The Preparation and Aqueous Basic Oxidation of Diethyl 1-Methyl-3-hydroxy-5-phenylpyrrole-2,4-dicarboxylate (1)

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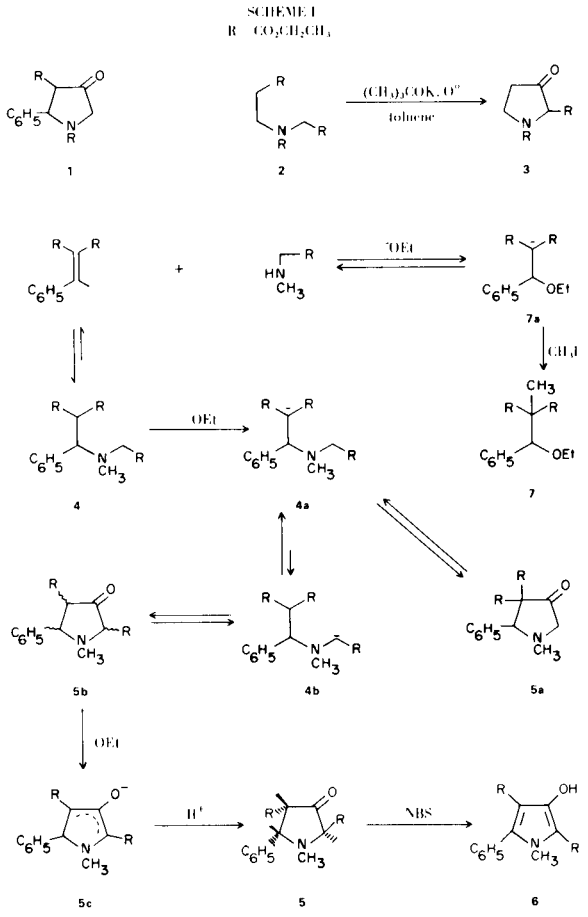
Diethyl 1-methyl-3-hydroxy-5-phenylpyrrole-2,4-dicarboxylate has been synthesized in good yield from readily available materials, diethyl benzylidenemalonate and ethyl sarcosinate. It was found to react with oxygen in aqueous base to give two oxidation products, ethyl 1-methyl-2-oxo-3-hydroxy-5-phenyl-3-pyrroline-4-carboxylate (**9**) and ethyl 1-methyl-2,3-dioxo-5-phenyl-4-pyrroline-4-carboxylate (**10**). These two oxidation products are postulated to arise from the decomposition of a common intermediate, diethyl 1-methyl-2-hydroperoxy-3-oxo-5-phenyl-4-pyrroline-2,4-dicarboxylate. Reaction of the title compound with oxygen in pyridine containing Triton B again produced two products, the dioxo compound (**10**) and diethyl 1-methyl-2-hydroxy-3-oxo-5-phenyl-4-pyrroline-2,4-dicarboxylate (**12**). Compound **12** was shown to react in aqueous base to give exclusively **9**. The hydration of **10** in acidic and basic media is also discussed.

Diethyl 1-methyl-3-hydroxy-5-phenylpyrrole-2,4-dicarboxylate (**6**) (Scheme I) was required for another purpose. We wish to report the large-scale synthesis of this key intermediate and to describe some of its chemistry, in particular its reaction with oxygen in aqueous base.

A number of 3-hydroxypyrrole esters have been prepared by the Dieckmann cyclization of Schiff bases (3) and Umio has used this method extensively to prepare 3-hydroxy-4-phenylpyrrole esters (*cf.* (4)) as antibiotics. Entry to the 3-hydroxypyrrole-2,4-dicarboxylate system may also be gained through the corresponding saturated, non-aromatic analogs, the 3-oxopyrrolidines. Rapoport *et al.* (5,6,7) have shown that such systems can be elaborated to 3-hydroxyprolines and 3-methoxypyrroles, so these 3-oxopyrrolidines seemed to be logical synthetic targets. The 2-aryl-4-oxopyrrolidine-3-carboxylate system (**1**) has been synthesized by a Michael addition and concomitant Dieckmann cyclization between ethyl *N*-ethoxycarbonylglycinate and ethyl cinnamate (8,9). Blake, Willson, and Rapoport (7) were successful in the synthesis of the 3-oxopyrrolidine-2-carboxylate system, **3**, *via* a Dieckmann cyclization of **2** but their method was not generally applied to the synthesis of 5-arylpyrrolidine derivatives.

We have been able to achieve the desired 3-oxo-2,4-dicarboxylate orientation on the pyrrolidine ring along with having the potential ability to incorporate various aryl groups at the 5-position by the Michael addition of ethyl sarcosinate to ethyl benzylidenemalonate followed by a Dieckmann cyclization to give the 5-phenyl-3-oxo-

SCHEME I



pyrrolidine diester, **5** (Scheme I).

