 3.64 (s, 3H, $-NCH_3$), 4.01 (q, 2H, J = 7 Hz, 4-$CO_2CH_2CH_3$), 4.16 (s, 3H, $-OCH_3$), 7.20-7.44 (m, 5H, 5-phenyl), 7.70 (d, 2H, J_{ortho} = 8 Hz), 8.18 (d, 2H, J_{ortho} = 8 Hz).

Anal. Calcd. for $C_{21}H_{20}N_4O_5$: C, 61.76; H, 4.94; N, 13.72; m.w. 408. Found: C, 61.96; H, 4.93; N, 13.65; M^+ 408.

1-Methyl-3-methoxy-5-phenylpyrrole-2,4-dicarboxylic Acid (**5**).

The methoxydiester, **2**, (1.8 g., 5.45 mmoles) was suspended in 20 ml. of 5*N* potassium hydroxide, 60 ml. of 95% ethanol added, and this reaction refluxed 30 minutes. The solution was poured into 100 ml. of water and extracted with two 30 ml. portions of methylene chloride. The aqueous phase was chilled and made strongly acidic with concentrated hydrochloric acid, then extracted with four 50 ml. portions of 2:1 methylene chloride-ether. These combined extracts were dried and concentrated under reduced pressure to give 1.33 g. (89%) of **5** as white crystals, m.p. 153-155° dec. The analytical sample was prepared by recrystallization from acetic acid-water (*ca* 3:1) and had m.p. 155-157° dec., but this material was usually used without further purification: ir (potassium bromide): 3.0-4.5 (-OH, acid), 6.1 μ (C=O, broad, aryl acids); nmr (deuteriochloroform-DMSO-d_6): δ 3.53 (s, 3H, $-NCH_3$), 3.90 (s, 3H, $-OCH_3$), 7.20-7.40 (m, 5H, aromatics). The acid protons were not generally visible in DMSO-d_6.

Anal. Calcd. for $C_{14}H_{13}NO_5$: C, 61.09; H, 4.76; N, 5.09; m.w. 275. Found: C, 61.37; H, 5.06; N, 5.21; M^+ 275.

1-Methyl-2-phenyl-4-methoxypyrrole-3-carboxylic Acid (**6**).

A. The methoxyester, **4a**, (0.3 g., 1.16 mmoles) was dissolved in 20 ml. of 95% ethanol and 5 ml. of 5*N* potassium hydroxide, then refluxed 30 minutes. At the end of this time the solution was poured into 50 ml. of water and extracted once with 25 ml. of chloroform. The aqueous phase was chilled and acidified to *p*H 3.0-4.0 with 10% hydrochloric acid. White crystals precipitated which were filtered and dried to yield 0.14 g. (52%) **6**, m.p. 166° dec., (ethyl acetate); ir (potassium bromide): 3.00-4.50 (-OH, acid), 6.00 μ (C=O, aryl acid); nmr (deuteriochloroform/-DMSO-d_6): δ 3.28 (s, 3H, $-OCH_3$), 3.68 (s, 3H, $-NCH_3$), 6.36 (s, 1H, H-5), 7.15-7.30 (m, 5H, aromatics).

Anal. Calcd. for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06; m.w. 231. Found: C, 67.68; H, 5.61; N, 5.98; M^+ 231.

The ester **4a** was unaffected by a 60 minutes reflux in 20 ml. of ethanol containing exactly one equivalent of 0.1*N* sodium hydroxide (11.6 ml.). Unreacted starting material was recovered from the original chloroform extract of the basic reaction mixture and acidification of the aqueous phase gave no organic material.

