(24.9 g, 0.12 mol) at 0 °C. After the mixture was stirred overnight at ambient temperature, the volatiles were removed in vacuo. Bulb-to-bulb distillation at 100 °C (0.2 mm) yielded a colorless oil: 26.55 g (98%); NMR ($CDCl_3/Me_4Si$) δ 1.5 (t, J = 7 Hz, 6 H), 4–4.7 (m, 4 H), 7.5–8.3 (m, 4 H); ^{31}P NMR ($CDCl_3$/85% H_3PO_4) δ 25.05.

[*m*-(Trifluoromethyl)phenyl]bis[*o*-(methoxymethyl)-phenyl]phosphine Oxide (22). Under a static N_2 atmosphere, a stirred solution of *o*-(methoxymethyl)phenyl bromide (5 g, 25 mmol) in 50 mL of ether was cooled in a dry ice–acetone bath. *n*-BuLi in hexane (15.6 mL, 25 mol, 1.6 M) was added dropwise. After the mixture was stirred for 0.5 h at −72 °C, a solution of **20** (6.8 g, 25 mmol) in 25 mL of ethyl ether was added rapidly in one portion. The temperature rose to −30 °C, and the yellow mixture was stirred for 1 h at −72 °C. After equilibrating to ambient temperature, the yellow mixture was poured into H_2O containing some EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to yield a yellow oil. Bulb-to-bulb distillation at 120 °C (0.2 mm) removed the low-boiling impurities as determined by GLC analysis. At 160 °C (0.1 mm) a colorless oil (4.35 g) was collected. Crystallization from methylcyclohexane yielded **22** as a white powder: 1.5 g (14%); Mp 90–92 °C; NMR ($CDCl_3/Me_4Si$) δ 3.17 (s, 6 H, 4.78 (s, 4 H), 6.8–8.1 (m, 12 H); mass spectrum, m/e (relative intensity) 434 (8), 419 (28), 403 (18), 387 (100).

Anal. Calcd for $C_{23}H_{22}F_3O_3P$: C, 63.59; H, 5.10. Found: C, 63.52; H, 5.05.

2-Bromobenzyl Ethyl [3-(Trifluoromethyl)phenyl]-phosphonate (23). Under a $CaSO_4$ drying tube, a magnetically stirred mixture of *o*-bromobenzyl alcohol (10 g, 53.5 mol) and DBU (8.5 g, 53.5 mmol) in 150 mL of anhydrous ether was treated drop wise with a solution of **20** (4.55 g, 0.0535 mol) in 100 mL of ether at 0.°C. The white suspension was stirred for 1 h at ambient temperature and then suction filtered. The ether filtrate was washed with H_2O and then with 5% HCl, dried over $MgSO_4$, and concentrated in vacuo to yield a yellow oil, 20.7 g. Bulb-to-bulb distillation at 110 °C (0.1 mm) removed starting alcohol. At 140 °C (0.05 mm), a pale yellow oil was collected: 15.5 g (68.5%); NMR (CCl_4/Me_4Si) δ 1.3 (t, J = 8 Hz, 3 H), 4.1 (pair of overlapping quintets, 2 H), 5.1 (AB, J = 13 Hz, 2 H), 7–8.2 (m, 8 H); ^{31}P NMR (CCl_4/85% H_3PO_4) δ 16.1; mass spectrum, m/e (relative intensity) 343 (85), 315 (100), 281 (32).

Anal. Calcd for $C_{16}H_{15}BrF_3O_3P$: C, 45.41; H, 3.57. Found: C, 44.65; H, 3.65.

^{31}P NMR indicated that diethyl [3-(trifluoromethyl)phenyl]-phosphonate was an impurity in **23**.

1-[2-(Trifluoromethyl)phenyl]-1,3-dihydro-2,1-benz-oxaphosphole 1-Oxide (24). Under a static N_2 atmosphere, a magnetically stirred solution of **23** (2.4 g, 0.00567 mol) in 50 mL of anhydrous THF was cooled in a dry ice–acetone bath and then treated dropwise with 6.1 mL (0.0116 mol) of 1.9 M *tert*-butyl-lithium in pentane (Alfa) such that the temperature never rose above −65 °C. The purple mixture was stirred at −72 °C for 1 h and then allowed to equilibrate to ambient temperature over a 45-min period. After the mixture was quenched with AcOH (1 mL), the solvents were removed in vacuo. The yellow residue was partitioned between CH_2Cl_2 and H_2O. The dried ($MgSO_4$) CH_2Cl_2 layer was concentrated in vacuo to yield a yellow glass, 1.7 g. Bulb-to-bulb distillation at 130 °C (0.2 mm) yielded a colorless oil which crystallized upon trituration with petroleum ether: 0.85 g (51%); mp 109–110 °C; ^{31}P NMR ($CDCl_3$/85% H_3PO_4) δ 47.4; ^{13}C NMR ($CDCl_3/Me_4Si$) δ 72.9 (CH_2); mass spectrum, m/e (relative intensity) 298 (70), 280 (10), 269 (26), 77 (100).

Anal. Calcd for $C_{14}H_{10}F_3O_2P$: C, 56.39; H, 3.38. Found: C, 56.41; H, 3.46.

Registry No. 1a, 15286-11-0; **1b**, 61820-30-2; **1c**, 80953-47-5; **2a**, 75777-37-6; **2b**, 80953-48-6; **3a**, 75777-31-0; **3b**, 75777-30-9; **3c**, 75777-29-6; **4b**, 61820-24-4; **4c**, 18593-18-5; **4c** methylester, 80953-49-7; **5b**, 80953-50-0; **5c**, 75777-35-4; **6**, 80953-51-1; **7**, 80953-52-2; **12a**, 80953-53-3; **12b**, 80953-54-4; **13b**, 78089-65-3; **13c**, 80953-55-5; **13c** acid, 80953-56-6; **14**, 75777-32-1; **17**, 52711-30-5; **19**, 54057-97-5; **20**, 80953-57-7; **22**, 80953-58-8; **23**, 77505-35-2; **24**, 75777-28-5; diethyl methylphosphonite, 15715-41-0; *m*-bromobenzotrifluoride, 401-78-5; diethyl chlorophosphate, 814-49-3.

Novel Syntheses of 5-Aroyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic Acids[1,2]

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A fundamentally new approach to the synthesis of the title compounds was devised in which the crucial step was the intramolecular displacement of methanesulfinate ion or bromide ion by the sodium enolates of properly disposed substituted malonate esters such as **13a–13c** and **20**. As integral parts of the above process, a new four-carbon alkylation of the pyrrole nitrogen atom, a novel synthesis of 2-(methylthio)pyrroles, and the use of the dimethylsulfonium moiety as a meta directing group in the pyrrole system were developed.

5-Aroyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic acids (**1**) are antiinflammatory and analgesic agents of considerable potency,[3] and linear, multistep syntheses of this class of compounds have been reported.[3,4] In this publication we describe new, short syntheses of these agents which embrace concepts not heretofore utilized for synthetic purposes in the pyrrole area.

One of the successful synthetic strategies, of several considered, was based on two important literature precedents. Firstly, the reaction of 1-(2-hydroxyethyl)-2-nitro-5-acetylpyrrole (**2**) with strong bases effects cyclization to the pyrrolo[2,1-*b*]oxazole derivative **3** by displacement of nitrile ion.[5] Secondly, spiro activated cyclopropanes, such as **4**, are transformed, with singular ease,

(1) Contribution No. 577 from the Syntex Institute of Organic Chemistry.

