Ring Opening Reactions of 6-Oxo-substituted Spiro-pyrrolidinediones: Synthesis of 4-Substituted-1,5-Dihydro-3-Hydroxy-2-oxo-1,5-diphenyl-2*H*-pyrroles

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Reaction of 2-oxocylalkaneglyoxylate esters with *N*-phenylmethyleneaniline yields spiro compounds such as 2-aza-3,4,6,-trioxo-1,2-diphenylspiro[4.4]nonane **4** and cycloalkane-2-aza-3,4,6-trioxo-1,2-diphenylspiro-[4.5]decanes **5-7**. These undergo solvolytic opening of the the oxocycloalkane ring to yield 4-substituted-1,5-dihydro-3-hydroxy-2-oxo-1,5-diphenyl-2*H*-pyrroles **12-17**.

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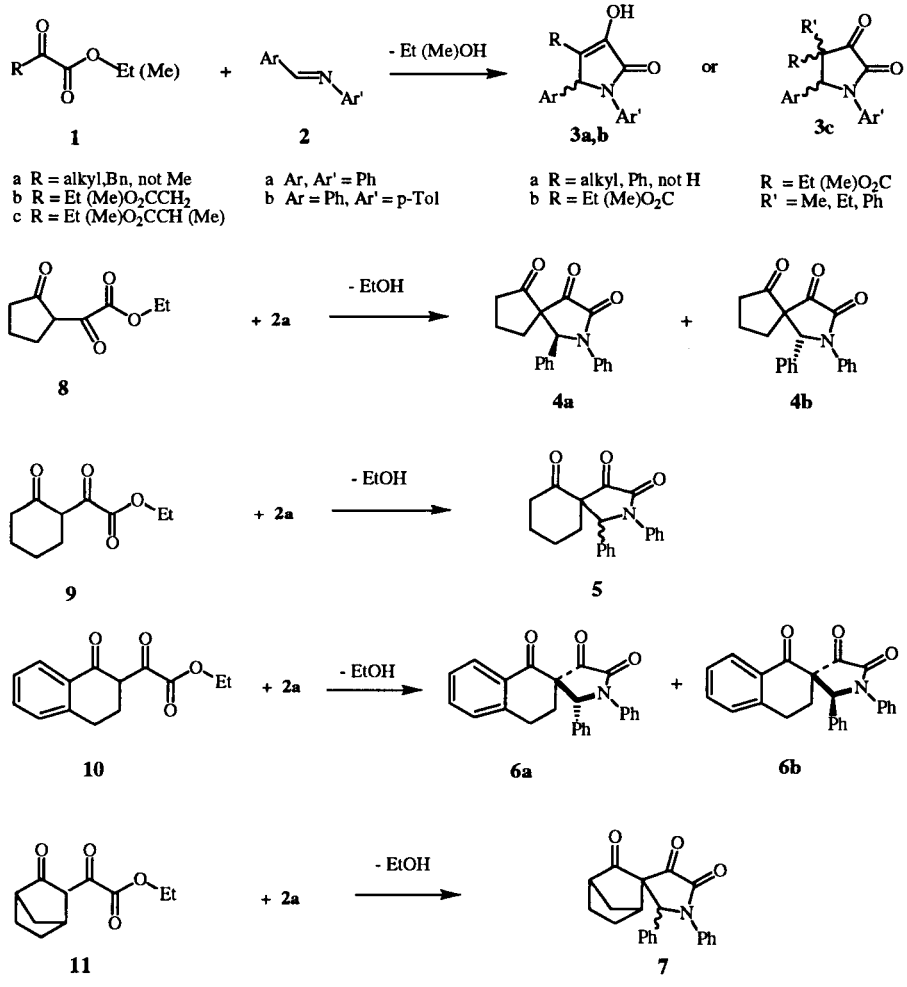
Esters of α-oxoacids, 2-oxobutanedioic acid and its 3-methyl derivatives, **1a,b,c**, react readily with Schiff bases such as *N*-benzylideneaniline, PhCH=NPh, **2a**, to form 1,5-dihydro-3-hydroxy-2-oxo-1,5-diphenyl-2*H*-pyrrole **3a** [1], 1,5-dihydro-3-hydroxy-2-oxo-1,5-diphenyl-2*H*-pyrrole-3-carboxylic acid esters **3b** [1,2], or 3-methyl-4,5-dioxo-1,2-diphenyl-3-pyrrolidinecarboxylic acid esters, **3c** [2,3,4]. Some of the last compounds have exhibited potential as antibiotics [3] or mold inhibitors [5]. We used this reaction to prepare spiro compounds such as 2-aza-3,4,6-trioxo-1,2-diphenylspiro[4.4]nonane, **4**, and the oxocycloalkane-2-aza-3,4,6-trioxo-1,2-diphenylspiro-[4.5]decanes, **5-7**, by reaction of **2a** with the ethyl glyoxylates, **8-11** (Scheme 1). Some of these spiro compounds

Scheme 1



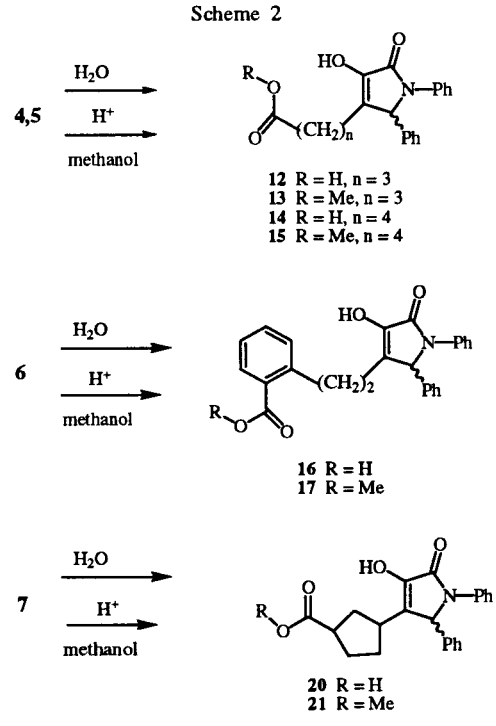
undergo a solvolytic opening of the carbocyclic ring with surprising ease and here we report our findings.