The acid **6** (0.10 g., 0.43 mmoles) was dissolved in a solution of 3 ml. of diethyl ether and 2 ml. of absolute ethanol and 0.9 ml. of a 0.49*M* (0.44 mmole) solution of 1-ethyl-3-*p*-tolyltriazine (available from Willow Brook Labs) in ether was added. After stirring for 48 hours, tlc indicated that the reaction was complete. The solution was poured into 20 ml. of ether and washed with two 10 ml. portions of 10% hydrochloric acid and one 10 ml. portion of saturated sodium bicarbonate solution. The organic phase was dried and concentrated under reduced pressure to give a yellow oil that was identical by tlc and nmr to the ester **4a**.

B. The diacid, **5**, (0.5 g., 1.82 mmoles) was heated at 180°/-0.5 mm in a sublimation apparatus with the cold finger at dry ice/-ethanol temperature. The 3-acid, **6**, was collected from the cold finger (0.35 g., 83%) and was identical in all aspects with the compound obtained as in A above.

1-Methyl-5-ethoxycarbonyl-4-hydroxy-2-phenylpyrrole-3-carboxylic Acid (**7a**).

A. The hydroxydiester, **1a** (10.0 g., 31.6 mmoles) was dissolved in 30 ml. concentrated sulfuric acid and allowed to remain undisturbed at room temperature for 20 hours. The dark solution was then poured over 200 g. of ice and made strongly basic with 10% sodium hydroxide. This basic solution was extracted with chloroform until the organic extracts were no longer colored (usually three 100 ml. portions) and then chilled and made strongly acidic with concentrated hydrochloric acid. Extraction with chloroform (three 100 ml. portions) followed by drying of the combined organic phases and concentration under reduced pressure gave 7.17 g. of brown crystals, m.p. 140-148°. One recrystallization from benzene/cyclohexane (*ca* 3:1) gave 5.1 g. (56%) of white crystals, m.p. 154-157° dec; The analytical sample required one more recrystallization from benzene/cyclohexane, m.p. 155-157° dec.; ir (potassium bromide): 3.00-4.30 (-OH, acid), 6.00 (C=O, aryl ester); 6.01 μ (C=O, aryl acid); nmr (deuteriochloroform): 1.38 (t, 3H, J = 7 Hz, 5-$CO_2CH_2CH_3$), 3.56 (s, 3H, $-NCH_3$), 4.35 (q, 2H, J = 7 Hz, 5-$CO_2CH_2CH_3$), 7.20-7.44 (m, 5H, aromatics), 9.40 (broad, 2H, exchanges with deuterium oxide, COOH, OH).

Anal. Calcd. for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84; m.w. 289. Found: C, 62.09; H, 5.21; N, 4.72; M^+ 289.

B. To a solution of **1a** (18.2 g., 57.5 mmoles) in 180 ml. of DMSO under nitrogen was added dropwise 110 ml. of 5*N* potassium hydroxide (550 mmoles). The mixture was heated at 95° (hot water bath) for 3 hours then poured into 100 ml. of ice and water. This solution was made strongly acidic with concentrated hydrochloric acid and then extracted with three 150 ml. portions of chloroform. After four 50 ml. washes with water to remove the residual DMSO, the combined chloroform extracts were dried and concentrated under reduced pressure to give tan crystals which after one recrystallization from ethanol/water (*ca* 5:1) yielded 13.2 g. (80%) of crystals, m.p. 153-155°, identical in all respects with the compound isolated as in A above.

1-Methyl-5-methoxycarbonyl-4-hydroxy-2-phenylpyrrole-3-carboxylic Acid (**7b**).

The hydroxydiester **1b** was treated in a manner analogous to **1a** under B above to give **7b** in 75% yield, m.p. 180-182° dec., (methanol); ir (potassium bromide): 3.00-3.50 (-OH, acid), 5.95 (C=O, aryl ester) 6.10 μ (C=O, aryl acid); nmr (deuteriochloroform-DMSO-d_6): δ 3.54 (s, 3H, $-NCH_3$), 3.82 (s, 3H, 5-CO_2CH_3), 7.26-7.40 (m, 5H, aromatics).