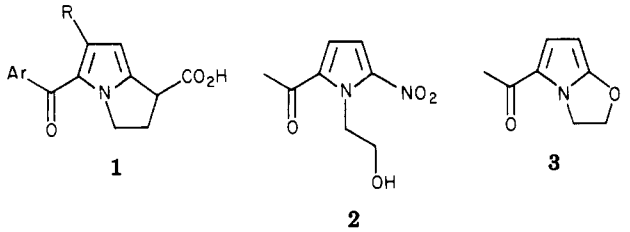
(2) Presented in part at the XV Congreso Méxicano de Quimica Pura y Aplicada, Acapulco, Gro., Mexico, Oct 19–23, 1980.

(3) Muchowski, J. M.; Kluge, A. F. German Patent 2 731 662, 1978; *Chem. Abstr.* **1978**, *88*, 136450w; German Patent 2 731 678, 1978; *Chem. Abstr.* **1978**, *89*, 6215h; U.S. Patent 4 097 579, 1978; *Chem. Abstr.* **1978**, *89*, 197331a; U.S. Patent 4 232 038, 1980; *Chem. Abstr.* **1981**, *94*, 103156a.

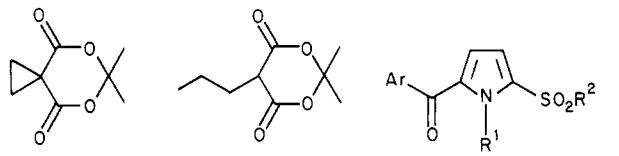
(4) Van Horn, A.; Gallegra, P. U.S. Patent 4 140 698, 1979.

(5) Vecchieti, V.; Dradi, E.; Lauria, F. *J. Chem. Soc. C* **1971**, 2554.

0022-3263/82/1947-1682$01.25/0



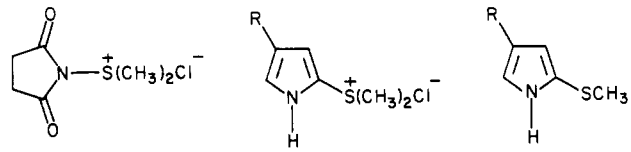
1 2 3



4 5 6

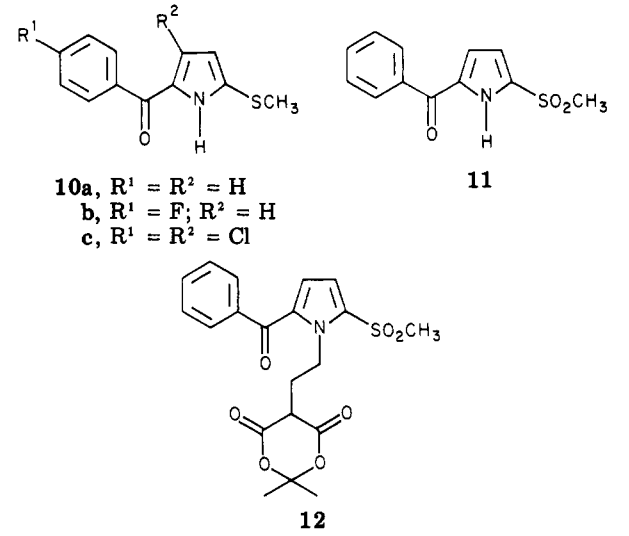
into Meldrum's acid derivatives **5** by a wide variety of nucleophiles.[6,7] From the standpoint of preparative efficiency, however, 2-nitro-5-aroylpyrroles are not ideal precursors of **1** because either of the substituents, when situated at C-2, preferentially direct electrophilic substitution to C-4. Thus, nitration of 2-acylpyrroles produces both the 2,4- and the 2,5-disubstituted isomers with the former usually predominating.[10] Inasmuch as alkanesulfinate ion is readily displaced by nucleophiles in various alkyl heteroaryl sulfones,[11] it was anticipated that analogous intramolecular reactions would occur with 2-aroyl-5-(alkylsulfonyl)pyrroles (**6**). These compounds were expected to be easily accessible, in isomerically pure form, via the appropriate 2-(alkylsulfenyl)pyrroles.

2-Methylthiopyrrole (**9a**), a potential starting material for the synthesis of the title compounds, was prepared by thermolysis of the sulfonium salt **8a** (neat or in boiling 1,2-dichloroethane) which in turn was obtained from pyrrole and the *N*-chlorosuccinimide–dimethyl sulfide adduct **7**. This synthesis,[12] which could be effected without purification of **8a**, provided the known[13] sulfide **9a** in good yield, and, because of the deactivating influence of the dimethylsulfonium group, gave a product free of disubstituted contaminants. An analogous process has been utilized by Tomita et al.[14] to prepare 3-(alkylthio)- and 3-(arylthio)indoles.

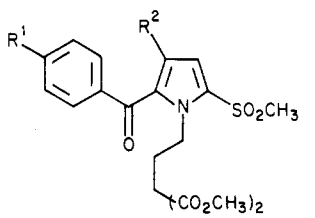


7 **8a**, R = H; b, R = Cl **9a**, R = H; b, R = Cl

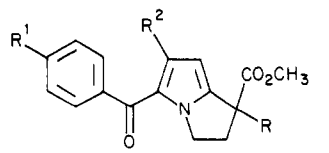
The acylation of 2-(methylthio)pyrrole with *N*,*N*-dimethylbenzamide and *N*,*N*-dimethyl-4-fluorobenzamide, under Vilsmeier–Haack conditions, occurred rapidly and gave exclusively the 5-aroyl compounds **10a** and **10b** in 80% and 54% yields, respectively. The benzoyl sulfide **10a** was oxidized to the sulfone **11** with *m*-chloroperbenzoic acid, and base-promoted homoconjugate addition of this substance to the spiro cyclopropane derivative **4** was examined. Under optimized conditions, a 35% yield (46% based on recovered starting material) of the 1:1 adduct **12** was obtained when equimolar amounts of the sodium salt of **11** and the cyclopropyl compound **4** were heated in dimethylformamide (DMF) solution at 90 °C for 4 h. It is noteworthy that the sodium salt corresponding to **12** did not cyclize under these or more vigorous conditions. Presumably this is a result of the low anion nucleophilicity or the sterically encumbered nature thereof, or perhaps a combination of both factors. This difficulty was avoided by conversion of **12** into the dimethyl ester **13a**, the sodium salt of which was transformed into a mixture, consisting mainly (83% yield) of the bicyclic malonate **14a** and a small amount of the corresponding methyl monoester **14b**, upon heating in DMF solution for 5 h at 85 °C. The monoester undoubtedly was formed as a result of the sodium methanesulfinate induced decarbomethoxylation of **14a**.[15] Alkaline hydrolysis of the mixture of esters (se-



10a, $R^1 = R^2 = H$; b, $R^1 = F$; $R^2 = H$; c, $R^1 = R^2 = Cl$ **11** **12**



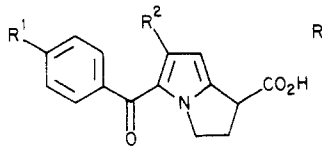
13a, $R^1 = R^2 = H$; b, $R^1 = F$; $R^2 = H$; c, $R^1 = R^2 = Cl$



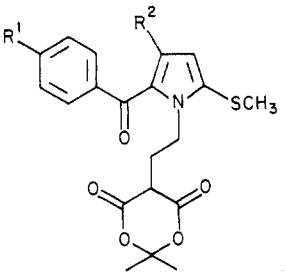
14a, $R^1 = R^2 = H$; $R^3 = CO_2CH_3$; b, $R^1 = R^2 = R^3 = H$; c, $R^1 = F$; $R^2 = H$; $R^3 = CO_2CH_3$; d, $R^1 = F$; $R^2 = R^3 = H$; e, $R^1 = R^2 = Cl$; $R^3 = CO_2CH_3$