A mixture of isomers, **4,** was prepared from an equimolar mixture of **8** and **2a.** The presence of a benzylic hydrogen at two different chemical shifts was detected in the ^1H nmr spectrum of the crude reaction product, but the diastereomers of **4** were not stable enough to be separated by preparative thin layer chromatography. Migration of the components in the expected manner did not occur, instead, material of very low R_f, reminiscent of carboxylic acids was detected. Treatment of a sample of **4** with aqueous methanol containing two drops of concentrated hydrochloric acid or with dilute aqueous acid readily produced the carboxylic acid **12,** identified by ir (FT), proton and C-13 nmr, and ms. The methyl ester, **13,** was readily prepared by briefly boiling a methanol solution of **4** containing 2,2-dimethoxypropane and a catalytic amount of a strong acid [6].

The first attempts to prepare **5** from an equimolar mixture of **2a** and **9** in ether led only to a mixture of intractable gums containing several components. Similar gum formation was reported in the reaction of **2a** with ethyl pyruvate [2]. The detection of the odors of aniline and benzaldehyde in the reaction mixture suggested that equilibration of **2a** and other Schiff bases might be occurring. Benzaldehyde was added to the reaction mixture in subsequent trials to suppress the formation of Schiff bases other than **2a.** In some trials, the addition of drying agents such as molecular sieve or 2,2-dimethoxypropane accelerated the reaction. No further problems were encountered in the synthesis although the product was unstable. Attempts to separateion of the diastereisomers by thin layer chromatography failed. Migration of the spots did not occur and material of very low R_f was detected. Treatment of a sample of **5** with aqueous tetrahydrofuran containing a drop of concentrated hydrochloric acid for 20 hours at room temperature readily produced the carboxylic acid **14,** identified by ir (FT), proton and C-13 nmr, and ms. The methyl ester, **15,** was readily prepared by briefly boiling **5** in methanol containing 1,2-dimethoxypropane and Amberlyst™-15(H^+). The reactions are summarized in Scheme 2.

Solvolytic ring-opening reactions of cyclic β-diketones are known, but seldom under mild conditions such as those required to open **4** and **5.** Cleavage of **9** by sodium hydroxide in methanol at an elevated temperature is a well-known synthetic procedure [7] for making heptanedioic acid. Cleavage of 2,6-dioxocyclohexaneacetic acid ethyl ester to 4-oxooctanedioic acid occurred in refluxing, concentrated hydrochloric acid [8]. Cleavage of 2-acetamido-2-(2,6-dioxocyclohexylmethyl)propanedioic acid diethyl ester by boiling hydrochloric acid led to 5-(3-carboxypropyl)-2-pyrroline-2-carboxylic acid presumably *via* the intermediate, 2-amino-5-oxononanedioic acid [9]. 2-Benzoylcyclopentanone was converted to 6-oxo-6-phenylhexanoic acid

Scheme 2



under similar conditions [10]. The facile hydrolysis and alcoholysis of cyclic β-diketones under *mild conditions* observed in the present study appeared to be rather unusual and merited closer examination.

Diastereomers of 2-aza-7,8-benzo-3,4,6-trioxo-1,2-diphenylspiro[4.5]decane, **6a** (high R_f, (1*R*),(5*S*) diastereomer shown) and **6b** (low R_f, (1*S*),(5*S*) diastereoenantiomer shown) formed slowly, in good yield, on mixing equimolar amounts of **2a** and **10** in ether. It was possible to separate the isomers by thin layer chromatography. The minor product, low R_f isomer was shown by nmr to have the structure **6b** since irradiation of the 3.45 δ and 2.46 δ signals produced a significant nuclear Overhauser enhancement (nOe) of the benzylic proton nmr signal at 5.69 δ of 6.8% and 9.7% respectively. Irradiation of any of the four methylene proton signals of the high R_f isomer failed to produce any significant enhancement of the benzylic proton signal at 6.12 δ showing it to correspond to the structure **6a.** The nOe experiments were conducted in deuteriochloroform. A mixture of **6a** and **6b** was cleaved to the carboxylic acid **16** by refluxing for 5 days an aqueous, acidified solution of the spiro compounds. The methyl ester **17** was extremely difficult to prepare. Attempted esterification of **16** using methanol, 2,2-dimethoxypropane and an acid catalyst failed. Prolonged heating of a mixture of **6a** and **6b** with methanol and an equivalent of acetyl chloride in a sealed tube resulted in cleavage of the compounds to methyl oxalanilate, **18,** and (*E*)-2-benzylidene-1-tetralone, **19** (Scheme 3). The ester **17** was prepared in low yield by methyl transfer from dimethyl *p*-tolylsulfon-

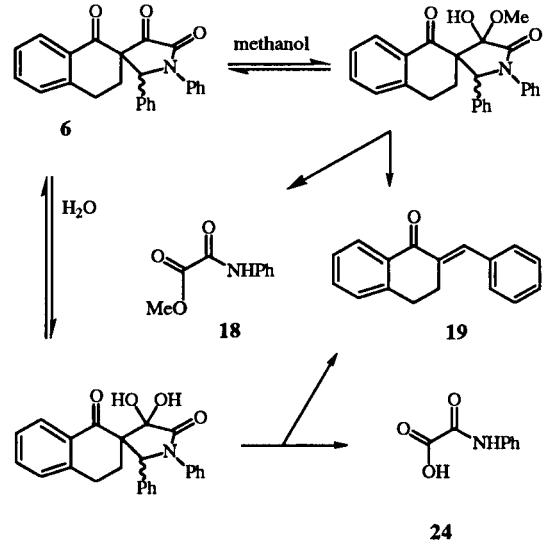
ium nitrate **25** to the potassium salt of the acid **16** [11], and by methylation of **16** using diazomethane.

Spiro compound **7** yielded only one isomer and was also somewhat resistant to hydrolysis and methanolysis, but after refluxing a slightly acidic aqueous dioxane solution for 3 days, the substituted carboxylic acid **20**, was obtained. After 3 days refluxing a methanol/tetrahydrofuran solution containing **7** and a trace of hydrochloric acid yielded the methyl ester, **21**.