Anal. Calcd. for $C_{14}H_{13}NO_5$: C, 61.09; H, 4.76; N, 5.09; m.w. 275. Found: C, 61.30; H, 4.79; N, 5.02; M^+ 275.

1-Methyl-5-ethoxycarbonyl-4-hydroxy-2-*p*-chlorophenylpyrrole-4-carboxylic Acid (**7c**).

The hydroxydiester **1c** was treated in a manner analogous to **1a** under B above to give **7c** in 72% yield, m.p. 193-195° dec., (methanol/water, *ca* 5:1) ir (potassium bromide): 3.00-4.00 (-OH, acid), 6.00 (C=O, aryl ester), 6.15 μ (C=O, aryl acid); nmr (deuteriochloroform): δ 1.37 (t, 3H, J = 7 Hz, 5-$CO_2CH_2CH_3$), 3.54 (s, 3H, $-NCH_3$), 4.30 (q, 2H, J = 7 Hz, 5-$CO_2CH_2CH_3$), 7.20 (d, 2H, J_{ortho} = 9 Hz), 7.36 (d, 2H, J_{ortho} = 9 Hz), 9.70 (broad, 2H, exchanges with deuterium oxide, -COOH, -OH).

Anal. Calcd. for $C_{15}H_{14}ClNO_5$: C, 55.64; H, 4.36; N, 4.33; Cl, 10.96; m.w. 323.5. Found: C, 55.52; H, 4.44; N, 4.34; Cl, 11.11; M^+ 323, 325 (^{37}Cl).

Ethyl 1-Methyl-3-hydroxy-5-phenylpyrrole-2-carboxylate (**8a**).

The 3-acid, **7a** (3.15 g., 10.9 mmoles) was heated under vacuum (0.5 mm) in a 200° oil bath. It decarboxylated rapidly and **8a** distilled from the foaming melt, b.p. 158-160°, yielding 1.98 g. (75%) ir (sodium chloride, chloroform): 5.90 (C=O, vinylogous amide), 6.1 μ (C=O, ester); nmr (deuteriochloroform): δ 1.35 (t, 3H, J = 7 Hz, 2-$CO_2CH_2CH_3$), 3.60 (s, 3H, $-NCH_3$), 4.28 (q, 2H, J = 7 Hz, 2-$CO_2CH_2CH_3$), 5.65 (s, 1H, H-4), 7.28 (s, 5H, aromatics), 8.10 (broad, 1H, exchanges with deuterium oxide, -OH).

Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.17; N, 5.71; m.w. 245. Found: C, 68.37; H, 6.20; N, 5.61; M^+ 245.

Methyl 1-Methyl-3-hydroxy-5-phenylpyrrole-2-carboxylate (**8b**).

The hydroxyacid, **7b**, (2.4 g., 8.8 mmoles) was dissolved in 8 ml. of trifluoroacetic acid and warmed on a steam bath 20 minutes. This mixture was then poured into 25 ml. methylene chloride and washed with 25 ml. of water, 25 ml. of saturated sodium bicarbonate solution, and 25 ml. of water again. The organic phase was dried and concentrated under reduced pressure to give an oil which crystallized as a slightly red compound from methanol (1.0 g. 50%). One recrystallization from petroleum ether (Norite) gave white crystals, m.p. 61-62°; ir (sodium chloride, chloroform): 5.88 (C=O, vinylogous amide), 6.10 μ (C=O, ester); nmr (deuteriochloroform): δ 3.63 (s, 3H, $-NCH_3$), 3.88 (s, 3H, $2-CO_2CH_3$), 5.78 (s, 1H, H-4), 7.30 (s, 5H, aromatics), 8.18 (s, 1H, exchanges with deuterium oxide, -OH).

Anal. Calcd. for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.66; N, 6.06; m.w. 231. Found: C, 67.75; H, 5.72; N, 5.96; M^+ 231.