(6) Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66.
(7) Although the concept of spiro activation was first enunciated by Danishefsky and Singh,[8] the synthesis and reactions of several cyclopropane derivatives activated by spiro fusion, in a somewhat different manner, had been described several years earlier.[9]
(8) Danishefsky, S.; Singh, R. K. *J. Am. Chem. Soc.* **1975**, *97*, 3239. Singh, R. K.; Danishefsky, S. *J. Org. Chem.* **1975**, *40*, 2969.
(9) Horning, D. E.; Lacasse, G.; Muchowski, J. M. *Can. J. Chem.* **1971**, *49*, 246.
(10) Jones, R. A.; Bean, G. P. "The Chemistry of Pyrroles"; Academic Press: London, 1977; pp 124–125.
(11) Berkoz, B.; Lewis, B.; Muchowski, J. M. U.S. Patent 4 064 135, 1977; *Chem. Abstr.* **1978**, *88*, 170130b.
(12) This process has some degree of generality for the preparation of 2-(alkylthio)- and 2-(arylthio)pyrroles: Greenhouse, R.; Landeros, R.; De Sales, J., Unpublished observations.
(13) Gronowitz, S.; Hörnfeldt, A. B.; Gestblom, B.; Hoffman, R. A. *J. Org. Chem.* **1961**, *26*, 2615; *Ark. Kemi* **1961**, *18*, 151. Olson, R. K.; Snyder, H. R. *J. Org. Chem.* **1965**, *30*, 184, 187.
(14) Tomita, K.; Terada, A.; Tachikawa, R. *Heterocycles* **1976**, *4*, 729.
(15) Krapcho, A. P.; Lovey, A. J. *Tetrahedron Lett.* **1973**, 957.

parable by TLC) and subsequent acidification gave the required monocarboxylic acid **15a** in 71% overall yield from **13a**. These results demonstrated that the above process would be viable for the synthesis of derivatives of **1** provided that the homoconjugate addition step could be improved. The poor efficiency of this reaction doubtless stemmed from the low nucleophilicity of the highly delocalized anion derived from the benzoyl sulfone **11**. As expected,[16] the anion corresponding to the benzoyl sulfide **10a** was considerably better in the above regard. Thus, the sodium salt of **10a** reacted more efficiently with **4** (74% yield of **16a**) and under milder conditions (5 h at 55 °C) than did the salt of **11**. Oxidation of the sulfide **16a** with *m*-chloroperbenzoic acid gave the previously described sulfone **12** in excellent (90%) yield. As a result of the above modification, the overall yield of compound **15a**, from 2-(methylthio)pyrrole, was improved from ca. 19% to 35%.



15a, $R^1 = R^2 = H$
b, $R^1 = F$; $R^2 = H$
c, $R^1 = R^2 = Cl$



16a, $R^1 = R^2 = H$
b, $R^1 = F$; $R^2 = H$
c, $R^1 = R^2 = Cl$

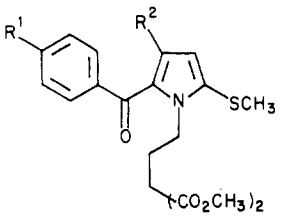
Application of a slightly modified synthetic sequence to 2-(methylthio)-5-(4-fluorobenzoyl)pyrrole (**10b**) gave the bicyclic carboxylic acid **15b** in 18% overall yield (no steps optimized). The specific changes entailed methanolysis of the Meldrum's acid derivative **16b** to the substituted malonate **17a** and subsequent oxidation of the latter compound to the sulfone **13b**.

The above process was also amenable to the synthesis of a pyrrolecarboxylic acid derivative bearing a chloro group at C-6, as outlined below.

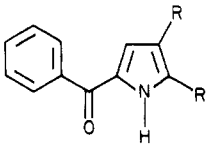
The dimethylsulfonium group in **8a** inductively deactivates the pyrrole moiety and, consequently, electrophilic or radical substitution of this salt should take place predominantly at C-4. As predicted, the low-temperature chlorination of **8a** with sulfuryl chloride gave a new sulfonium salt, in 56% yield, which, on the basis of NMR spectral and analytical data, was clearly the 4-chloro compound **8b**.

The synthesis of **8b** meant that access to the 6-chloro derivatives of the title compounds was now possible. Thus, brief heating of **8b** in xylene at reflux temperature, generated the exceedingly unstable 2-(methylthio)-4-chloropyrrole (**9b**), which, without further ado, was acylated in situ under Vilsmeier–Haack conditions, with *N,N*-dimethyl-4-chlorobenzamide. In this way, 2-(methylthio)-4-chloro-5-(4-chlorobenzoyl)pyrrole (**10c**) was obtained in 46% overall yield from the sulfonium salt **8b**. (*p*-Chlorobenzoyl)pyrrole **10c** was then transformed into 5-(4-chlorobenzoyl)-6-chloro-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]-pyrrole-1-carboxylic acid (**15c**) via a reaction sequence identical with that used for the synthesis of fluoro compound **15b**.

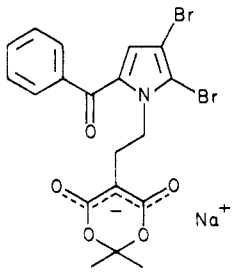
In the above reaction sequence, the formation of the bicyclic system was based on the intramolecular displacement of methanesulfinate ion. It was of interest to determine if other leaving groups, such as bromide ion, could be utilized in the cyclization step. Therefore, 2-benzoylpyrrole (**18a**) was reacted with bromine at 0 °C, and the dibromide **18b** thus produced was converted into the sodium salt and heated at ca. 80 °C with **4** in DMF solution. After 4 h the sodium salt **19** could be isolated in very high yield. The dimethyl ester **20** derived from **19** was transformed into the sodium salt, which, on heating at 75 °C in DMF, gave a 1:6 mixture of the mono- and diesters **21a** and **21b** in about 95% yield. Saponification of the mixture and sequential hydrogenolytic debromination, over palladium on charcoal in the presence of magnesium oxide, and acidification gave the bicyclic monocarboxylic acid **15a**. If the reaction sequence, commencing with the dibromo diester **20** was effected without purification of intermediates, **15a** could be isolated in 71% yield. The overall yield of this substance, based on 2-benzoylpyrrole, was thus 47%, and therefore this process is even more efficient than the sulfinate displacement sequence. In the present form, however, it is restricted to those derivatives of **1** which will tolerate the hydrogenolysis conditions.



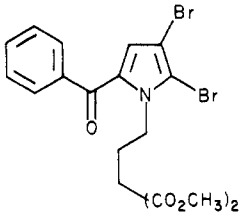
17a, $R^1 = F$; $R^2 = H$
b, $R^1 = R^2 = Cl$



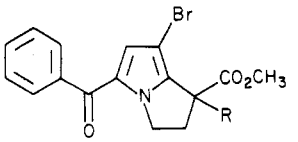
18a, R = H
b, R = Br



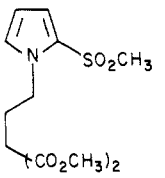
19



20



21a, R = H
b, R = CO_2CH_3



22

In summary, a unique synthesis of 5-aroyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic acids has been developed, the distinguishing feature of which is the intramolecular displacement of methanesulfinate or bromide ion by a substituted malonate anion. Displacements by carbon nucleophiles are extremely rare for pyrrole systems, and those which are known are mediated by copper.[17,18] The displacement reactions described herein are crucially dependant on the presence of an electron-withdrawing group in the pyrrole moiety. For example, the sodium salt

(16) We thank Professor G. Stork, Columbia University, for this suggestion.