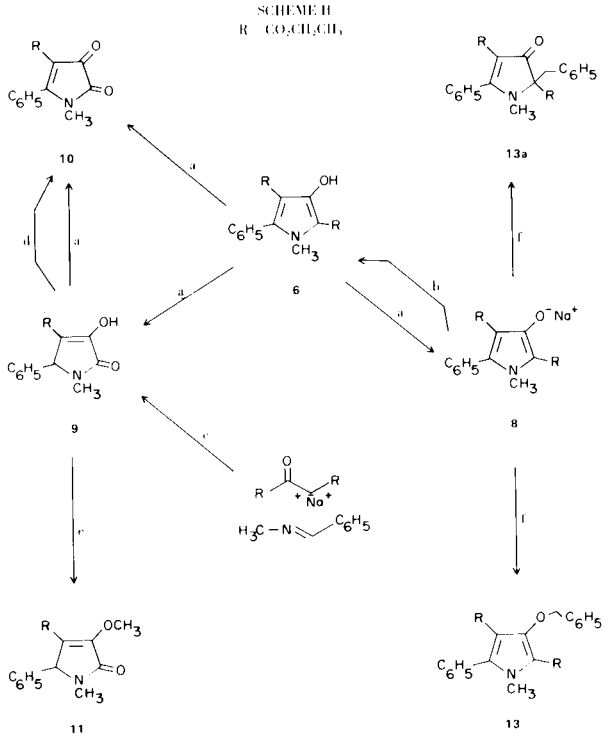
Additions of ammonia and amines to ethyl benzylidenemalonate are known to proceed without catalysis (10,11) so it was planned to add ethyl sarcosinate to ethyl benzylidenemalonate to give Michael adduct **4** and then to subject this adduct to the conditions of the Dieckmann cyclization. Although Rapoport, *et al.* (7) found it necessary to cyclize the Michael adduct **2** under very carefully controlled conditions, since **3** was the kinetically fovared but thermodynamically less stable product, the cyclization of Michael adduct **4** should, under equilibrating conditions, lead primarily to the desired **5** since the other isomer (**5a**) could not form a stable enolate analogous to **5c** (Scheme I) (12). It was found, however, that the Michael adduct **4** could not be isolated and characterized because it was always in equilibrium with ethyl benzylidenemalonate and ethyl sarcosinate, and attempted isolation reversed this equilibrium. It was possible, though, to optimize the shift of this equilibrium toward **4** by mixing two equivalents of ethyl sarcosinate with one equivalent of ethyl benzylidenemalonate and then chilling the mixture at 0°. If one equivalent of each reactant was mixed at room temperature the Michael adduct was observed by thin layer chromatography as a new material developing slightly behind ethyl benzylidenemalonate and of qualitatively equal intensity. When an extra equivalent of the aminoester was added and the mixture chilled, the Michael adduct was seen by tlc to increase at the expense of the ethyl benzylidenemalonate. This increase was qualitatively the same at either 0° or -40°, but diminished if the mixture was warmed again to room temperature.

Thus, by mixing the two reactants in this ratio, chilling, and adding the cold mixture to an equivalent of ethanolic sodium ethoxide, the 5-phenyl-3-oxopyrrolidine diester **5** was obtained in 69% yield. A white precipitate appeared soon after the Michael adduct mixture was added to the sodium ethoxide solution and then disappeared after warming the reaction mixture several hours. It was felt that this might be the sodium salt (**4a**) of the Michael adduct. However, alkylation of the precipitate with methyl iodide gave diethyl methyl α-ethoxybenzylmalonate, **7**. It is apparent that sodium ethoxide rapidly adds in a Michael fashion to the ethyl benzylidenemalonate in the equilibrium mixture, giving **7a**, and that this unstable adduct eventually equilibrates back to ethyl benzylidenemalonate as the Michael adduct **4** is siphoned off as the more stable enolate **5c**.

The 3-oxopyrrolidine diester **5** is not a tautomeric hydroxypyrroline (see Balke, Willson, and Rapoport (7)) as shown by spectra and chemical characteristics. Since **5** has three asymmetric centers it probably exists as a mixture of diastereomers, and it was never crystallized, although tlc and nmr indicate that one diasteroisomer predominates.

SCHEME II

R = $CO_2CH_2CH_3$



(a) Sodium hydroxide (0.1 N), oxygen, room temperature. (b) Acidification. (c) Refluxing ethanol. (d) Chloranil, refluxing *p*-xylene. (e) Dimethyl sulfate, potassium carbonate, refluxing acetone. (f) Benzyl bromide, methanol, room temperature.

Breuer and Melumad (13) have demonstrated that the α-protons of *cis*-1-methyl-2,5-diphenylpyrrolidine absorb at 3.34 ppm in deuteriochloroform while those of the *trans*-isomer absrob at 4.10 ppm because they are shielded only 50% of the time by the nitrogen lone pair electrons. The proton on the 5-position of **5** was demonstrated to be buried under the multiplet centered around 4.10 ppm by integration and by the slow exchange of the 2- and 4-protons with deuterium oxide. We infer from this that the 2-ethoxycarbonyl group and the 5-phenyl substituent are *trans* to each other in the predominant diastereomer. Furthermore, examination of a model reveals that the 3-oxopyrrolidine system is relatively planar, so that *cis* 4- and 5-protons are eclipsed, but in the *trans* case, the dihedral angle is about 120°. The large coupling between the 4- and 5-protons (10 Hz) is consistent with the *cis* configuration (*cf.* (Castagnoli (14)), and the predominant diastereomer of **5** must be as indicated (Scheme I).

The 3-oxopyrrolidine **5** has been found to undergo a favile oxidation to the hydroxypyrrole **6**. This conversion takes place in refluxing benzene with a stream of oxygen, in refluxing ethanol with palladium on carbon, and in benzene at room temperature with chloranil or even benzoquinone itself. However the most efficient method for carrying out this oxidation on a large scale requires an

equivalent of *N*-bromosuccinimide in aqueous dioxane, buffered with a slight excess of sodium bicarbonate. If the bicarbonate is omitted from the reaction and hydrogen bromide is allowed to accumulate, the hydroxypyrrole is still produced but is contaminated by a large amount of an anomalous material, observed by tlc, which results in a dark intractable mixture upon workup. Kuhn and Osswald (8) obtained 1,2-diethoxycarbonyl-4-ethoxypyrrole in 30% yield from 1,2-diethoxycarbonyl-4-ethoxy-4-pyrroline by using *N*-bromosuccinimide and triethylamine, but Rapoport (5) found this method unsatisfactory for the synthesis of the homologous 4-methoxy compound and used direct catalytic dehydrogenation of the dimethyl ketal instead.

It should be noted that some pyrrole (**6**) is produced directly in the Dieckmann cyclization and can be isolated from the reaction residue after the somewhat more acidic 3-oxopyrrolidine is removed by extraction with base (see Experimental). In concurrence with this, Miyazuki, Mizuno, and Umio (15) isolated ethyl 3-hydroxy-4-isopropylpyrrole-2-carboxylate in low yield by the Dieckmann cyclization of ethyl *N*-(2-isopropyl-2-ethoxycarbonylethyl)-glycinate with sodium hydroxide. Since the amount of **6** formed was not reduced when air was excluded (see below), it may be formed by disproportionation of **5c**.