A plausible mechanistic path for the cleavage at the C-6 carbonyl group is illustrated in Scheme 4 using the cleavage of **4** as an example. It invokes a protonated hydrate or hemiacetal of the carbocyclic keto group, **22**, as an intermediate. A concerted reaction to form the product then appears unlikely because coplanarity cannot be attained, but the intermediate could open to form the protonated form of the carboxylic acid **23**, which, by loss of a proton, would yield the acid. Two lines of evidence support the hypothesis that the hydrate or hemiacetal of the carbocyclic ketone are reactive intermediates. The equilibrium constant for hydration of a typical aliphatic ketone, acetone [12], exceeds that for hydration of a typical aryl alkyl ketone, acetophenone, [13] by about three orders of magnitude. Furthermore, the rate of reaction of cyclohexanone with nucleophiles exceeds that of cyclopentanone by a factor of about fifteen [14]. Assuming that ring opening of the hydrate or hemiacetal is rate determining, leading, respectively, to the acid or to the ester, the steric and electronic factors taken in concert suggest the reactivity order **5** > **4** >> **7** > **6**, which is observed. The methano bridge in **7** would impart greater steric resistance to hydration than would be encountered in either **4** or **5**, accounting for the slow rate of reaction of **7**. We rejected a pathway involving an acylium ion formed from the protonated keto oxygen of the heterocyclic ring such as **26**. If this were the path, **6** would be the most reactive because the acylium ion would be conjugated with the aromatic ring. Compound **6** is, however, the least reactive.

In one attempt to separate **6a** and **6b** by preparative thin layer chromatography several hours elapsed between application of the sample and development of the plate and a few days elapsed between development of the plate and elution of the sample. We observed the anomalous cleavage of the compounds to **19** and oxanilic acid **24** (Scheme 3). The material applied to a thin layer chromatography plate separated into four bands, one of which did not move from the point of application. Each of the migrating bands contained **19** but none of the expected **6a** or **6b**, indicating that most of the cleavage of **6** occurred *after* the plate was developed. Extraction by sodium bicarbonate of the coating at the point of application to the plate also yielded **24**, identified by mass and ir (FT) spectra. That the pathways leading to **19**, and **18** or **24** prevail over those leading to **16** or **17**, underscores the pronounced

Scheme 3

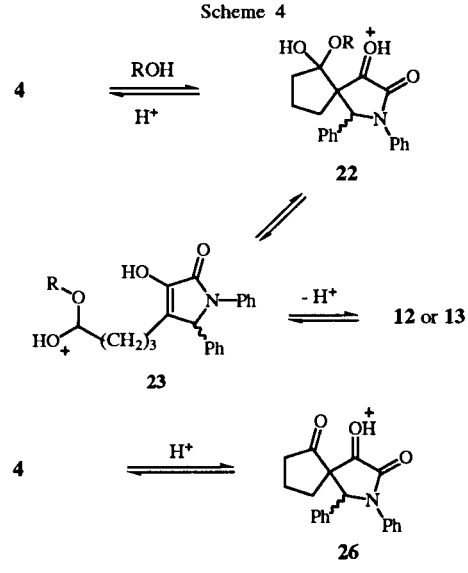


resistance of the carbocyclic ketone ring of **6** to methanolytic or hydrolytic cleavage compared to spiro compounds **4**, **5**, and **7**.

Conclusions.

Pyrrolidinediones with a spiro attachment of a carbocyclic ring at the 5-position and a keto function at the 6-position in the carbocyclic ring adjacent to the spiro atom are readily made by reaction of a Schiff base with appropriate glyoxylic acid esters. The carbocyclic ring can be opened by water or low molecular weight alcohols to yield carboxylic acids or esters attached through a chain or ring to the 4-position of 1,5-dihydro-3-hydroxy-2-oxo-1,5-diphenyl-2*H*-pyrrole. The ease of ring opening varies greatly depending on the structure of the spiro compound.

Scheme 4



EXPERIMENTAL

All melting and boiling points are uncorrected. Organic intermediates were obtained from the Aldrich Chemical Company unless otherwise indicated and were used without further purification. Potassium hydride, 20-25% suspension in mineral oil was supplied by Johnson-Mathey. Amberlyst-15 is a registered trademark of the Rohm & Haas Chemical Co. The C, H, and N analyses were determined by Desert Analytics, Tucson, AZ. Satisfactory results were obtained on all new compounds except for **17**. The spectra of **17** are, however, consistent with the structure proposed. The glyoxylic esters, **8-11** were made by two different methods, A or B. No attempt was made to optimize the syntheses. The workup in each method consisted of adding water to the reaction mixture and extracting with ether. This layer was discarded. The aqueous solution was acidified with sulfuric acid and extracted with ether. The combined ether extract was dried over sodium sulfate, concentrated, and distilled by a Kugelrohr distillation at <1 Torr and a heart cut was collected. Compound **10** was crystallized from aqueous alcohol.

Method A.

A suspension of potassium hydride in tetrahydrofuran was cooled to 0° in a nitrogen atmosphere. An equimolar mixture of the diethyl oxalate and the ketone in tetrahydrofuran was added to the mixture which was allowed to reach room temperature. The product was worked up as described.

Method B.

A solution of the ketone in tetrahydrofuran was placed in a flask, nitrogen blanketed and cooled in a solid carbon dioxide bath. A solution of lithium diisopropylamide [15] in hexane was added. After 20 minutes, an amount of diethyl oxalate in ethyl ether, equivalent to the amount of lithium diisopropylamide and ketone was added over a period of 10 minutes. The mixture was stirred for 20 minutes, allowed to warm to room temperature, and worked up.

Preparation of *N*-Phenylmethylenebenzenamine, (**2a**).

The compound was prepared from benzaldehyde and aniline in ethanol by the method of Vogel [16].

Preparation of 2-Aza-3,4,6-trioxo-1,2-diphenylspiro[4.4]nonane (**4**).