(17) Anderson, H. J.; Lee, S. F. *Can. J. Chem.* **1965**, *43*, 409.
(18) Sundukova, T. A; Vasilevskii, S. F.; Shvartsberg, M. S; Kotlarevskii, I. L. *Izv. Akad. Nauk SSSR, Ser. Khim* **1980**, 726; *Chem. Abstr.* **1980**, *93*, 71446f.

of **22**, which lacks this activating substituent, fails to undergo the reaction (addition–elimination[5]) even in boiling DMF solution.[19] In spite of this limitation, processes analogous to those described above can be utilized for the synthesis of natural products such as the simpler necine bases.[19]

Experimental Section

The melting points were determined in a Mel-Temp melting point apparatus and are corrected. The infrared spectra were measured with a Perkin-Elmer Model 237 grating infrared spectrophotometer. The ultraviolet spectra were recorded on a Perkin-Elmer Model 402 ultraviolet–visible spectrophotometer. The NMR spectra were measured with a Varian T-60 spectrometer and are expressed as parts per million (δ) from internal tetramethylsilane. The high-pressure liquid chromatographic separations were effected with a Du Pont Model 841 apparatus.

Dimethyl(2-pyrrolyl)sulfonium Chloride (8a). A solution of dimethyl sulfide (20.5 g, 0.33 mol) in dry dichloromethane (125 mL) was added, in a dropwise manner, to a stirred solution of *N*-chlorosuccinimide (40 g, 0.3 mol), in anhydrous dichloromethane (3 L) at −30 to −40 °C (nitrogen atmosphere). One hour after the addition was completed, a solution of pyrrole (20 g, 0.295 mol) in dichloromethane (175 mL) was added dropwise at −30 to −40 °C, and stirring at this temperature was then continued for 2 h. The product was precipitated from solution by the addition of ether, and the solid was collected by filtration, washed well with ether, and dried to give the salt **8a** as a white solid (40 g, 83% yield). For analysis, a sample was recrystallized from a small volume of dichloromethane at −20 °C to give material which had the following: mp 115–116 °C; UV (MeOH) 221, 249 nm (ϵ 5130, 1020); NMR (D_2O) δ 3.18 (s, 6 H, $(CH_3)_2S$), 6.44 (dd, 1 H, $J_{3,4}$ = 4.1 Hz, $J_{4,5}$ = 2.5 Hz, H-4), 7.12 (dd, 1 H $J_{3,4}$ = 4.1 Hz, $J_{3,5}$ = 1.7 Hz, H-3), 7.37 (dd, 1 H, $J_{4,5}$ = 2.5 Hz, $J_{3,5}$ = 1.7 Hz, H-5).

Anal. Calcd for $C_6H_{10}ClNS$: C, 44.02; H, 6.10. Found: C, 43.84; H, 5.94.

2-(Methylthio)pyrrole (9a). For preparation of the methylthio compound, a portion of the above salt was heated at 76 °C in 1,2-dichloroethane (ca. 50 mL/g) for 1 h. The solvent was removed in vacuo at 30 °C and the residue was distilled at 60–65 °C (3 mm) to give the sulfide **9a** (70% yield). This material was identical, in all respects, with an authentic sample prepared from 2-(thiocyano)pyrrole.[13]

Dimethyl(4-chloro-2-pyrrolyl)sulfonium Chloride (8b). The sulfonium salt (**8a**) (25.0 g, 0.152 mol) was dissolved in dry dichloromethane (3.2 L) at room temperature and then the solution was cooled to −76 °C. Sulfuryl chloride (18.2 mL, 0.305 mol) was added with efficient stirring and the solution was left at −76 °C for 8 h. The product was precipitated by addition of ether (4 L) to the cold, well-stirred solution; it was collected by filtration and dried in vacuo. The white solid (16.8 g, 56%) thus obtained was of sufficient purity for use in the next step. For analysis, it was crystallized from methanol–ether to give a solid which decomposed at 150–200 °C: UV (MeOH) 222, 258 nm (ϵ 5890, 8320); NMR (D_2O) δ 3.37 (s, 6 H, $(CH_3)_2S$), 7.24 (d, 1 H, $J_{3,5}$ = 1.4 Hz, H-3 or H-5), 7.49 (d, 1 H, $J_{3,5}$ = 1.4 Hz, H-5 or H-3).

Anal. Calcd for $C_6H_9Cl_2NS$: C, 36.37; H, 4.57. Found: C, 36.15; H, 4.55.

2-(Methylthio)-5-benzoylpyrrole (10a). A solution of *N,N*-dimethylbenzamide (2.37 g), in anhydrous 1,2-dichloroethane (60 mL) containing phosphorus oxychloride (2.43 g), was heated at reflux temperature (nitrogen atmosphere) for 0.75 h. To the cooled solution was added 2-(methylthio)pyrrole (0.9 g) in 1,2-dichloroethane (40 mL) and the resulting solution was heated at reflux temperature for 1 h. The reaction mixture was cooled, a solution of sodium acetate (5.41 g) in water (80 mL) was added, and the mixture was heated under reflux for 1.5 h. The organic phase was separated and combined with a dichloromethane extract of the aqueous phase, and the combined extracts were washed with water, dried, and evaporated in vacuo. The residue was subjected to column chromatography on silica gel, the product being eluted with dichloromethane–hexane (1:1). After crystallization from methanol, the product (1.19 g, 79%) had the following: mp 106–108 °C; UV (MeOH) 249, 340 nm (ϵ 8510, 15 500); IR ($CHCl_3$) 3420, 3215, 1610, 1554, 1535 cm^{-1}; NMR ($CDCl_3$) δ 2.41 (s, 3 H, SCH_3), 6.16 (m, 1 H, H-3), 6.73 (m, 1 H, H-4), 7.38 (m, 3 H, H-3′,4′,5′), 7.78 (m, 2 H, H-2′,6′), 10.16 (m, 1 H, NH).

Anal. Calcd for $C_{12}H_{11}NOS$: C, 66.33; H, 5.10; N, 6.44. Found: C, 66.58; H, 5.10; N, 6.36.

2-(Methylthio)-5-(4-fluorobenzoyl)pyrrole (10b). This compound was prepared in the same manner as compound **10a**. The crude product was purified by column chromatography on silica gel, using ethyl acetate–hexane (1:9) as the eluting solvent. After crystallization from ether–hexane, the product (3.2 g, 54%) had the following: mp 112–113 °C; UV (MeOH) 219, 248, 343 nm (ϵ 9770, 8510, 13 800); IR ($CHCl_3$) 3440, 1610 cm^{-1}; NMR ($CDCl_3$ δ 2.48 (s, 3 H, SCH_3), 6.25 (dd, 1 H, $J_{1,3}$ = 2.5 Hz, $J_{3,4}$ = 4 Hz, H-3), 6.80 (dd, 1 H, $J_{1,4}$ = 2.5 Hz, $J_{3,4}$ = 4 Hz, H-4), 7.12 (dd, 2 H, $J_{3'F}$ = 8 Hz, $J_{2',3'}$ = 8 Hz, H-3′,5′), 7.92 (dd, 2 H, $J_{2'F}$ = 5.5 Hz, $J_{2',3'}$ = 8 Hz, H-2′,6′), 10.67 (m, 1 H, W_H = 22 Hz, NH).

Anal. Calcd for $C_{12}H_{10}FNOS$: C, 61.24; H, 4.28. Found: C, 61.01; H, 4.21.

2-(Methylthio)-4-chloro-5-(4-chlorobenzoyl)pyrrole (10c). The chloro sulfonium salt **8b** (1.20 g, 0.006 mol) was converted into 2-(methylthio)-4-chloropyrrole (**9b**) by heating with dry xylene (20 mL) in an oxygen-free atmosphere for 0.25 h.

In a separate reaction, *N,N*-dimethyl-4-chlorobenzamide (1.10 g, 0.006 mol) was converted into the corresponding Vilsmeier–Haack reagent by heating a solution thereof in dry 1,2-dichloroethane (20 mL), containing phosphorus oxychloride (0.55 mL, 0.006 mol) for 0.5 h.