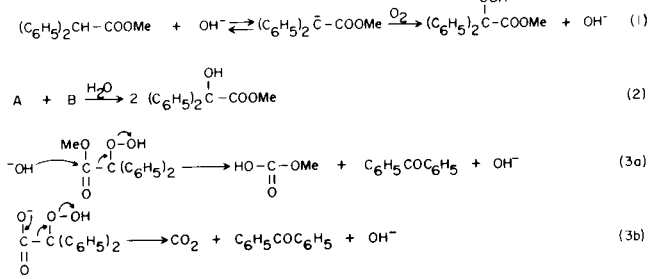
During the experiment on the preparation of **5**, several unusual oxidation products were found, if water and air were not rigorously excluded. It was believed that these products were derived from the *N*-methylpyrrole **6**, shown to be present in the reaction mixture. Therefore **6** was subjected to oxidation in aqueous base. When **6** was stirred overnight in 0.1 *N* sodium hydroxide while a stream of oxygen bubbled through the suspension, three products were obtained. The first was the sodium salt of the starting material (**8**) (Scheme II). The second was ethyl 1-methyl-2-oxo-3-hydroxy-5-phenyl-3-pyrroline-4-carboxylate (**9**), and the third was ethyl 1-methyl-2,3-dioxo-5-phenyl-4-pyrroline-4-carboxylate (**10**). Under these conditions **9** and **10** were obtained in a total of 27%.

Compound **8** was identified simply by acidifying it in aqueous solution and recovering starting material. It could also be alkylated with benzyl bromide to give the benzyloxy compound **13** and a small amount of the *C*-alkylated product **13a**. Compound **9** was identified by comparing it with the known compound, synthesized unambiguously by the method of Castagnoli (14) from sodium diethyl oxalacetate, benzaldehyde, and methyl amine. The material obtained in this manner proved to be identical with **9** by ir, nmr, tlc, and mixture melting point. It was also possible to methylate **9** with dimethyl sulfate, giving **11**. Finally, compound **10** was identified by comparing it with the material obtained from the oxidation of **9** with chloranil. Again, the two materials were proved to be identical by spectroscopic and chromatographic techniques. The above reactions are outlined in Scheme II.

Since **9** was not converted to **10** under the conditions of the reaction, it was evident that **9** and **10** were arising from the decomposition of a common intermediate. An examination of the literature dealing with the oxidation of pyrroles (16) suggested that a hydroperoxide might qualify as this common intermediate. Although pyrroles are known to form hydroperoxides by the light-catalyzed addition of oxygen to give an initial endoperoxide (16), **6** contains a β-ketoester moiety, masked through the 2- and 3-carbons as the enol, which could generate a hydroperoxide in the presence of a base and oxygen. In a similar system Davoll (17) observed the oxidation of 2,5-dimethyl-4-oxo-1-phenyl-2-pyrroline in air to give 5-hydroxy-2,5-dimethyl-4-oxo-1-phenyl-2-pyrroline. Since the benzyloxy compound, **13**, could not form the enolate anion, but could still add singlet oxygen, it was subjected to 0.1 *N* sodium hydroxide under a stream of oxygen. No reaction was observed.

Activated methylene compounds have been demonstrated to react with oxygen in the presence of various bases to produce hydroperoxides (18,19,20). Although this reaction is often depicted as a free radical chain process, there is some evidence for the direct interaction of a carbanion with oxygen (21).

Of particular relevance to this work were the experiments performed by Avramoff and Sprinzak (22) in which they demonstrated that α-arylesters formed crystalline hydroperoxides when reacted in pyridine with oxygen in the presence of Triton G. Furthermore, they were able to demonstrate that these hydroperoxides decomposed in two ways to give ketones and α-hydroxy acids. Specifically, methyl diphenylacetate, reacted at -18°, gave a 31% yield of the α-hydroperoxyester, **B**. When carried out at room temperature this reaction afforded a 47% yield of methyl benzilate and benzilic acid and a 26% yield of benzophenone.