A mixture containing 1.77 g (9.5 mmoles) of **8**, 1.75 g (9.5 mmoles) of **2a**, 2.1 g (20 mmoles) of benzaldehyde and ethyl ether began to yield a solid almost at once. After 7 days ether was added to the flask and the crude material was isolated; 2.15 g, 71%. A 0.75 g portion of this was recrystallized from a mixture of benzene and tetrahydrofuran yielding 0.48 g of product, mp 208-209°; ^{1}H nmr (300 MHz, deuteriochloroform): δ 7.59 (2H, d), 7.33 (5H, m), 7.20 (1H, m), 7.10 (2H, m), 5.46 (1H, s), 2.62 (1H, m), 2.39 (2H, m), 2.05 (1H, m), 1.92 (1H, m), 1.46 (1H, m); ^{13}C nmr (75 MHz, deuteriochloroform): δ 208.3, 194.7, 157.1, 137.3, 136.2, 129.4, 129.1, 127.3, 126.9, 122.3, 67.4, 65.5, 37.2, 30.9, 18.7; ir (potassium bromide): 1763, 1719, 1696, 1497, 1390, 756 cm^{-1}; ms: m/z 319 (14, M$^+$), 172 (24), 171 (65), 129 (29), 128 (22), 116 (45), 115 (100), 91 (33), 77 (67), 55 (31), 51 (28).

Preparation of 2-Aza-3,4,6-trioxo-1,2-diphenylspiro[4.5]decane (**5**).

Under nitrogen, 0.21 g (2.0 mmoles) of benzaldehyde, 0.36 g (2.0 mmoles) of **2a**, 0.40 g (2.0 mmoles) of **9** and 1.03 g (10 mmoles) of 2,2-dimethylpropane yielded after 9 days a solid tinged with orange patches. This was thrice triturated with ether and most of the liquid was removed each time and placed in a test tube. Some benzene/hexane mixture was added to the solid and the mixture was filtered and washed with a benzene/hexane/ether mixture yielding 0.26 g of solid, mp, 233-234°. The ether washings yielded 0.05 g of a second crop and 0.04 g of a third crop of solid; total crude product, 0.35 g, 52.4%; ^{1}H nmr (300 MHz, deuteriochloroform): δ 7.63 (2H, d), 7.31 (2H, m), 7.19 (1H, t), 7.14 (5H, m), 6.19 (1H, s), 2.79 (1H, m), 2.58 (1H, m), 2.43 (1H, m), 2.16 (1H, m), 1.63 (3H, m), 1.20 (1H, m); ^{13}C nmr (75 MHz, deuteriochloroform): δ 200.9, 195.5, 157.1, 137.2, 135.6, 129.1, 129.1, 128.8, 127.1, 122.1, 66.7, 63.2, 39.4, 34.4, 26.7, 20.8; ir (potassium bromide): 1761, 1723, 1702, 1499, 1389 cm^{-1}; ms: (direct injection probe) m/z 333 (12, M$^+$), 185 (43), 129 (32), 115 (55), 91 (51), 77 (100).

Preparation of 2-Aza-7,8-benzo-3,4,6-trioxo-1,2-diphenylspiro-[4.5]decane Isomers **6a** and **6b**.

A mixture of 1.23 g (5.00 mmoles) of **10**, 0.905 g (5.0 mmoles) of **2a**, ether, and 0.53 g (5.0 mmoles) of benzaldehyde was allowed to stand under nitrogen for 12 days. The solid was filtered to produce, 0.33 g, melting range 207-220°. Concentration of the filtrate yielded an additional 1.4 g of crude product, 89%. The length of time required for this preparation is quite variable and some batches took several months to give a reasonable yield. In another experiment, there was a 10% yield after 14 days and 96% after 210 days. Analysis (tlc) revealed the presence of two isomers. These were separated by preparative tlc using 9/1 v/v dichloromethane/ethyl acetate. The higher (R_f = 0.64) isomer, **6a**, mp 233-234°, could also be obtained by recrystallization from glacial acetic acid. The lower (R_f = 0.51) isomer, **6b**, melted at 244-246°. The spectral data for **6a** are: ^{1}H nmr (300 MHz, deuteriochloroform): δ 8.04 (d), 7.66 (d), 7.54 (t), 7.35 (m), 7.23 (m), 7.16 (broad), 6.12 (s), 3.65 (m), 2.78 (m), 1.89 (m), 1.75 (m); ^{1}H nmr (300 MHz, dimethyl-d_6 sulfoxide): δ 7.94 (1H, d), 7.73 (2H, d), 7.65 (1H, t), 7.38 (9H, m), 7.24 (1H, t), 6.37 (1H, s), 3.21 (1H, m), 2.80 (1H, m), 2.01 (1H, m), 1.68 (1H, m); ^{13}C nmr (75 MHz, dimethyl-d_6 sulfoxide): δ 197.3, 191.4, 156.9, 144.1, 137.2, 135.8, 134.9, 129.6, 129.1, 129.0, 128.9, 128.7, 127.9, 127.1, 126.8, 121.9, 63.6, 60.4, 27.0, 23.8; ir (potassium bromide): 1749, 1705, 1673, 1596, 1496, 1228, 749, 706 cm^{-1}; ms: (direct injection probe) m/z: 381 (60, M$^+$), 308 (35), 233 (100), 180 (39), 115 (38), 91 (46), 90 (46), 77 (54).

The spectral data for **6b** are: ^{1}H nmr (300 MHz, deuteriochloroform): δ 7.55 (d), 7.47 (d), 7.40 (t), 7.30 (t), 7.17 (m), 7.00 (s), 5.69 (s), 3.45 (m), 3.21 (m), 2.85 (m), 2.46 (m); ^{1}H nmr (300 MHz, dimethyl-d_6 sulfoxide): δ 7.56 (d), 7.40 (t), 7.28 (m), 7.11 (m), 6.89 (m), 6.16 (1H, s), 3.53 (1H, m), 3.08 (1H, m), 2.75 (1H, m), 2.59 (1H, m); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 199.9, 193.3, 157.7, 143.1, 136.5, 134.2, 134.0, 131.2, 128.7, 128.6, 128.4, 128.1, 127.8, 126.6, 126.4, 126.2, 123.4, 64.7, 59.2, 30.2, 24.1; ir (potassium bromide): 1770, 1706, 1656, 1599, 1456, 1226, 736 cm^{-1}; ms: (direct injection probe) m/z: 381 (6, M$^+$), 234 (34), 233 (100), 181 (48), 180 (27), 115 (34), 91 (38), 90 (39), 89 (27), 77 (50).