Ethyl 1-Methyl-3-hydroxy-5-(*p*-chlorophenyl)pyrrole-2-carboxylate (**8c**).

The hydroxyacid, **7c**, (7.70 g., 23.8 mmoles) was treated as for **8b** above, giving, after one recrystallization from cyclohexane, white crystals (4.7 g., 71%) m.p. 105-106°; ir (sodium chloride, chloroform): 5.90 (C=O, vinylogous amide) 6.10 μ (C=O, ester); nmr (deuteriochloroform): δ 1.38 (t, 3H, J = 7 Hz, $2-CO_2CH_2CH_3$), 3.60 (s, 3H, $-NCH_3$), 4.35 (q, 2H, J = 7 Hz, $2-CO_2CH_2CH_3$), 5.76 (s, 1H, H-4), 7.18 (d, 2H, J_{ortho} = 9 Hz), 7.30 (d, 2H, J_{ortho} = 9 Hz), 8.20 (broad, 1H, exchanges with deuterium oxide, -OH).

Anal. Calcd. for $C_{14}H_{14}ClNO_3$: C, 60.11; H, 5.04; N, 5.01; Cl, 12.68; m.w. 279.5. Found: C, 60.35; H, 4.97; N, 5.03; Cl, 12.83; M^+ 279, 281 (^{37}Cl).

Ethyl 1-Methyl-3-methoxy-5-phenylpyrrole-2-carboxylate (**9a**).

The hydroxyester, **8a** (10.45 g., 42.5 mmoles) was dissolved in 1 l. of dry acetone and treated with dimethyl sulfate (12 g., 95.4 mmoles) and anhydrous potassium carbonate (40 g., 290 mmoles) in a manner analogous to the production of **2**. Workup as for **2** gave 10.2 g. (92%) of an oil, b.p. 151-153°/0.3 mm. This material crystallized after standing several days to give a solid, m.p. 42-44°; ir (sodium chloride, neat) 5.98 μ (C=O, aryl ester); nmr (deuteriochloroform): δ 1.28 (t, 3H, J = 7 Hz, $2-CO_2CH_2CH_3$), 3.66 (s, 6H, $-NCH_3$, $-OCH_3$), 4.18 (q, 2H, J = 7 Hz, $2-CO_2CH_2CH_3$), 5.70 (s, 1H, H-4), 7.20 (s, 5H, aromatics).

Anal. Calcd. for $C_{15}H_{17}NO_3$: C, 69.47; H, 6.61; N, 5.40; m.w. 259. Found: C, 69.43; H, 6.68; N, 5.73; M^+ 259.

The hydrazide of **9a** was made by standard methods (22) although tlc indicated that the reaction was complete only after three days of refluxing in ethanol, m.p. 101-102° (ethanol/water, *ca* 5:1).

Anal. Calcd. for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13. Found: C, 63.75; H, 6.35; N, 16.94.

The ester **9a** (0.5 g., 1.93 mmoles) was dissolved in 30 ml. of dry pyridine and anhydrous lithium iodide (2.5 g., 18 mmoles) was added. After refluxing 16 hours, the reaction was cooled, poured into 40 ml. of chloroform, and washed with 20 ml. portions of 5% hydrochloric acid until the washes remained strongly acidic. The organic phase was then extracted with two 30 ml. portions of *N* sodium hydroxide and the combined aqueous extracts were made strongly acidic (concentrated hydrochloric acid) and extracted with chloroform. These last extracts were shown to contain no organic material (tlc) but the original chloroform phase was shown by tlc to contain **8a** as the major component with a small amount of starting material present. Some of this material was purified by preparative tlc and shown to be identical with **8a** by its mass spectrum and nmr.

Methyl 1-Methyl-3-methoxy-5-phenylpyrrole-2-carboxylate (**9b**).