The solution containing the Vilsmeier–Haack reagent was added to the above chloro sulfide solution and the mixture was heated at reflux temperature, in a nitrogen atmosphere, for 24 h. At this time, a solution of sodium acetate (2 g, 0.03 mol) in water (10 mL) was added cautiously and the mixture was heated at reflux temperature for 2 h. The organic solvent was removed in vacuo, water was added to the residue, and the product was extracted into ethyl acetate. The extract was dried over sodium sulfate and evaporated in vacuo. The residue was subjected to column chromatography on silica gel (100 g), the product (0.787 g, 46%) being eluted by ethyl acetate–hexane (1:4). After crystallization from hexane, the product had the following: mp 142–143 °C; UV (MeOH) 220, 261, 340 nm (ϵ 13 800, 12 300, 13 800); IR ($CHCl_3$) 3450, 3250, 1620 (sh), 1608, 1577 cm^{-1}; NMR ($CDCl_3$) δ 2.80 (s, 3 H, SCH_3), 6.57 (s, 1 H, H-3), 8.00 (q, 4 H, J_{AB} = 8.7 Hz, H-2′,3′,5′,6′).

Anal. Calcd for $C_{12}H_9Cl_2NOS$: C, 50.36; H, 3.17; N, 4.89. Found: C, 50.07; H, 3.22; N, 4.78.

2-(Methylsulfonyl)-5-benzoylpyrrole (11). A solution of the sulfide **10a** (0.300 g) and *m*-chloroperbenzoic acid (0.550 g, 86%) in anhydrous dichloromethane (50 mL) was stirred at 5 °C for 3 h. The solution was washed with 20% sodium carbonate solution, and the organic phase was dried and evaporated in vacuo. The residue (0.320 g, 100%), after crystallization from acetone–hexane, had the following: mp 148–150 °C; UV (MeOH) 258, 294 nm (ϵ 8710, 16 600); IR ($CHCl_3$) 3565, 3410, 3255, 1640, 1580, 1342, 1140 cm^{-1}; NMR ($CDCl_3$) δ 3.22 (s, 3 H, SO_2CH_3), 6.86, 6.90 (s, 2 H, H-3,4), 7.50 (m, 3 H, H-3′,4′,5′), 7.91 (m, 2 H, H-2′,6′), 11.10 (m, 1 H, W_H = 16 Hz, NH).

Anal. Calcd for $C_{12}H_{11}NO_3S$: C, 57.81; H, 4.45; N, 5.60. Found: C, 57.85; H, 4.44; N, 5.57.

Reaction of 11 with Spiro Cyclopropane Derivative 4. Synthesis of 12. A solution of the sulfone **11** (12.0 g, 0.048 mol), in dry DMF (30 mL), was added to a stirred suspension of sodium hydride (1.56 g, 0.048 mol, 50% in mineral oil), in anhydrous DMF (100 mL), maintained in a nitrogen atmosphere. When hydrogen evolution had ceased, the cyclopropyl compound **4**[8] (8.16 g, 0.048 mol) was added and the solution was heated at 90 °C for 4 h. The cooled solution was diluted with 10% hydrochloric acid and extracted with ethyl acetate. The extract was washed with water, dried over sodium sulfate, and evaporated in vacuo. The residue was subjected to column chromatography on silica gel (600 g), using hexane–ethyl acetate (3:2) as the eluting solvent. In this way there was obtained the starting material (3.0 g, 25%) and the product **12** (7.0 g, 35% based on starting material consumed). Recrystallization of the product from aqueous acetone gave material with the following: mp 159 °C; UV (MeOH) 260, 292

(19) Greenhouse, R., unpublished data.

nm (ε 10 200, 17 000); IR (KBr) 1780, 1746, 1649 cm^{-1}; NMR pyridine-d_5) δ 1.62 (s, 6 H, $C(CH_3)_2$), 3.02 (s, 2 H, J = 6.8 Hz, CH_2), 3.57 (s, 3 H, SO_2CH_3), 5.28 (t, 2 H, J = 6.8 Hz, NCH_2), 6.58 (d, 1 H, J = 4.1 Hz, H-4), 7.03 (d, 1 H, J = 4.1 Hz, H-3), 7.42 (m, 3 H, H-3′,4′,5′), 7.85 (m, 2 H, H-2′); the methine protron was not visible in this solvent or in Me_2SO-d_6.

Anal. Calcd for $C_{20}H_{21}NO_7S$: C, 57.28; H, 5.05; N, 3.34. Found: C, 57.20; H, 5.25; N, 3.29.

Synthesis of 12 by *m*-Chloroperbenzoic Acid Oxidation of Sulfide 16a. *m*-Chloroperbenzoic acid (85%, 0.600 g, 0.00347 mol) was added to a solution of the sulfide **16a** (0.500 g, 0.001 29 mol; for synthesis, see below) in dry dichloromethane (100 mL) cooled in an ice bath. After 3 h at ice-bath temperature, the solvent was evaporated and the residue was washed with ether to remove *m*-chlorobenzoic acid. The residual solid (0.486 g, 90%) had mp 154–155 °C, and after crystallization from aqueous acetone, material with mp 159 °C, identical with that described above, was obtained.

Synthesis of Sulfide 16a by Reaction of 4 with 2-(Methylthio)-5-benzoylpyrrole (10a). Acylpyrrole **10a** (0.741 g, 0.00341 mol) was added to a stirred suspension of sodium hydride (0.177 g, 0.368 mol, 50% in mineral oil), in dry DMF (80 mL), maintained in an argon atmosphere. After 1 h at room temperature, the spiro cyclopropyl compound **4** (0.625 g, 0.00368 mol) was added. The solution was heated to 55 °C and maintained at that temperature for 5 h. The cooled solution was diluted with water, and the starting material was extracted with ethyl acetate. This extract was dried and evaporated in vacuo to give recovered **10a** (0.110 g, 15%). The aqueous phase from above was made acidic with 0.01 N hydrochloric acid and the product was extracted into ethyl acetate. The extract was dried and evaporated in vacuo to give a residue which was subjected to column chromatography on silica gel (ethyl acetate–hexane, 1:1). Compound **16a** was obtained as a solid (0.978 g, 75%; 87% based on starting material consumed) which had mp 124–125 °C after crystallization from ethyl acetate–hexane: UV (MeOH) 216, 254, 340 nm (ε 8510, 10 000, 14 100); IR ($CHCl_3$) 1795, 1755, 1716 cm^{-1}; NMR ($CDCl_3$) δ 1.75, 1.82 (s, total 6 H, $C(CH_3)_2$), 2.48 (s, 3 H, SCH_3), 2.60 (m, 2 H, CH_2) 4.20 (t, 1 H, J = 6 Hz, CH), 4.73 (t, 2 H, J = 6 Hz, NCH_2), 6.17 (d, 1 H, J = 4 Hz, H-3), 6.72 (d, 1 H, J = 4 Hz, H-4), 7.55 (m, 5 H, C_6H_5).

Anal. Calcd for $C_{20}H_{21}NO_2S$: C, 62.00; H, 5.46. Found: C, 62.01; H, 5.45.