Preparation of 2-Aza-7,10-methano-3,4,6-trioxo-1,2-diphenylspiro[4.5]decane (**7**).

In ether, 0.36 g (2.0 mmoles) of **2a** and 0.42 g (2.0) mmoles of 3-oxonorbornaneglyoxylic acid ethyl ester, **11**, stood for 6 days. The reaction mixture contained a small quantity of solid and smelled strongly of benzaldehyde. Benzaldehyde, 0.21 g (2.0 mmoles) was added to the nitrogen blanketed flask and the mixture was allowed to stand for 21 days. Hexane was added to the cloud point and the mixture was filtered. The solid was washed with ether and weighed

0.28 g, yield, 40%; mp 230.5-232° with discoloration, ^{1}H nmr (300 MHz, deuteriochloroform): δ 7.59 (2H, m), 7.30 (5H, m), 7.19 (1H, m), 7.12 (2H, m), 5.47 (1H, s), 3.02 (1H, m), 2.57 (1H, m), 2.28 (1H, m), 1.87 (4H, m), 1.66 (1H, m); ^{13}C nmr (75 MHz, deuteriochloroform): 207.5, 196.5, 157.6, 137.1, 135.2, 129.2, 129.1, 127.1, 126.7, 121.5, 68.4, 67.8, 50.2, 50.0, 36.4, 24.6, 22.2; ir (potassium bromide): 1761, 1723, 1712, 1498, 1399, 1302, 1228, 756, 700 cm^{-1}; ms: (direct injection probe) m/z 345 (4, M$^+$), 141 (27), 128 (36), 115 (32), 102 (24), 91 (51), 77 (100), 65 (23), 51 (34).

Preparation of α,2-Dioxocyclopentaneacetic Acid Ethyl Ester (**8**).

Method A.

Upon distillation a forerun of 0.41 g, boiling at an oven temperature of 105-110° and a center cut, 110-115°, lit 152-153°/15 Torr [17], 130-131°/3 Torr [18], 0.56 g were collected, yield, 35% including the forerun; ^{1}H nmr (300 MHz, deuteriochloroform): δ 13.01 (enol), 4.35 (2H, q), 2.97 (2H, t), 2.50 (2H, t), 2.01 (2H, p), 1.39 (3H, t); ^{13}C nmr (75 MHz, deuteriochloroform): (enol + keto) δ 214.2, 162.6, 158.0, 152.4, 150.5, 116.7, 63.3, 61.9, 39.8, 37.0, 28.3, 27.2, 20.2, 19.3, 13.9, 13.7; ir (neat): 1732, 1671, 1240 cm^{-1}; ms: m/z 184 (4, M$^+$), 112 (5), 111 (100), 83 (4), 82 (2), 55 (10), 53 (3).

Preparation of α,2-Dioxocyclohexaneacetic Acid Ethyl Ester (**9**).

Method A.

A center cut boiling at an oven temperature of 130-140° over a nominal 1 Torr pressure was retained; gc/ms analysis showed the material to be nearly pure **9** with small peaks at mass 152 and 170. The Mass, ^{13}C, and ^{1}H, and ir (FT) spectra of **9** have been previously reported [19].

Preparation of α,1-Dioxotetrahydronaphthalene-2-acetic Acid Ehyl Ester (**10**).

Method B.

The solid weighed 2.70 g, mp 44.5-46°, lit [20] 44-45°. The filtrates were combined, diluted with water and chilled yielding 0.56 g of product, total yield, 43%. The mass ^{13}C, ^{1}H, mass, and ir (FT) spectra have been reported [19].

Preparation of 3-Oxonorbornaneglyoxylic Acid, Ethyl Ester (**11**).

Method A.

Upon distillation, fraction 1, up to 125° oven temperature amounted to 0.32 g, 13%; fraction 2 (center cut) had 127-132°, yellow liquid, 1.03 g, 43%; leaving a residue of 0.53 g a dark brown viscous liquid, lit bp, 118-120°/2 Torr [21]; ^{1}H nmr (300 MHz, deuteriochloroform): δ (enol + keto) 15.83 (s), 11.35 (br), 4.35 (m), 3.81 (m), 2.82 (m), 2.06 (m), 1.39 (m); ^{13}C nmr (75 MHz, deuteriochloroform): δ (enol + keto) 213.3, 211.7, 208.1, 163.5, 162.6, 147.8, 146.4, 124.0, 122.3, 63.1, 62.9, 62.0, 50.1, 49.2, 49.1, 40.0, 39.6, 39.3, 38.2, 38.0, 37.0, 35.5, 28.0, 27.1, 26.9, 24.6, 24.2, 24.1, 14.1, 14.0; ir (neat): 1728, 1689, 1271, 1239, 1185, 1095 cm^{-1}; ms: m/z 210 (10, M$^+$), 182 (10), 137 (100), 109 (46), 108 (42), 81 (44), 79 (14), 53 (10).

Preparation of 4-(1,5-Dihydro-3-hydroxy-2-oxo-1,5-diphenyl-2*H*-pyrrol-4-yl)butanoic Acid (**12**).

To 0.30 g (0.97 mmole) of **4** were added 6 ml of tetrahydrofuran, 0.11 g (0.61 mmole) of concentrated hydrochloric acid, and 1.03 g (57.2 mmoles) of water. The flask was stoppered and allowed to stand. For the first two hours, the temperature remained about 2° above room temperature. After 3 days water was added to the reaction mixture and it was chilled. The crude product weighed 0.31 g, 98%. The material was recrystallized from aqueous isopropyl alcohol yielding 0.17 g of product, mp 173-174°, 56%; ^{1}H nmr (300 MHz, dimethyl-d_6 sulfoxide): δ 12.00 (1H, s), 9.52 (1H, s), 7.56 (2H, d), 7.23 (7H, m), 6.98 (1H, t), 5.78 (1H, s), 2.17 (3H, m), 1.63 (3H, m); ^{13}C nmr (75 MHz, dimethyl-d_6 sulfoxide): δ 174.1, 166.1, 141.8, 137.5, 137.0, 128.7, 128.5, 127.9, 127.0, 126.3, 123.8, 120.9, 62.0, 33.3, 23.3, 22.7; ir (potassium bromide): 3257, 1702, 1685, 1599, 1369, 698 cm^{-1}; ms: (direct injection probe) m/z: 337 (22, M$^+$), 171 (17), 129 (27), 128 (25), 115 (43), 91 (25), 77 (100), 65 (13), 55 (18), 51 (30).