The methoxyester **9a** (0.85 g., 3.28 mmoles) was refluxed for 2 hours in 50 ml. of anhydrous methanol containing 0.5 g. (22 mmoles) of sodium. The mixture was poured into 50 ml. of water and extracted with two 30 ml. portions of chloroform. Drying and concentration of the combined chloroform phases gave an oil which crystallized from methanol/water (*ca* 5:1) to give 0.75 g. (94%) of white crystals, m.p. 67-69°; ir 5.97 μ (C=O, ester); nmr (deuteriochloroform): δ 3.65 (s, 3H, $-NCH_3$), 3.67 (s, 6H, $-OCH_3$, $2-CO_2CH_3$), 5.70 (s, 1H, H-4), 7.21 (s, 5H, aromatics).

Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.16; N, 5.71; m.w. 245. Found: C, 68.82; H, 6.35; N, 5.73; M^+ 245.

Ethyl 1-Methyl-3-methoxy-5-(*p*-chlorophenyl)pyrrole-2-carboxylate (**9c**).

The hydroxyester, **8c** (1.65 g., 5.9 mmoles) was treated with dimethyl sulfate in a manner analogous to the synthesis of **9a** above. Workup gave 1.3 g. (75%) of white crystals, m.p. 107-108° (ethanol); ir (potassium bromide): 6.00 μ (C=O, aryl ester); nmr (deuteriochloroform): δ 1.36 (t, 3H, J = 7 Hz, $2-CO_2CH_2CH_3$), 3.70 (s, 3H, $-NCH_3$), 3.80 (s, 3H, $=OCH_3$), 4.30 (q, 2H, J = 7 Hz, $2-CO_2CH_2CH_3$), 5.82 (s, 1H, H-4), 7.23 (d, 2H, J_{ortho} = 8 Hz) 7.34 (d, 2H, J_{ortho} = 8 Hz).

Anal. Calcd. for $C_{15}H_{16}ClNO_3$: C, 61.33; H, 5.49; N, 4.77; Cl, 12.07; m.w. 293.5. Found: C, 61.52; H, 5.54; N, 4.71; Cl, 12.06; M^+ 293, 295 (^{37}Cl).

The hydrazide of **9c** had m.p. 144-145° (methanol).

Anal. Calcd. for $C_{13}H_{14}ClN_3O_2$: C, 55.82; H, 5.04; N, 15.02; Cl, 12.68. Found: C, 55.51; H, 5.07; N, 14.84; Cl, 12.70.

1-Methyl-3-methoxy-5-hydroxy-5-phenyl-3-pyrroline-2-one (**10a**).

The 2-ester, **9a** (0.5 g., 1.93 mmoles) was dissolved in 8 ml. of 95% ethanol and 38.6 ml. of 0.1 *N* sodium hydroxide (3.86 mmoles) was added. Tlc showed the ester to be unchanged after standing four days at room temperature, so to another 0.50 g. portion in 8 ml. of 95% ethanol was added 7 ml. of 5*N* potassium hydroxide (35 mmoles). This solution was refluxed 30 minutes then poured into 30 ml. of water and extracted with 10 ml. of chloroform. The aqueous phase was then carefully acidified with hydrochloric acid to *p*H 3.0-3.5 and extracted with three 15 ml. portions of chloroform. These last extracts were dried and concentrated under reduced pressure to give a very dark oil, from which crystallized 50 mg. **10a** (12%) m.p. 195-200° dec., (ethanol/ethyl acetate, *ca* 1:1); ir (potassium bromide): 3.05 (-OH, sharp), 5.90 (C=O, amide), 6.05 μ (C=C, vinyl ether); nmr (deuteriochloroform/DMSO-d_6): δ 2.52 (s, 3H, $-NCH_3$), 3.64 (s, 3H, $-OCH_3$), 5.78 (s, 1H, H-4), 6.42 (s, 1H, exchanges with deuterium oxide, -OH), 7.26 (s, 5H, aromatics).