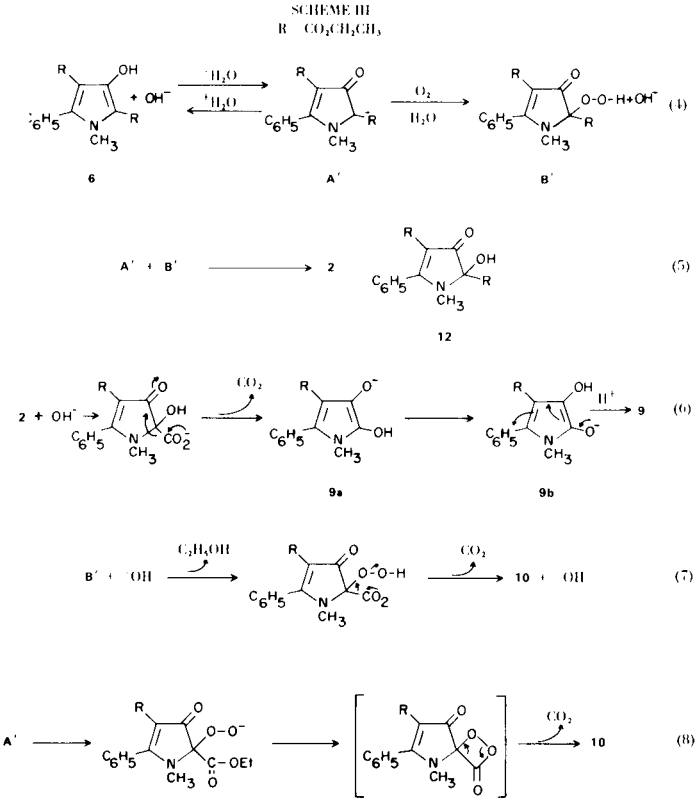


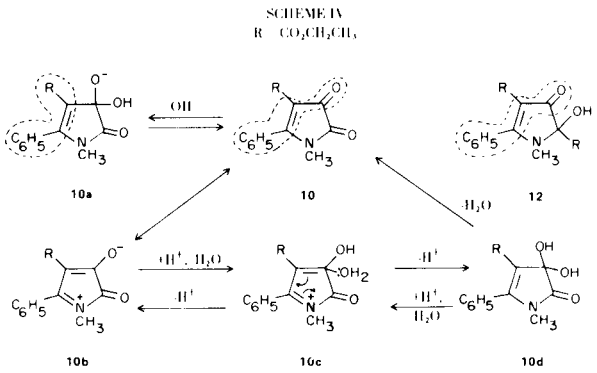
The occurence of reaction (2) was confirmed by an experiment in which equivalent quantities of methyl diphenylacetate and methyl diphenylhydroperoxyacetate were treated with Triton B in pyridine in the absence of oxygen, giving methyl benzilate and benzilic acid as before. Reactions (3) were demonstrated by an experiment in

which the hydroperoxyester alone was submitted to the action of the base, giving a 70% yield of benzophenone. Although the presence of carbonate as a reaction product was established, it could not be determined whether the reaction involved the ester directly (3a) or an intermediate carboxylate produced by its hydrolysis (3b).

Reactions analogous to these could account for the product, **9** and **10**; observed in the case at hand (Scheme III). Reaction (7) is a direct analogy to reactions (3), giving rise to the dione **10** *via* a decarboxylative displacement. Reaction (5) is analogous to reaction (2), leading to the production of the hydroxyester, **12**. However, in order to account for the production of **9** a decarbethoxylation step is required. A simple hydrolysis, followed by decarboxylation through a six-centered intermediate upon acidification, could accomplish this, but would require that carbon dioxide be released immediately upon acidification. This was not observed. Reaction (6), which permits elimination of carbon dioxide from the carboxylate anion, provides a reasonable route for this transformation.

Again, as in the case of reactions (3), reaction (6) may proceed *via* direct participation of hydroxide or intervention of carboxylate. Either way, instead of the electrons from the carbethoxy group serving to displace hydroxide from the hydroperoxy function as in (7), they are transferred into the heterocyclic nucleus to give enolates **9a** and





9b. Since **9a** and **9b** are salts of **9**, and since **9** is soluble in 5% aqueous bicarbonate, **9a** and **9b** must have considerable stability, possibly due to the stabilization gained in attaining the fully aromatic pyrrole ring. Thus the reaction of **12** with hydroxide to give **9a** and **9b** should be quite facile.

At attempt was made to isolate the hydroperoxyester **B'** by subjecting **6** to Avramoff and Sprinzak's conditions (22), oxygen and Triton B in pyridine. Two products were obtained from this reaction in a total yield of *ca.* 60%: the dione **10** and, somewhat surprisingly, the hydroxyester, **12**. When **12** was subjected to the original conditions, *i.e.* 0.1 *N* sodium hydroxide, but in the absence of oxygen, **9** was obtained exclusively.

Thus it was established that **12** is an intermediate in this oxidation and that it leads directly to **9** when treated with aqueous base. Although the hydroperoxy ester **B'** has not been isolated (23), it still seems to be the logical intermediate, leading to **10** and **12** in the competitive processes (7) and (5) respectively. It was somewhat surprising that reaction (6) does not proceed with Triton B in pyridine to give **9** while it goes quite smoothly in water. This may be due to the limited amount of hydroxide ion available for hydrolysis. However, hydrolysis is not necessary for the production of compound **10** since it can still be produced in dry pyridine in an ester cleavage assisted by the hydroperoxide ion (reaction 8).

Finally, the dione **10** possesses an unusual property that is worthy of discussion. It was noted on several occasions that when the acidic material **9** was extracted from an organic phase into aqueous base, **10** was extracted also, if present. Since **10** is obviously not acidic, it seemed reasonable that is was forming a water soluble hydrate in aqueous base which was hydrolyzed under acidic or neutral conditions. To test this hypothesis, an aqueous solution of **10** was monitored by its ultraviolet spectrum as the *p*H was adjusted between very acidic and very basic. The results are shown in Table I.

This compound displayed an absorption at 317 nm (ϵ, 7,800) which was quite similar to the absorption observed for **12** at 315 nm (ϵ, 6,000). Presumably this absorption

was due to the *trans* β-phenylenone systems outlined in Scheme IV. When **10** was made slightly basic and then strongly basic this absorption decreased and an absorption band at 290 nm of approximately equal intensity appeared. It would seem that the hydration of the ketone carbonyl of **10** must give structure **10a**, destroying the *trans* chromophore and leaving in its place the *cis* system indicated. It appears that both **10** and **10a** exist in equilibrium which is shifted toward **10a** as the *p*H increases. This would account for the hypsochromic shift of absorption.

The initial absorption was regenerated when the *p*H was adjusted back near neutrality and decreased again when the solution was made acidic.

It was surprising to discover that the ultraviolet absorption intensity of **10** decreased in acidic solution. Since **10** can be extracted from acidic solution, it may be that it is present in the acidic solution as an equilibrium mixture of the protonated species (**10c**) and the hydrated species (**10d**), which dehydrates on extraction.

TABLE I

The Ultraviolet Absorption of **10** in Acidic and Basic Solution (a)

	Absorbance (b)	
*p*H	290 nm	317 nm
5-6 (c)	0.18	0.34
8-9	0.29	0.24
>13	0.28	0.15
5-6	0.18	0.31
2-3	0.15	0.10
<1	0.16	0.12

(a) Compound **10** (4.5 mg.) was dissolved in 10 ml. of ethanol and diluted with sufficient water to make a 4.34×10^{-5} *M* solution. The *p*H of this solution was adjusted in the sample cell with a few drops of *N* hydrochloric acid or *N* sodium hydroxide. (b) An absorbance at 236 nm remained constant throughout this experiment. (c) Initial run in distilled water.