Preparation of 4-(1,5-Dihydro-3-hydroxy-2-oxo-1,5-diphenyl-2*H*-pyrrol-4-yl)butanoic Acid Methyl Ester, (**13**).

To 0.50 g of crude **4** (1.6 mmoles) were added 15 ml of methanol and 3 drops of concentrated hydrochloric acid. The mixture was heated to boiling and on cooling, 0.28 g of silky white needles were collected, yield (0.81 mmole), 51%, mp 143-144°; ^{1}H nmr (300 MHz, deuteriochloroform): δ 7.63 (1H, s), 7.49 (2H, d), 7.23 (7H, m), 7.04 (1H, t), 5.40 (1H, s), 3.62 (3H, s), 2.31 (3H, m), 1.99 (1H, m), 1.80 (2H, m); ^{13}C nmr (75 MHz, deuteriochloroform): δ 173.8, 167.1, 141.7, 137.0, 135.8, 129.0, 128.8, 128.5, 127.1, 125.6, 124.8, 121.3, 64.6, 51.6, 33.4, 23.7, 22.9; ir (potassium bromide): 3278, 1732, 1662, 1499, 1364, cm^{-1}; ms: (direct inlet probe) m/z: 351 (13, M$^+$), 143 (17), 129 (29), 128 (30), 115 (55), 91 (24), 77 (100), 59 (17), 55 (21), 51 (25).

Preparation of 5-(1,5-Dihydro-3-hydroxy-2-oxo-1,5-diphenyl-2*H*-pyrrol-4-yl)pentanoic Acid (**14**).

To a solution of 0.12 g of the crude spiro compound **5** in 5 ml of tetrahydrofuran were added 1.01 g deionized water and 0.03 g of concentrated hydrochloric acid. The flask was allowed to stand for 20 hours. The reaction mixture was evaporated to dryness and weighed 0.18 g. The residue was yellow and had a strong odor of something resembling the starting ester **9**. The crude product was triturated with ether and the ether was decanted and the residue weighed 0.17 g. The material was dissolved in hot methanol and water was added to the cloud point, then a little more methanol was added. A small quantity of solid remained so the solution was filtered and the product precipitated on cooling the filtrate. The dry product which weighed 0.06 g, yield, 47%, was a light tan color so it was extracted with a small quantity of hot toluene. The cooled mixture yielded a colorless product which was recrystallized from methanol/water, mp 175-176.5°; ^{1}H nmr (300 MHz, dimethyl-d_6 sulfoxide): δ 12.00 (1H, s), 9.48 (1H, s), 7.56 (2H, d), 7.35 (1H, s), 7.22 (6H, m), 6.98 (1H, t), 5.77 (1H, s), 2.25 (1H, m), 2.14 (2H, m), 1.70 (1H, m), 1.40 (4H, m); ^{13}C nmr (75 MHz, dimethyl-d_6 sulfoxide): δ 174.4, 166.1, 141.6, 137.5, 137.1, 128.7, 128.5, 128.3, 127.9, 127.0, 126.7, 123.8, 120.8, 61.9, 33.3, 26.6, 24.1, 23.4; ir (potassium bromide): 3277, 1705, 1655, 1597, 1499, 1356, 703 cm^{-1}; ms: (direct injection probe) m/z 351 (2, M$^+$), 129 (13), 128 (15), 115 (44), 91 (34), 77 (100), 65 (14), 60 (32), 55 (26), 51 (29).

Preparation of 5-(1,5-Dihydro-3-hydroxy-2-oxo-1,5-diphenyl-2*H*-pyrrol-4-yl)pentanoic Acid Methyl Ester, (**15**).

Various residues remaining from the preparation and purification of **5** were combined. Methanol, 2,2-dimethoxypropane, and 0.2 g of Amberlyst-15(H$^+$) were added and the mixture was boiled until all of the solid dissolved, then allowed to cool. After 24 hours the liquid was transferred to a tared round bottom flask and the solvent

was removed yielding 0.12 g of solid residue. Recrystallization from aqueous methanol yielded 0.07 g of product. This crude material was dissolved in a mixture of 2,2-dimethoxypropane, methanol, and benzene, Amberlyst-15(H^+) was added and the flask was allowed to stand. The solvents were evaporated in a stream of air and the solid was redissolved in benzene. Hexane was added and the product precipitated. It was filtered, and washed with a benzene/hexane mixture, yield, 0.06 g, mp 139.7-140.5°; ^{1}H nmr (300 MHz, deuteriochloroform): δ 7.48 (2H, m), 7.26 (5H, m), 7.18 (2H, m), 7.04 (1H, m), 6.76 (1H, br), 5.83 (1H, s), 3.65 (3H, s), 2.29 (3H, m), 1.95 (1H, m), 1.52 (4H, m); ^{13}C nmr (75 Mz, deuteriochloroform): δ 173.9, 167.0, 141.0, 137.1, 135.8, 129.0, 128.8, 128.5, 127.1, 125.9, 124.7, 121.1, 64.6, 51.5, 33.6, 27.0, 24.5, 24.0; ir (potassium bromide): 3293, 1732, 1661, 1597, 1358, 1175, cm^{-1}; ms: (direct injection probe) m/z: 365 (5, M^+), 129 (20), 128 (20), 120 (17), 115 (49), 91 (37), 77 (100), 59 (70), 55 (26), 51 (24).

Preparation of 2-[(1,5-Dihydro-3-hydroxy-2-oxo-1,5-diphenyl-2*H*-pyrrol-4-ylethyl)]benzoic Acid, (**16**).