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.73; H, 5.97; N, 6.39; m.w. 219. Found: C, 65.46; H, 5.93; N, 6.22; M^+ 219.

1-Methyl-3-methoxy-5-hydroxy-5-(*p*-chlorophenyl)-3-pyrroline-2-one (**10b**).

The 2-ester **9b** was treated in a manner analogous to **9a** to give again in very low yield, **10b** as white crystals, m.p. 235-237° dec., (ethanol/ethyl acetate); ir (potassium bromide): 3.00 (-OH,

sharp), 5.95 (C=O, amide), 6.05 μ (C=C, vingyl ether); nmr (deuteriochloroform/DMSO-d_6): δ 2.52 (s, 3H, $-NCH_3$), 3.64 (s, 3H, $-OCH_3$), 5.70 (s, 1H, H-4), 6.44 (s, 1H, exchanges with deuterium oxide, -OH), 7.26 (s, 4H, aromatics).

Anal. Calcd. for $C_{12}H_{12}ClNO_3$: C, 56.81; H, 4.77; N, 5.52; Cl, 13.97; m.w. 253.5. Found: C, 56.46; H, 4.74; N, 5.48; Cl, 13.96; M^+ 253, 255 (^{37}Cl).

1-Methyl-3,5-dimethoxy-5-phenyl-3-pyrroline-2-one (**10c**).

The hydroxy compound, **10a**, (0.11 g., 0.5 mmole) was dissolved in 2 ml. of dry DMF and added under nitrogen to a suspension of sodium hydride (0.05 g., 2.1 mmoles) in 2 ml. of dry DMF. Methyl iodide (0.2 g., 1.4 mmoles) was added after hydrogen evolution had ceased and the mixture was stirred 48 hours. At the end of this time the solution was poured into 50 ml. of water and extracted with three 25 ml. portions of chloroform. The combined organic phase was dried and concentrated under reduced pressure to give dark crystals which, after one recrystallization from acetonitrile/water (*ca* 1:1), amounted to 70 mg. of **10c** (60%), m.p. 105-107°; ir (potassium bromide): 5.85 (C=O, amide) 6.05 μ (C=C, vinyl ether); nmr (deuteriochloroform): δ 2.60 (s, 3H, $-NCH_3$), 3.18 (s, 3H, 5-OCH_3), 3.74 (s, 3H, 3-OCH_3), 5.36 (s, 1H, H-4), 7.28 (s, 5H, aromatics).

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.01; m.w. 233. Found: C, 66.83; H, 6.35; N, 5.89; M^+ 233.

1-Methyl-3-methoxy-5-phenylpyrrole-2-methanol (**11**).

To a suspension of lithium aluminum hydride (0.04 g., 1.0 mmole) in dry THF (2 ml.) was added the methoxyester **9a** (0.2 g., 0.77 mmole) in 1.5 ml. of dry THF. After 30 minutes the reaction was quenched with 0.1 ml. of water, then 0.1 ml. of 20% sodium hydroxide, then 0.3 ml. of water. The inorganic salts were filtered from the solution and washed well with hot THF. When the combined THF phase was examined by tlc, a broad band resulted which turned a brilliant red in several minutes. Concentration of the organic phase (colorless) under reduced pressure gave only purple and black tars. If, however, 0.5 ml. of pyridine-d_5 was added to the dried organic phase (potassium carbonate) and the THF carefully removed under reduced pressure at less than 50°; nmr indicated the presence of pure **11**; nmr (pyridine-d_5): δ 3.57 (s, 3H, $-NCH_3$), 3.65 (s, 3H, $-OCH_3$), 4.84 (s, 2H, $-CH_2-$), 5.74 (s, broad, 1H, -OH), 6.00 (s, 1H, H-4), 7.20-7.38 (m, 5H, aromatics).