EXPERIMENTAL

Melting points were obtained on a Mel-Temp capillary melting point apparatus and are uncorrected. Ir spectra were obtained on a Perkin-Elmer model 137 infrared spectrometer and ultraviolet spectra were measured on a Bausch and Lomb Spectronic 505. Nmr spectra were obtained 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 70 eV. Magnesium sulfate was used as a drying agent. When a reaction was run under nitrogen, the apparatus was kept at least an hour in a 100° oven and allowed to cool with nitrogen sweeping through it.

Thin layer chromatography was done on pre-coated flexible slides (2.5 cm x 7.5 cm) containing silica gel 1B-F and available from J. T. Baker and Co. Visualization was by uv light. Several solvents were used for eluting the slides and are designated as follows: A, 10% tetrahydrofuran in benzene; B, ethyl acetate; C, acetone; D, chloroform. Analyses were obtained courtesy of Galbraith Laboratories, Knoxville, Tennessee.

Ethyl Sarcosinate.

Ethyl sarcosinate was synthesized according to the following modification of the procedure of Brenner and Huber (24) for making amino acid ester hydrochlorides.

The thionyl chloride used in this experiment was distilled once at atmospheric pressure and was still slightly yellow. The ethanol was distilled from magnesium ethoxide. Thionyl chloride (79 ml.) was added dropwise to 400 ml. of stirring ethanol in a three liter 3-neck flask. The reaction mixture was maintained at -10 to -5° during this addition with a dry ice/acetone bath. When the addition was complete sarcosine (89.0 g., 1.0 mole) was added in small portions, with the temperature again maintained below -5°. When this addition was complete the temperature of the reaction was raised to 45° and the reaction was stirred overnight. After 16 hours the solution had become clear and homogenous. At this time a distillation condenser was attached to the glask, replacing the dropping funnel, and most of the excess ethanol was distilled from the reaction at *ca.* 25 mm (water aspirator). The reaction was then cooled to room temperature and diethyl ether (2.4 l.) was added to the remaining oil with vigorous stirring so that the precipitated hydrochloride was pulverized into a finely divided suspension. Ammonia which was dried by passage through a bed of potassium hydroxide was then bubbled into this suspension for 2 hours. At the end of this time the ammonium chloride was filtered from the ether and washed well with additional ether. Evaporation of the combined ethereal residues under reduced pressure and vacuum distillation of the remaining oil gave 88.7 g. (76%) of the desired ethyl sarcosinate, b.p. 52-54°/20-25 mm (Lit. (25), b.p. 59-60°/25 mm). This amino ester could be kept several weeks in the refrigerator without decomposition.

Diethyl 1-Methyl-3-oxo-5-phenylpyrrolidine-2,4-dicarboxylate (**5**).

Ethyl sarcosinate (10.5 g., 0.09 mole) was added dropwise to ethyl benzylidenemalonate (11.1 g., 0.045 mole) in a 100 ml. 3-neck flask, stirring under a nitrogen atmosphere. The flask was quickly sealed and stored overnight in a cold room at 0° while stirring was continued. After 16 hours tlc (A) showed that, relative to a control experiment in which the two reactants had been mixed in 1:1 proportion and stirred at room temperature, the qualitative ratio of Michael adduct (rf *ca.* 0.7) to ethyl benzylidenemalonate (rf *ca.* 0.8) was significantly larger in the cold reaction. If the cold reaction was allowed to warm to room temperature over a period of several hours, tlc showed that the Michael adduct was qualitatively present in an amount comparable to the control. Chilling the reaction again overnight regenerated the amount of Michael adduct to its former high level.

This cold mixture was added dropwise to a solution of 1.05 g. freshly cut sodium (0.046 mole) in 75 ml. of absolute ethanol (distilled from magnesium ethoxide) at 0-5° under nitrogen. This addition was made through an ice-water cooled dropping funnel, keeping the Michael adduct cold until the instant of contact with the cold ethanolic sodium ethoxide. A white solid precipitated from the reaction in about ten minutes. This suspension was stirred for an additional 30 minutes, then warmed to 40° and stirring continued overnight. After 16 hours the reaction mixture, which had become homogeneous, was poured into 150 ml. of benzene containing 2.7 g. of glacial acetic acid (0.045 mole), and extracted with five 50 ml. portions of 0.1 *N* sodium hydroxide solution and one 25 ml. portion of *N* sodium hydroxide. The aqueous extracts were combined, acidified to *p*H 5.0-6.0 with concentrated hydrochloric

acid, and extracted with five 50 ml. portions of chloroform. These organic extracts were combined, dried, and concentrated under reduced pressure to give 9.88 g. (69%) of the desired 3-oxopyrrolidine **5** as a yellow-orange oil. A portion of this oil was chromatographed on a silica gel column to eliminate the dark colored materials and then distilled at 0.03-0.05 mm (90° oil bath) in a short path apparatus of the molecular distillation type, giving a pale yellow oil. This oil gave a negative test with ferric chloride; ir (neat, silver chloride): 5.65 (C=O, 5-membered ring) 5.80 μ (C=O, broad, ester); nmr (carbon tetrachloride): δ 1.08-1.36 (m, 6H, $CO_2CH_2CH_3$), 2.26 (s, 3H, N-CH_3), 3.32 (d, 1H, $J_{4,5}$ = 10 Hz, exchanges with deuterium oxide in 1 hour, H-4) 3.54 (s, 1H, exchanges with deuterium oxide in 1 hour, H-2), 3.96-4.30 (m, 5H, $CO_2CH_2CH_3$, H-5), 7.04-7.40 (m, 5H, aromatics).

Anal. Calcd. for $C_{17}H_{21}NO_5$: C, 63.92; H, 6.62; N, 4.39; m.w. 319. Found: C, 63.80; H, 6.66; N, 4.48; m.w. (mass spectrum): m/e 319.