Synthesis of the 4-Fluorobenzoyl Sulfide 16b. 2-(Methylthio)-5-(4-fluorobenzoyl)pyrrole (1.00 g, 0.00425 mol) was added to a stirred suspension of sodium hydride (0.204 g, 0.00425 mol, 50% in mineral oil), in dry DMF (66 mL), maintained in an argon atmosphere. After 0.5 h the cyclopropano compound **4** (0.731 g, 0.00425 mol) was added and the solution was heated to 65 °C where it was maintained for 1.5 h. The reaction mixture was worked up as described above for **16a** to give recovered starting material (0.18 g, 18%) and crude **16b**. This latter material was purified by column chromatography on silica gel, using ethyl acetate–hexane–methanol (9:10:1) as the eluting solvent. Compound **16b** was thus obtained as a solid (1.24 g, 72%; 88% based on starting material consumed) which, after crystallization from ethyl acetate–hexane, had the following: mp 92 °C; UV (MeOH) 217, 266, 340 nm (ε 5370, 8130, 7760); IR ($CHCl_3$) 1795; 1755, 1620, 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.77, 1.82 (s, total 6 H, $C(CH_3)_2$, 2.50 (s, 3 H, SCH_3), 2.60 (m, 2 H, CH_2), 4.15 (t, 1 H, J = 5.5 Hz, CH), 4.70 (t, 2 H, J = 6 H, NCH_2), 6.17 (d, 1 H, J = 4 Hz, H-3), 6.68 (d, 1 H, J = 4 Hz, H-4), 7.05 (dd, 2 H, $J_{2',3'}$ = 8 Hz, $J_{3'F}$ = 8 Hz, H-3′,5′), 7.72 (dd, 2 H, $J_{2',3'}$ = 8 Hz, $J_{2'F}$ = 6 Hz, H-2′,6′).

Anal. Calcd for $C_{20}H_{20}FNO_5S$: C, 56.72; H, 5.24; N, 3.31. Found: C, 56.84; H, 5.15; N, 3.24.

Synthesis of Dimethyl Ester 13a by Methanolysis of 12. Methanol (25 mL), which had been saturated with hydrogen chloride, was added to a solution of **12** (0.419 g) in methanol (25 mL) and the solution was heated at reflux temperature for 0.5 h. The solvent was removed in vacuo and the residue was percolated through a column of silica gel, using ethyl acetate–hexane (1:4) as the percolating solvent. The diester **13a** (0.386 g, 95%) was obtained as a viscous oil: UV (MeOH) 221, 261, 293 nm (ε 7590, 10 700, 1590); IR ($CHCl_3$) 1755, 1740, 1650 cm^{-1}; NMR ($CDCl_3$) δ 2.48 (m, 2 H, CH_2), 3.22 (s, 3 H, SO_2CH_3), 3.55 (t, 1 H, J = 7.2 Hz, CH), 3.72 (s, 6 H, OCH_3), 4.80 (m, 2 H, NCH_2), 6.67 (d, 1 H, J = 4 Hz, H-4), 6.88 (d, 1 H, J = 4 Hz, H-3), 7.60 (m, 5 H, C_6H_5).

Anal. Calcd for $C_{19}H_{21}NO_7S$: C, 56.01; H, 5.19; N, 3.43. Found: C, 55.87; H, 5.25; N, 3.24.

Synthesis of Dimethyl Ester 17a by Methanolysis of 16b. Compound **17a** was prepared from **16b** in 95% yield in exactly the same manner as described for **13a**. This substance also was obtained as an oil: UV (MeOH) 215, 248, 334 nm (ε 10 000, 8510, 15 500); IR ($CHCl_3$) 1755, 1735, 1620, 1600 cm^{-1}; NMR ($CDCl_3$) δ 2.47 (s, 3 H, SCH_3), 2.42 (m, 2 H, CH_2), 3.48 (t, 1 H, J = 7 Hz, CH), 3.72 (s, 6 H, OCH_3), 4.58 (t, 2 H, J = 7 Hz, NCH_2), 6.17 (d, 1 H, J = 4 Hz, H-3), 6.67 (d, 1 H, J = 4 Hz, H-4), 7.07 (dd, 2 H, $J_{3'F}$ = 8.5 Hz, $J_{2'3'}$ = 8.5 Hz, H-3′,5′), 7.75 (dd, 2 H, $J_{2'F}$ = 5.5 Hz, $J_{2'3'}$ = 8.5, H-2′,6′).

Anal. Calcd for $C_{19}H_{20}FNO_5S$: C, 58.01; H, 5.12; N, 3.55. Found: C, 57.82; H, 5.16; N, 3.33.

Synthesis of Meldrum's Acid Derivative 16c and Methanolysis to 17b. Sodium hydride in mineral oil (50%, 0.686 g, 0.014 mol) was added to a stirred solution of **10c** (4.10 g, 0.014 mol) in dry DMF (44 mL) maintained in a nitrogen atmosphere. After 40 min, the spiro cyclopropane derivative **4** (2.43 g, 0.014 mol) was added and the temperature was raised to 70 °C and maintained there for 3 h. The cooled solution was added slowly to ether (880 mL) with good agitation, and the sodium salt of **16c** which precipitated was collected by filtration, washed with ether, and dried in vacuo. The crude salt (6.8 g, 99%) was dissolved in methanol (100 mL) and a saturated solution of hydrogen chloride in methanol (150 mL) was added. The solution was left at room temperature for 12 h, the solvent was then removed in vacuo at 25 °C, and the oil which remained was subjected to column chromatography on silica gel (350 g), using dichloromethane as the eluting solvent. Removal of the solvent in vacuo gave the malonate ester **17b** as a yellow oil: UV (MeOH) 213, 266, 338 (ε 14 800, 14 100, 11 800); IR ($CHCl_3$) 1757, 1738, 1592 cm^{-1}; NMR ($CDCl_3$) δ 2.24 (m, 2 H, CH_2), 2.49 (s, 3 H, SCH_3), 3.47 (t, 1 H, J = 7.2 Hz, CH), 3.77 (s, 6 H, OCH_3), 4.16 (m, 2 H, NCH_2), 6.21 (s, 1 H, H-3), 7.65 (q, 4 H, J_{AB} = 8.6 Hz, H-2′,3′,5′,6′).

Anal. Calcd for $C_{19}H_{19}Cl_2NO_5S$: C, 51.36; H, 4.31; N, 3.15. Found: C, 51.61; H, 4.39; N, 3.08.

Synthesis of Dimethyl Ester 13b by *m*-Chloroperbenzoic Acid Oxidation of 17a. A solution of compound **17a** (0.700 g, 0.0018 mol) in dry dichloromethane (50 mL) containing 85% *m*-chloroperbenzoic acid (0.700 g, 0.004 mol) was stirred at 0 °C for 1 h. The solvent was removed in vacuo, the residue was shaken with 10% sodium bicarbonate solution, and the product was extracted into ether. The extract was washed with water, dried, and evaporated in vacuo. The residue was subjected to column chromatography on silica gel, using ethyl acetate–hexane (3:7) as the eluting solvent. The product **13b** (0.558 g, 74%) was obtained as an oil: UV (MeOH) 219, 259, 292 nm (ε 8510, 8710, 13 500); IR ($CHCl_3$) 1755, 1735, 1650, 1600 cm^{-1}; NMR ($CDCl_3$) δ 2.42 (m, 2 H, CH_2), 3.23 (s, 3 H, SO_2CH_3), 3.60 (m, 1 H, CH), 3.75 (s, 6 H, OCH_3), 4.78 (m, 2 H, NCH_2), 6.65 (dd, 1 H, J = 4 Hz, H-4), 6.92 (dd, 1 H, J = 4 Hz, H-3), 7.03 (m, 4 H, C_6H_4F).

Anal. Calcd for $C_{19}H_{20}FNO_7S$: C, 53.64; H, 4.74, N, 3.29. Found: C, 53.82; H, 4.91; N, 3.06.