This pyrrole-2-methanol could be oxidized without isolation in the following manner: 26 ml. of 5% silver nitrate (7.8 mmoles) was diluted with water to make 160 ml. of solution. To this was added 2.0 ml. of 5*N* potassium hydroxide (10.0 mmoles), followed by 50 ml. of pyridine. The clear, colorless solution was chilled in an ice bath and to it was added (slowly and with stirring) the THF solution that resulted from the LAH reduction of 0.5 g. (1.93 mmoles) of the ester **9a** as described above. Stirring was continued 16 hours. At the end of this time a silver mirror had had been deposited on the sides of the reaction flask. The solution was filtered, poured into 75 ml. of methylene chloride, and the organic layer separated and washed with 20% hydrochloric acid until the washes were strongly acidic. After one 50 ml. wash with saturated sodium bicarbonate all the aqueous washes were back-extracted with one 25 ml. portion of methylene chloride. The combined methylene chloride phases were dried and concentrated under reduced pressure to give, after trituration with ethyl acetate, 0.26 g. (61%) of white crystals that were identical in every way to the material isolated under **10a** above.

1-Methyl-2-phenyl-4-methoxypyrrole (**12a**).

The methoxydiacid, **5**, (0.3 g., 1.1 mmoles) was heated (190° oil bath) under vacuum (0.5 mm) in a Hickman type distilling flask fitted with a stopcock. A pale yellow liquid distilled. The stopcock was closed and the vacuum pump replaced with a nitrogen line so that as the stopcock was slowly opened the Hickman flask was filled with nitrogen. The stopcock, attached to the Hickman flask with a gound glass joint, was removed and quickly replaced with a rubber septum. This arrangement allowed the yellow liquid, **12a**, to be dissolved in 1 ml. of carbon tetrachloride and transferred *via* syringe to a nitrogen-filled nmr tube; nmr (carbon tetrachloride): δ 3.44 (s, 3H, $-OCH_3$), 3.56 (s, 3H, $-NCH_3$), 5.68 (d, 1H, $J_{2,4}$ = 2 Hz, H-4), 6.02 (d, 1H, $J_{2,4}$ = 2 Hz, H-2), 7.10-7.21 (m, 5H, aromatics).

The oil, **12a**, which resulted from the decarboxylation of 1.0 g. (3.64 mmoles) of **5** was treated under nitrogen with a solution of maleic anhydride (0.36 g., 3.67 mmoles) in 1 ml. of dry benzene. The solution turned dark immediately and crystals began to separate. After standing overnight the crystals were filtered and washed with benzene to give 0.35 g. (34%) of **12b**, α-(1-methyl-3-methoxy-5-phenyl-2-pyrryl)succinic anhydride, m.p. 169-171° (2-propanol); ir (potassium bromide): 3.40, 3.62 μ (anhydride); nmr (deuteriochloroform/DMSO-d_6): 3.00-3.40 (m, 2H, AB of ABX, J_{AB} = 17 Hz, α'-CH_aH_b(23)), 3.49 (s, 3H, $-OCH_3$), 3.64 (s, 3H, $-NCH_3$), 4.56 (d of d, 1H, X of ABX, $J_{AX} + J_{BX}$ = 16 Hz, α-CH), 5.88 (s, 1H, H-4), 7.26 (s, 5H, aromatics).

Anal. Calcd. for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91; m.w. 285. Found: C, 67.22; H, 5.12; N, 4.90; M^+ 285.

In another experiment, the pale yellow oil, **12a** which resulted from the decarboxylation of 1.0 g. (3.64 mmoles) of **5** was dissolved in 2 ml. of dry THF and transferred as described above for the carbon tetrachloride solution to a 25 ml. flask fitted with a rubber septum and flushed with nitrogen. A stream of pure oxygen was passed over this solution for 15 minutes and then the reaction was opened to the air, chilled, and triturated with ethyl acetate. A white crystalline solid was isolated by filtration (0.20 g., 25%) which was identical in all respects to the compound **10a** described above.

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