In initial runs of this reaction, potassium *t*-butoxide in toluene was used to effect the Dieckmann cyclization but gave lower yields than ethanolic sodium ethoxide, presumably because the ethoxide helps promote the equilibration outlined in Scheme I. A lower yield was also obtained in an experiment in which ethyl benzylidenemalonate and ethyl sarcosinate were added to ethanolic sodium ethoxide without prior mixing and chilling.

The excess ethyl sarcosinate was recovered from the dried, base-extracted, benzene solution by evaporation under reduced pressure, and precipitation of ethyl sarcosinate hydrochloride from an ether solution of the resulting oil.

When the ethereal filtrate was washed with water, then saturated with aqueous sodium bicarbonate and dried, examination by tlc (A) showed two materials to be present. The first was found to be ethyl benzylidenemalonate by chromatography with an authentic sample. The second was shown to be diethyl 1-methyl-3-hydroxy-5-phenylpyrrole-2,4-dicarboxylate, **6**, also by chromatography with an authentic sample (see below). Removal of the ether under reduced pressure gave an oil which crystallized upon chilling and scratching to give, after one crystallization from methanol, typically 1.0 to 1.5 g. of the crystalline pyrrole, **6**, m.p. 90-91°. The total yield of **5** and **6** from this reaction, then, was 76-80%.

Diethyl 1-Methyl-3-hydroxy-5-phenylpyrrole-2,4-dicarboxylate (**6**).

The crude 3-oxopyrrolidine (**5**) (40.0 g., 0.125 mole) was dissolved in 400 ml. of dioxane and water (9:1), chilled in ice and sodium bicarbonate (12.0 g., 0.143 mole) suspended in the solution. *N*-Bromosuccinimide (22.3 g., 0.125 mole) was added at a rate which kept the effervescence under control (*ca.* 15 minutes). The reaction was stirred in the cold an additional 30 minutes and then allowed to warm to room temperature over another 15 minutes. At the end of this time the reaction was poured into 400 ml. of chloroform, the water separated, and the organic phase washed once again with 100 ml. of water. Concentration of the dried organic phase under reduced pressure gave an oil which crystallized and could be recrystallized from methanol containing 3-5% water to give 28.2 g. (71%) of the desired 3-hydroxypyrrole **6** as white amorphous crystals, m.p. 90-91°. Analytically pure material was obtained by one more recrystallization from aqueous methanol or diethyl ether to give material of m.p. 92-93° (27). This material gave a positive test with ferric chloride; λ max (methanol); 234.9 (ε, 29,700), 269.7 nm (ε, 19,000); ir (potassium bromide): 3.20 (broad, bonded OH), 5.95 (C=O, shoulder), 6.05 μ (C=O, broad); nmr (carbon tetrachloride): δ 0.96 (t, 3H, J = 6 Hz, 4-$CO_2CH_2CH_3$), 1.38 (t, 3H, J = 6 Hz, 2-$CO_2CH_2CH_3$), 3.58 (s, 3H, N-CH_3), 4.02 (*q*, 2H, J = 6 Hz, 4-$CO_2CH_2CH_3$), 4.30 (q, 2H, J = 6 Hz, 2-$CO_2CH_2CH_3$), 7.20-7.40 (m, 5H, aromatics), 8.06 (s, 1H, exchanges with deuterium oxide, OH).

Anal. Calcd. for $C_{17}H_{19}NO_5$: C, 64.35; H, 6.04; N, 4.42; m.w. 317. Found: C, 64.33; H, 6.13; N, 4.34; (mass spectrum): m/e 317.

Diethyl Methyl-α-ethoxybenzylmalonate (**7**).

The white precipitate that developed initially when the Michael adduct was added to ethoxide solution (See Preparation of **5**, above.) was collected, in a separate experiment, under a nitrogen cone, washed with absolute ether, and allowed to dry to a white, fluffy powder. This solid was suspended in dry tetrahydrofuran (distilled from lithium aluminum hydride) under nitrogen and excess methyl iodide added. This mixture was stirred overnight. At the end of this time the reaction was poured into 200 ml. of water and extracted with three 50 ml. portions of chloroform. Removal of the combined solvent under reduced pressure after drying gave 39% of **7** as a yellow oil; b.p. 100-101°/0.1 mm; ir (sodium chloride, neat) 5.80 μ (C=O, broad, ester); nmr (carbon tetrachloride) δ 1.02-1.30 (m, 12H, CH_3), 3.32 (*q*, 2H, J = 6 Hz, OCH_2CH_3), 3.94 (*q*, 2H, J = 6 Hz, $CO_2CH_2CH_3$), 4.13 (*q*, 2H, J = 6 Hz, $CO_2CH_2CH_3$), 5.08 (s, 1H, ArCH), 7.08-7.18 (m, 5H, aromatics).

Anal. Calcd. for $C_{17}H_{24}O_5$: C, 66.22; H, 7.84; m.w. 308. Found: C, 65.96; H, 7.96; m.w. (mass spectrum): *m/e* 279-(M^+-C_2H_5).

Reaction of **6** with Oxygen in Aqueous Base.