To 0.58 g of spiro compounds, **6a** and **6b**, (1.5 mmoles) were added 6 ml of dioxane and 1.0 g of water (56 mmoles) and the mixture was refluxed for 5 days. The mixture was evaporated to dryness on the rotary evaporator and the residue was treated with water containing 0.38 g (3.6 mmoles) of sodium carbonate. The mixture was filtered and the filtrate was acidified yielding 0.18 g of solid which was twice recrystallized from glacial acetic acid yielding 0.10 g of product, mp 234-235°. It turned orange on melting. The solid residue, 0.33 g, was treated with aqueous ethanol containing hydrochloric acid, filtered, and washed with ethanol, yield, 0.25 g. This material was recrystallized once from glacial acetic acid yielding 0.19 g of product, mp 234-235°. The hydrolysis can also be carried out in aqueous acetic acid; ^{1}H nmr (300 MHz, dimethyl-d_6 sulfoxide): δ 12.90 (1H, s), 9.50 (1H, s), 7.77 (1H, d), 7.52 (2H, d), 7.43 (1H, t), 7.22 (9H, m), 6.99 (1H, t), 5.64 (1H, s), 3.15 (1H, m), 2.96 (1H, m), 2.57 (1H, m), 1.94 (1H, m); ^{13}C nmr (75 MHz, dimethyl-d_6 sulfoxide): δ 168.7, 166.1, 142.2, 141.7, 137.5, 136.9, 131.7, 130.6, 130.4, 130.2, 128.7, 128.6, 127.9, 127.0, 126.3, 128.2, 123.9, 120.8, 62.2, 31.7, 25.7; ir (potassium bromide): 3204, 1701, 1643, 1406, 1242, 749 cm^{-1}; ms: (direct injection probe) m/z: 399 (0.3, M^+), 264 (10), 135 (28), 115 (32), 91 (22), 89 (11), 79 (22), 77 (100), 51 (20).

Preparation of 2-[(1,5-Dihydro-3-hydroxy-2-oxo-1,5-diphenyl-2*H*-pyrrol-4-ylethyl)]benzoic Acid Methyl Ester, (**17**).

To 10 mg (0.025 mmole) of acid **16**, in a 10 ml round bottom flask were added 1.7 mg of anhydrous potassium carbonate, 5.6 mg of dimethyl *p*-tolylsulfonium nitrate, and 3 ml of dichloromethane [11]. An air condenser was placed on the flask and the mixture was stirred for 20 hours. There was an unmistakable odor of methyl *p*-tolyl sulfide but there was still some undissolved material which resembled the original acid. An additional 2.0 mg of potassium carbonate which had been ground in a mortar just before addition and an additional 3 mg of the sulfonium salt **257** were added and stirring was continued for 50 hours. Some precipitate settled to the bottom of the flask. The clear supernatant was withdrawn and transferred to a clean, tared 10 ml round bottom flask and evaporated to yield 8.4 mg of slightly yellowish solid. In the proton nmr showed methyl protons were observed at about 3.85, 3.86, and 3.95 ppm and together with two benzylic hydrogen signals. The solution was placed in a 10 ml round bottom flask and the contents of the nmr tube was rinsed into the flask with a little chloroform. The solvent was evaporated and 0.75 ml of benzene was added to the gummy residue. A solid precipitated immediately. Hexane, 1 ml, was added and the flask was stoppered and allowed to stand for 16 hours. The reaction flask was washed out with a little benzene and this solution was passed through a 3 mm column of silica gel. This was followed by a dichloromethane wash of the reaction flask and passage of the solution through the silica gel column and retention in the same tube as the benzene wash.

The wash solution was evaporated to dryness. About 0.3 ml of benzene was added and the solution was added to the flask with the precipitate. The slurry of solvent and precipitate was transferred to a centrifuge tube and spun down. The supernatant was removed and the precipitate was triturated with hexane and centrifuged again. The hexane was removed. The white crystals had a proton nmr , C-13 nmr , an ir (FT) and a mass spectrum ($M^+ = 413$) all consistent with the methyl ester. The sample recovered from the C-13 nmr measurement weighed 1.5 mg, yield, 15%. A second preparation was accomplished using diazomethane in a tetrahydrofuran solution of **16** containing a little methanol. The crude product contained some material methylated on the enol oxygen. Recrystallization from benzene afforded the ester, mp 176-178°; ^{1}H nmr (300 MHz, deuteriochloroform): δ 7.89 (1H, d), 7.47 (d), 7.41 (t), 7.24 (m), 7.14 (m), 7.03 (1H, t), 6.60 (1H, s), 5.27 (1H, s), 3.86 (3H, s), 3.19 (1H, m), 2.99 (1H, m), 2.59 (1H, m), 2.24 (1H, m); ^{13}C nmr (75 MHz, deuteriochloroform): δ 167.9, 166.7, 143.0, 141.2, 137.2, 135.8, 132.2, 131.1, 130.9, 129.1, 128.8, 128.8, 128.3, 127.2, 126.3, 125.6, 124.6, 121.0, 64.6, 52.1, 32.6, 26.3; ir (potassium bromide): 3274, 1709, 1681, 1365, 1289, 1268, 751, 704 cm^{-1}; ms: (direct injection probe) m/z 413 (15, M^+), 264 (65), 191 (34), 182 (43), 115 (43), 104 (50), 91 (52), 77 (100).

Preparation of Oxalanilic Acid Methyl Ester (**18**).

A mixture of dimethyl oxalate, 1.18 g (10 mmoles) and 0.93 g (10 mmoles) of aniline was heated under nitrogen for 2 hours. Methanol was added, the mixture was heated to boiling and filtered while hot removing 0.36 g of a high melting solid. The filtrate was concentrated and the resulting solid was extracted with a hot mixture of cyclohexane and 2-propanol. On cooling, the clear extract yielded a yellow solid which was filtered and washed with a little 2-propanol; mp 110.2-111.4°, lit [22], 114°; ^{1}H nmr (300 MHz, deuteriochloroform): δ 8.89 (1H, s), 7.65 (2H, d), 7.38 (2H, t), 7.20 (1H, t), 3.97 (3H, s); ^{13}C nmr (75 MHz, deuteriochloroform): δ 161.5, 153.6, 136.2, 129.2, 125.6, 119.9, 54.1; ir (potassium bromide): 1724, 1700, 1601, 1541, 1443, 1305, 1294, 1171, 761 cm^{-1}; ms: m/z 179 (22, M^+), 120 (67), 119 (32), 92 (89), 77 (100), 65 (98), 59 (59), 51 (72).