Synthesis of Dimethyl Ester 13c by *m*-Chloroperbenzoic Acid Oxidation of 17b. A solution of 86% *m*-chloroperbenzoic acid (4.11 g, 0.0236 mol) in dichloromethane (200 mL) was added in a dropwise manner to a stirred solution of the sulfide **17b** (2.90 g, 0.006 54 mol) in dichloromethane (100 mL). After 2.5 h the reaction was worked up as described for the synthesis of **13b** but using dichloromethane as the extracting solvent. The crude product was percolated through a column of silica gel (120 g), using ethyl acetate–hexane (3:7) as the percolating solvent. Evaporation of the solvent gave a solid (2.95 g, 95% yield, pure by TLC) which was crystallized from dichloromethane–hexane to give the sulfone **17b**: mp 127 °C; UV (MeOH) 211, 229, 275 nm (ε 10 000, 11 800, 15 900); IR ($CHCl_3$) 1756, 1738, 1649, 1589 cm^{-1}; NMR ($CDCl_3$) δ 2.33 (m, 2 H, CH_2), 3.24 (s, 3 H, SO_2CH_3), 3.50 (t, 1 H, J = 7.2 Hz, CH), 3.73 (s, 6 H, OCH_3), 4.58 (m, 2 H, NCH_2), 6.92 (s, 1 H, H-3), 7.70 (q, 4 H, J_{AB} = 8.7 Hz, H-2′,3′,5′,6′).

Anal. Calcd for $C_{19}H_{19}Cl_2NO_7S$: C, 47.90; H, 4.02; N, 2.94. Found: C, 47.97; H, 3.98; N, 2.87.

Dimethyl 5-Benzoyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]-pyrrole-1,1-dicarboxylate (14a) and Methyl 5-Benzoyl-1,2-

dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate (14b). A solution of the diester **13a** (0.728 g, 0.00179 mol) in anhydrous DMF (10 mL) was added to a stirred suspension of 60% sodium hydride in mineral oil (0.072 g, 0.0018 mol), in dry DMF (5 mL), at room temperature (nitrogen atmosphere). When hydrogen solution had ceased, the solution was heated at 85 °C for 5 h. The solution was poured into water and extracted with ethyl acetate. The extract was washed with water, dried over sodium sulfate, and evaporated in vacuo. The residue was subjected to column chromatography on silica gel (25 g) and the column was developed with ethyl acetate–hexane (1:4). In this way there was isolated the diester **14a** (0.484 g, 83%), a small amount of the monoester **14b**, and starting material (0.058 g, 8%).

The diester **14a** was an oil: IR ($CHCl_3$) 1745, 1740, 1620, 1575 (w) cm^{-1}; NMR ($CDCl_3$) δ 3.00 (t, 2 H, J = 6.4 Hz, 2-CH_2), 3.63 (s, 6 H, OCH_3), 4.36 (t, 2 H, J = 6.4 Hz, 3-CH_2), 6.04 (d, 1 H, J = 4 Hz, H-7), 6.56 (d, 1 H, J = 4 Hz, H-6), 7.24 (m, 5 H, C_6H_5).

Anal. Calcd for $C_{18}H_{17}NO_5$: C, 66.04; H, 5.23. Found: C, 66.07; H, 5.44.

The monoester **14b** also was an oil: IR ($CHCl_3$) 1742, 1620, 1577 cm^{-1}; NMR ($CDCl_3$) δ 2.70 (m, 2 H, 2-CH_2), 3.62 (s, 3 H, OCH_3), 3.88 (t, 1 H, J = 6.8 Hz, H-1), 4.32 (m, 3 H, 3-CH_2), 5.87 (d, 1 H, J = 3.8 Hz, H-7), 6.55 (d, 1 H, J = 3.8 Hz, H-6), 7.17 (m, 3 H, H-3′,4′,5′), 7.50 (m, 2 H, H-2′,6′).

This ester was not characterized further.

5-Benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic Acid (15a). Normally, the mixture of **14a** and **14b** was converted without separation into the carboxylic acid **15a** as described below.

A solution of the above mixture of esters (0.793 g) in water (1 mL) and methanol (3 mL) containing potassium hydroxide (0.65 g) was heated at reflux temperature for 0.5 h. The solvent was removed in vacuo, the residue was taken up in water and the solution was made acidic with 10% hydrochloric acid. The product was extracted into ethyl acetate, and the extract was washed with water, dried, and evaporated in vacuo. The residue (0.232 g, 71% based on recovered **13a**) had mp 158 °C, and after crystallization from ethyl acetate–ether an analytical specimen had the following: mp 160–161 °C; UV (MeOH) 245, 312 nm (ϵ 7080, 17400); IR (KBr) 1725, 1615, 1600, 1575 cm^{-1}; NMR ($CDCl_3$) δ 2.88 (m, 2 H, 2-CH_2), 4.05 (dd, 1 H, J_{AX} = 6 Hz, J_{BX} = 7 Hz, H-1), 4.34 (m, 2H, 3-CH_2), 6.03 (d, 1 H, J = 4 Hz, H-7), 6.63 (d, 1 H, J = 4 Hz, H-6), 7.42 (m, 3 H, H-3′,4′,5′), 7.74 (m, 2 H, H-2′,6′), 10.52 (s, 1 H, COOH).

Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.69; H, 5.27; N, 5.56.

Dimethyl 5-(4-Fluorobenzoyl)-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1,1-dicarboxylate (14c). A solution of the sulfone **13b** (0.577 g, 0.001 36 mol) in dry DMF (10 mL) was added to a stirred suspension of 60% sodium hydride in mineral oil (0.060 g, 0.001 49 mol) in anhydrous DMF (5 mL) in the manner described above for the synthesis of **14a**. The solution was heated at 70–80 °C for 5 h and the reaction mixture was worked up precisely as described for **14a**. After column chromatography on silica gel (25 g) there was obtained by elution with ethyl acetate–hexane (1:4) the expected bicyclic diester **14c** (0.380 g, 81%), a trace of the monoester **14d**, and the starting material (0.060 g, 10%).

The diester **14c** was an oil: UV (MeOH) 213, 251, 311 nm (ϵ 11200, 7760, 20000); IR (neat) 1741, 1625, 1600 cm^{-1}; NMR ($CDCl_3$) δ 3.15 (t, 2 H, J = 7.0 Hz, CH_2), 3.85 (s, 6 H, OCH_3), 4.57 (t, 2 H, J = 7.0 Hz, NCH_2), 6.33 (d, 1 H, J = 4.4 Hz, H-7), 6.88 (d, 1 H, J = 4.4 Hz, H-6), 7.17 (t, 2 H, $J_{3'F}$ = $J_{2',3'}$ = 9.2 Hz, H-3′,5′), 7.92 (dd, 2 H, $J_{2',3'}$ = 9.2 Hz, $J_{2'F}$ = 6.0 Hz, H-2′,6′).

Anal. Calcd for $C_{18}H_{16}FNO_5$: C, 62.61; H, 4.67. Found: C, 62.62; H, 4.81.

5-(4-Fluorobenzoyl)-1,2-dihydro-3H-pyrrolo[1,2-a]-pyrrole-1-carboxylic Acid (15b). A solution of the diester **14c** (0.200 g, 0.000 58 mol) in methanol (5 mL) and water, (3 mL) containing 85% potassium hydroxide (0.50 g), was heated at reflux temperature for 1 h. After the usual workup, the crude product was crystallized from ethyl acetate–hexane to give **15b** (0.124 g, 78%), mp 168 °C. Further crystallizations gave material with the following: mp 179.5–180.5 °C; UV (MeOH) 248, 313 nm (ϵ 7080, 18200) IR (KBr) 1725, 1615, 1600, 1590 cm^{-1}; NMR ($CDCl_3$) δ 2.80 (m, 2 H, 2-CH_2), 3.98 (dd, 1 H, J_{AX} = 6 Hz, J_{BX} = 7 Hz, H-1), 4.45 (m, 2 H, 3-CH_2), 6.03 (d, 1 H, J = 4 Hz, H-7), 6.67 (d, 1 H, J = 4 Hz, H-6), 7.14 (t, 2 H, $J_{3'F}$ = $J_{2'3'}$ = 8.6 Hz, H-3′,5′), 7.83 (dd, 2 H, $J_{2'F}$ = 5.6 Hz, $J_{2',3'}$ = 8.6 Hz, H-2′,6′), 8.40 (s, 1 H, W_H = 14 Hz, COOH).