Diethyl 1-methyl-3-hydroxy-5-phenylpyrrole-2,4-dicarboxylate, **6**, (1.0 g., 3.16 mmoles) was stirred for 16 hours in 60 ml. of 0.1 *N* sodium hydroxide while a stream of oxygen was bubbled through the suspension. At the end of this time the mixture was filtered and the filtrate acidified to *p*H 1.0-2.0 with concentrated hydrochloric acid and extracted with chloroform. Examination of the solid which was filtered from the original reaction mixture showed that it was not **6**, but rather a substance of m.p. 220-225° dec., which left a residue upon ignition. (This residue gave a basic solution in water.) By dissolving this material in hot water, acidifying, extracting with chloroform and examining this extract by tlc (A) this new solid was demonstrated to be **8**, the sodium salt of **6**; ir (potassium bromide): 6.00 (C=O, broad, esters), 6.20 μ (very strong, possibly the double bond of the enolate). Tlc (A) of the chloroform extract showed two materials to be present. Evaporation of chloroform after drying gave 0.22 g. of an orange oil which crystallized upon trituration with carbon tetrachloride. Thorough washing of these crystals with carbon tetrachloride gave a white product that was soluble in 5% sodium bicarbonate. After two recrystallizations from chloroform-hexane, this material had the following characteristics: m.p. 163-165°; m.w. (mass spectrum): m/e 261; ir (chloroform) 5.85 (C=O, ester), 5.95 μ (C=O, amide); nmr (deuteriochloroform) δ 1.10 (t, 3H, J = 7 Hz, $CO_2CH_2CH_3$), 2.80 (s, 3H, N-CH_3), 4.08 (q, 2H, J = 7 Hz, $CO_2CH_2CH_3$), 4.96 (s, 1H, 5-H), 7.04-7.32 (m, 6H, becomes 5H after exchange with deuterium oxide, aromatics, OH) λ max (methanol): 248 (ε, 11,600), 280-310 nm (ε, 6,000). This material reacted with dimethyl sulfate in refluxing acetone in the presence of anhydrous potassium chloride to give a new compound which crystallized after filtering the inorganic salts from the reaction and removing the solvent under reduced pressure. Two recrystallizations from water gave white crystals of **11** with the following characteristics: m.p. 74-76°; ir (sodium chloride, chloroform): 5.85 (C=O, ester), 5.95 μ (C=O, amide); nmr (deuteriochloroform): δ 1.04 (t, 3H, J = 6 Hz, $CO_2CH_2CH_3$), 2.72 (s, 3H, N-CH_3), 4.00 (q, 2H, J = 6 Hz,

$CO_2CH_2CH_3$), 4.28 (s, 3H, O-CH_3), 4.96 (s, 1H, 5-H), 7.06-7.30 (m, 5H, aromatics); λ max (methanol): 248 nm (ε, 10,200).

Anal. Calcd. for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.08; m.w. 275. Found: C, 65.47; H, 6.09; N, 4.93; m.w. (mass spectrum): m/e 275.

This data suggested the structure **9** for the new compound of m.p. 163-165°. When this 2-oxo-3-pyrroline was synthesized according to the literature method (14) it proved to be identical with this new product by ir, nmr, mixture melting point (164-166°), elemental analysis and tlc (A,B,C,D). Methylation of this compound with dimethyl sulfate gave compound **11**. Concentration of the combined carbon tetrachloride washes by evaporation under a stream of nitrogen gave a few orange crystals shown to be **10**. (See below).

Ethyl 1-Methyl-2,3-dioxo-5-phenyl-4-pyrroline-4-carboxylate (**10**).

The 2-oxo-3-pyrroline, **9**, (4.5 g., 0.017 mole) was dissolved in 60 ml. of *p*-xylene and refluxed 16 hours with chloranil (4.3 g., 0.017 mole). At the end of this time the solution was quite dark, but tlc (B) indicated that it contained only starting materials and one new substance. (It should be noted that 24 hours reflux in benzene produced no indication by tlc of any new material.) The reaction mixture was filtered through a pad of filter aid and the solvent removed under reduced pressure. Careful crystallization of the resulting crude, dark oil from carbon tetrachloride gave 0.35 g. (7.8%) (28) of bright orange crystals, m.p. 167-168°; ir (potassium bromide): 5.68 (C=O, 5-membered ring ketone), 5.85 (C=O, broad, ester), 6.0 μ (C=O, sh, amide); nmr (deuteriochloroform): δ 1.07 (t, 3H, J = 6 Hz, $CO_2CH_3CH_3$), 2.97 (s, 3H, N-CH_3), 4.04 (q, 2H, J = 6 Hz, $CO_2CH_2CH_3$), 7.32-7.58 (m, 5H, aromatics); λ max (water): 236 (ε, 11,500), 317 nm (ε, 7,800).

Anal. Calcd. for $C_{14}H_{13}NO_4$: C, 64.84; H, 5.05; N, 5.40; m.w. 259. Found: C, 64.56; H, 5.02; N, 5.50; m.w. (mass spectrum): m/e 259.

This material was proved by its mass spectral fragmentation pattern and tlc (A,B) to be identical with the orange crystals isolated from the reaction of **6** with aqueous base. The 0.22 g. isolated from the oxidation in aqueous base represents, then, a combined yield of 27% for both products **9** and **10** based on the molecular weight of 260.

Diethyl 1-Methyl-3-benzyloxy-5-phenylpyrrole-2,4-dicarboxylate (**13**).

The sodium salt, **8**, (0.40 g., 1.18 mmoles) was suspended in 20 ml. of absolute methanol and benzyl bromide (1.0 g., 5.7 mmoles) added dropwise. After stirring overnight tlc (A) showed that two products were present. The reaction mixture was poured into 50 ml. of benzene, washed twice with 50 ml. of water, and the organic phase dried. After concentrating the organic phase under reduced pressure, it was chromatographed on a column containing 75 g., of silica gel (D).

i). The first product eluted from the column crystallized readily upon evaporation of the solvent and was recrystallized from cyclohexane to give analytically pure **13**, 0.12 g. (25%), m.p. 79.0-79.5°; ir (potassium bromide) 5.85 μ (C=O, unsaturated ester); nmr (carbon tetrachloride): δ 0.88 (t, 3H, J = 7 Hz, 4-$CO_2CH_2CH_3$), 1.22 (t, 3H, J = 7 Hz, 2-$CO_2CH_2CH_3$), 3.56 (s, 3H, N-CH_3), 3.90 (q, 2H, J = 7 Hz, 4-$CO_2CH_2CH_3$), 4.17 (q, 2H, J = 7 Hz, 2-$CO_2CH_2CH_3$), 5.00 (s, 2H, $ArCH_2$), 7.12-7.40 (m, 10H, aromatics).