Preparation of (*E*)-3,4-Dihydro-2-phenylmethylene-1-2*H*-naphthalenone (**19**).

To 1.51 g of α-tetralone (98%, 10 mmoles) were added 1.06 g of benzaldehyde, ethanol, and 0.08 g of potassium hydroxide. The flask was purged with nitrogen stoppered, and allowed to stand: mp 105°, lit [23], 105°; ^{1}H nmr (300 MHz, deuteriochloroform): δ 8.13 (1H, d), 7.88 (1H, s), 7.42 (7H, m), 7.24 (1H, d), 3.13 (2H, t), 2.94 (2H, t); ^{13}C nmr (75 MHz, deuteriochloroform): δ 187.9, 143.2, 136.6, 135.8, 135.4, 133.4, 133.3, 129.9, 128.5, 128.4, 128.2, 128.2, 127.0, 28.9, 27.2; ir (potassium bromide): 1661, 1605, 1590, 1297, 1246, 1223, 1140, 954, 756, 742, 696 cm^{-1}; ms: m/z 234 (44, M^+), 233 (100), 128 (21), 115 (46), 91 (30), 90 (51), 89 (54), 63 (26).

Preparation of 3-[(1,5-Dihydro-3-hydroxy-2-oxo-1,5-diphenyl-2*H*-pyrrol-4-yl)]cyclopentanecarboxylic Acid, (**20**).

A mixture of 0.08 g (0.2 mmole) of spiro compound **7**, 5 ml of dioxane, 1 ml of water and 0.04 g of concentrated hydrochloric acid was refluxed for 3 days. The solvents were evaporated. The residue was dissolved in tetrahydrofuran and water was added to the cloud point. The solution was chilled and crystals separated. The solid was dissolved in 2.5 ml of hot acetic acid. Water was added to the cloud point and a solid slowly crystallized. The solid weighed 74 mg, 88%. It was again recrystallized from acetic acid to which water was added after dissolution was complete. The solid weighed 46 mg, yield, 55%, mp, with discoloration, 213-215°; ^{1}H nmr (300 MHz, dimethyl-d_6 sulfoxide): δ 11.99 (1H, s), 9.47 (1H, s), 7.54 (2H, d), 7.23 (7H, m), 6.98 (1H, t), 5.77 (1H, s), 2.54 (1H, m), 2.37 (1H, m), 1.71 (6H, m); ^{13}C nmr (75 MHz, dimethyl-d_6 sulfoxide): δ 176.6, 166.2, 141.2, 137.2, 137.1, 128.6, 128.5, 128.4, 128.0, 127.4, 124.0, 121.1, 62.4, 42.9, 37.2, 34.7, 29.8, 27.9; ir (potassium bromide): 3267, 1697, 1669 cm^{-1}; ms: (direct injection probe) m/z: 363 (3, M$^+$), 141 (19), 128 (24), 120 (20), 115 (23), 91 (43), 77 (100), 67 (24), 55 (22), 51 (27).

Preparation of 3-[(1,5-Dihydro-3-hydroxy-2-oxo-1,5-diphenyl-2*H*-pyrrol-4-yl)]cyclopentanecarboxylic Acid, Methyl Ester (**21**).

A mixture of 0.12 g (0.30 mmole) of of the spiro compound **7**, 6 ml of methanol, 0.20 g of 2.2-dimethoxypropane, 2 ml of tetrahydrofuran, and 0.04 g of concentrated hydrochloric acid was refluxed for 3 days. The solution was evaporated to dryness. The solid was dissolved in a small amount of methanol and boiled with a few charcoal pellets, then filtered through a very short column of alumina which turned the solution slightly pink. The filtrate was heated and water was added to the cloud point. A little more methanol was added and solid precipitated on cooling. The solid was washed with a little methanol/water mixture, 0.05 g, mp 153-154°. An additional 0.03 g of product was recovered from the filtrate; total yield, 61%; ^{1}H nmr (300 MHz, deuteriochloroform): δ 7.46 (2H, d), 7.23 (7H, m), 7.03 (1H, t), 6.64 (1H, s), 5.36 (1H, s), 3.66 (3H, s), 2.68 (1H, m), 2.43 (1H, m), 1.88 (6H, m); ^{13}C nmr (75 MHz, deuteriochloroform): δ 176.5, 166.9, 140.4, 137.0, 136.0, 128.9, 128.8, 128.5, 127.5, 127.3, 124.8, 121.3, 64.9, 51.8, 43.4, 37.3, 34.7, 30.7, 28.7; ir (potassium bromide): 3268, 1734, 1671, 1378, 1336, 1187 cm^{-1}; ms: (direct injection probe) m/z: 377 (6, M$^+$), 250 (21), 141 (27), 128 (28), 120 (22), 115 (25), 91 (46), 78 (24), 77 (100), 71 (45), 59 (91).

Preparation of Dimethyl-4-methylphenylsulfonium nitrate, (**25**).

To a chilled solution of 1.04 g (7.5 mmoles) of methyl *p*-tolyl sulfide, 1.07 g of iodomethane (7.5 mmoles) and 5 ml of acetonitrile was added 1.28 g (7.5 mmoles) of solid silver nitrate in portions with stirring. The solution was filtered and the filtrate was evaporated on a watch glass yielding 0.75 g, 47% of crude product. The residue was dissolved in a minimum of deionized water and a solution of sodium chloride in water was added dropwise until no more precipitate of silver chloride formed. The solid was extracted with chloroform, and the extract was filtered through a short column containing alumina and evaporated. The solid was dried in a vacuum desiccator; ^{1}H nmr (300 MHz, deuteriochloroform): δ 2.12 (s, 3H), 3.21 (s, 6H), 7.33 (m, 2H), 7.71 (m, 2H); ^{13}C nmr (75 MHz, deuteriochloroform): δ 145.6, 131.9, 129.6, 122.0, 29.335, 29.358, 21.6.

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