Anal. Calcd. for $C_{24}H_{25}NO_5$: C, 70.73; H, 6.18; N, 3.44. Found: C, 70.64; H, 6.19; N, 3.51.

ii). The second product eluted from the column crystallized by dissolving it in ethyl acetate and adding hexane. It was recrystallized from this solvent system to give the C-alkylated product, **13a**, 0.06 g. (12%), m.p. 90.5-92.0°; ir (sodium chloride, carbon tetrachloride): 5.70 (C=O, 5-membered ring ketone), 5.75 (C=O, aliphatic ester), 5.85 μ (C=O, unsaturated ester), nmr (carbon tetrachloride): δ 1.02 (t, 3H, J = 6 Hz, 4-$CO_2CH_2CH_3$), 1.30 (t, 3H, J = 6 Hz, 2-$CO_2CH_2CH_3$), 2.78 (s, 3H, N-CH_3), 3.20 (d, 1H, $J_{a,b}$ = 14 Hz, $ArCH_aH_b$), 3.66 (d, 1H, $J_{a,b}$ = 14 Hz, $ArCH_aH_b$), 3.83 (q, 2H, J = 6 Hz, 4-$CO_2CH_2CH_3$), 4.19, 4.20 (doublet of quartets, 2H, J = 6 Hz within each doublet, 2-$CO_2CH_aH_bCH_3$), 6.60-7.28 (m, 10H, aromatics).

Anal. Calcd. for $C_{24}H_{25}NO_5$: C, 70.73; H, 6.18; N, 3.44. Found: C, 70.31; H, 5.90; N, 3.55.

The benzyl ether, **13**, (0.05 g., 0.12 mmole) was suspended in 3 ml. of 0.1 *N* sodium hydroxide and a stream of oxygen bubbled through the suspension for 15 hours. At the end of this time a solid was filtered from the reaction mixture which proved to be unchanged **13** by tlc (A). Acidification of the basic filtrate and examination by tlc again showed no organic material present.

Attempted Oxidation of **9** to **10** in Aqueous Base.

The 2-oxo-3-pyrroline, **9**, (0.50 g., 1.92 mmoles), m.p. 164-166°, was dissolved in 30 ml. of 0.1 *N* sodium hydroxide with stirring and oxygen was bubbled through this solution for 15 hours. At the end of this time the solution was acidified with concentrated hydrochloric acid and the precipitated solid filtered off and dried on the filter funnel. Obtained were 0.45 g. of white crystals, m.p. 162-164°, whose ir spectrum was congruent with that of **9**, representing a 90% recovery of starting material. Thin-layer examination (A) of the aqueous filtrate showed no organic material present.

Oxidation of **6** in Pyridine and Triton B.

Triton B in pyridine (40%) was prepared according to the method of Sprinzak (29) and his oxidation procedure was employed on 1.0 g. **6** (3.16 mmoles). Oxygen absorption began after 5 minutes once a drop of Triton B was added and ceased after 5 hours when *ca.* 70 ml. (3.1 mmoles) had been absorbed. At this time the reaction mixture was poured over 100 ml. of cracked ice and concentrated hydrochloric acid and extracted with four 20 ml. portions of chloroform. The combined chloroform extracts were then extracted with two 15 ml. portions of *N* sodium hydoxide.

i). After washing with an additional 10 ml. of chloroform, the combined aqueous phase was acidified with concentrated hydrochloric acid and extracted with four 10 ml. portions of chloroform. Drying and concentration of this organic phase under reduced pressure gave an orange oil which crystallized when triturated with carbon tetrachloride to give 0.30 g. (36.6%) of the dione **10**, identified by tlc (A,B).

ii). The original chloroform phase, after being extracted with base, was dried and concentrated under reduced pressure to give a colorless oil which crystallized upon trituration with carbon tetrachloride to give 0.25 g. (23.7%) of white crystals of diethyl 1-methyl-2-hydroxy-3-oxo-5-phenyl-4-pyrroline-2,4-dicarboxylate (**12**), m.p. 110-111°. After one recrystallization from carbon tetrachloride the m.p. was constant at 112-113°; ir (sodium chloride, carbon tetrachloride): 2.87 (-OH), 5.68 (C=O, 5-membered ring ketone), 5.75 (C=O, aliphatic ester), 5.95 μ (C=O, conjugated ester); nmr (deuteriochloroform): δ 1.01 (t, 3H, J = 7 Hz, 4-$CO_2CH_2CH_3$), 1.27 (t, 3H, J = 7 Hz, 2-$CO_2CH_2CH_3$), 2.85 (s, 3H, N-CH_3), 3.98 (q, 2H, J = 7 Hz, 4-$CO_2CH_2CH_3$), 4.14 (s, 1H, exchanges with deuterium oxide, OH), 4.29, 4.30 (doublet of quartets, 2H, J = 7 Hz within each doublet, 2-CO $CH_aH_bCH_3$),

7.30-7.50 (m, 5H, aromatics); λ max (methanol): 315 nm (ε, 6,000).

Anal. Calcd. for $C_{17}H_{19}NO_6$: C, 61.25; H, 5.75; N, 4.20; m.w. 333. Found: C, 61.44; H, 5.83; N, 4.11; m.w. (mass spectrum): 333.

Hydrolysis of **6** in Aqueous Base.

The hydroxyester (**12**) (0.051 g., 0.153 mmole) was suspended in 5 ml. of 0.1 *N* sodium hydroxide which was being stirred and flushed with nitrogen. This stirring suspension was stoppered to retain the nitrogen atmosphere and allowed to remain undisturbed overnight. At the end of this time the reaction was extracted with two 5 ml. portions of chloroform, acidified with two drops of concentrated hydrochloric acid, and extracted with two additional 5 ml. portions of chloroform. The first extracts showed a trace of starting material by tlc (A). Drying and concentration of the second extracts gave 0.026 g. (65%) of crystalline material which was proved to be **9** by nmr and tlc (A,B).

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