Anal. Calcd for $C_{15}H_{12}FNO_3$: C, 65.93; H, 4.43; F, 6.95. Found: C, 65.95; H, 4.27; F, 6.65.

Dimethyl 5-(4-Chlorobenzoyl)-6-chloro-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1,1-dicarboxylate (14e). The sulfone **13c** (2.00 g, 0.0042 mol) was added to a stirred suspension of 50% sodium hydride in mineral oil (0.220 g, 0.0044 mol) in dry DMF (35 mL). When hydrogen evolution had ceased, the solution was heated at 60 °C in an oil bath for 4 h. After workup of the reaction mixture was described for **14a**, the crude product was chromatographed on silica gel (100 g/g of substrate), using ethyl acetate–hexane (1:4) as the eluting solvent. The product was obtained as a solid (1.33 g, 80%) which was crystallized from ether–hexane to give material with the following: mp 127–128 °C; UV (MeOH) 215, 264, 309 nm (ϵ 12000, 11200, 15800); IR ($CHCl_3$) 1757, 1625, 1596 cm^{-1}; NMR ($CDCl_3$) δ 3.09 (t, 2 H, J = 7.1 Hz, CH_2), 3.86 (s, 6 H, OCH_3), 4.49 (t, 2 H, J = 7.1 Hz, NCH_2), 6.33 (s, 1 H, H-7), 7.62 (q, 4 H, J_{AB} = 3.4 Hz, H-2′,3′,5′,6′).

Anal. Calcd for $C_{18}H_{15}Cl_2NO_5$: C, 54.54; H, 3.81; N, 3.53. Found: C, 54.68; H, 3.81; N, 3.43.

5-(4-Chlorobenzoyl)-6-chloro-1,2-dihydro-3H-pyrrolo-[1,2-a]pyrrole-1-carboxylic Acid (15c). A solution of the diester **14e** (0.500 g, 0.001 26 mol) in methanol (10 mL) and water (3 mL) containing sodium hydroxide (0.30 g, 0.0075 mol) was heated at reflux temperature for 0.5 h. The reaction mixture was worked up as described for the synthesis of **15a** except that ether was used as the extractant. The crude, nearly white solid (0.380 g, 93%), after being washed with a little ether, had mp 197 °C. On crystallization from methanol, this substance had the following: mp 200 °C; UV (MeOH) 259, 313 nm (ϵ 10000, 13800); IR (KBr) 2565, 2500, 1740, 1586, 1554 cm^{-1}; NMR ($CDCl_3$ + Me_2SO-d_3) δ 2.68–2.89 (m, 2 H, 2-CH_2), 3.90–4.57 (m, 3 H, CH, NCH_2), 6.12 (s, 1 H, H-7), 7.53 (q, 4 H, J_{AB} = 8.4 Hz, H-2′,3′,5′,6′).

Anal. Calcd for $C_{15}H_{11}Cl_2NO_3$: C, 55.57; H, 3.42; Cl, 21.87; N, 4.32. Found: C, 55.34; H, 3.46; Cl, 21.59; N, 4.25.

2,4-Dibromo-5-benzoylpyrrole (18a). Bromine (15.16 g, 0.0947 mol) in dichloromethane (250 mL) was added dropwise, at 0 °C, to a stirred solution of 2-benzoylpyrrole[20] (8.12 g, 0.004 75 mol) in dry dichloromethane (250 mL) over a 1 h 10 min period. The reaction was left to reach room temperature and after 2.5 h the solvent was removed in vacuo. The residue was crystallized from dichloromethane–hexane to give the product (11.95 g, 77%) in three crops (product still present in the mother liquors): mp 177–177.5 °C; UV (MeOH) 249, 314 nm (ϵ 8700, 16200); IR ($CHCl_3$) 3415, 1626, 1576 cm^{-1}; NMR ($CDCl_3$) δ 6.86 (s, 1 H, H-4), 7.51 (m, 3 H, H-3′,4′,5′), 7.88 (m, 2 H, H-2′,6′), 10.78 (s, 1 H, W_H = 20 Hz, NH).

Anal. Calcd for $C_{11}H_7Br_2NO$: C, 40.15; H. 2.14; Br, 48.58; N, 4.26. Found: C, 40.10; H, 2.11; Br, 48.62; N, 4.19.

Synthesis of Dibromo Dimethyl Ester 20. Sodium hydride in mineral oil (50%, 1.06 g, 0.0221 mol) was added in portions to a stirred and cooled (ice bath) solution of 2,3-dibromo-5-benzoylpyrrole (6.52 g, 0.0198 mol) in DMF (50 mL) maintained in an argon atmosphere. When the vigorous reaction had subsided, the mixture was stirred at room temperature for 1 h and then the spiro compound **4** (3.50 g, 0.0206 mol) was added. The temperature was then raised slowly to 75–80 °C and maintained there for 4 h. After workup of the reaction mixture as described for **16c**, the crude salt **19** (9.92 g, 94%) was converted into the methyl ester **20** as follows. A saturated solution of hydrogen chloride gas in methanol (200 mL) was prepared at 0 °C and the above sodium salt was added thereto. The suspension was stirred at 0 °C for 2 h and an additional volumn of methanol (200 mL) was added. The solution temperature was slowly allowed to reach ambient temperature, and after a total elapsed time of 5 h the methanol was removed in vacuo at 10–20 °C. The residue was partitioned between ether and water, the aqueous phase was extracted with ether, and the ether phase were combined, dried, and evaporated in vacuo. The residue (8.44 g) was taken up in the minimum amount of ether and filtered through a column of Florisil (100

(20) White, J.; McGillvray, G. *J. Org. Chem.* **1977**, *42*, 4248.

g) to remove a colored impurity. Elution with ether gave the ester **20** (8.26 g, 86%) as an oil which crystallized on seeding. After trituration with hexane the solid was recrystallized from ether–hexane to give material with the following: mp 96–96.5 °C; UV (MeOH) 256, 315 nm (ε 9550, 14800); IR ($CHCl_3$) 1756, 1740, 1636, 1603, 1582 cm^{-1}; NMR ($CDCl_3$) δ 2.39 (q, 2 H, J = 7.3 Hz, CH_2), 3.50 (t, 1 H, J = 7.3 Hz, CH), 3.73 (s, 6 H, OCH_3), 4.54 (t, 2 H, J = 7.3 Hz, NCH_2), 7.59 (m, 5 H, C_6H_5).

Anal. Calcd for $C_{18}H_{17}Br_2NO_5$: C, 44.38; H, 3.52; Br, 32.81; N, 2.88. Found: C, 44.63; H, 3.54; Br, 32.95; N, 2.87.

Methyl 5-Benzoyl-7-bromo-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylate (21a) and Dimethyl 5-Benzoyl-7-bromo-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1,1-dicarboxylate (21b). Sodium hydride in mineral oil (50%, 0.030 g, 0.0006 mol) was added all at once to a stirred solution of the diester **20** (0.0005 mol) in anhydrous DMF (2 mL) maintained in a nitrogen atmosphere. After 20 min the solution was slowly heated in an oil bath to 75 °C, and after 1.5 h at this temperature, the solution was cooled and poured into ether. The ethereal solution was washed with water, dried, and evaporated in vacuo, leaving an oil (0.235 g) which was filtered through a short column of Florisil, using ether as the solvent. The material obtained in this way was subjected to high-pressure liquid chromatography on a Lichrosorb column (50 cm × 9.5 mm) with ethyl acetate–hexane (15:85) as the developing solvent, at a flow rate of 8 mL/min at 1200 psig. The mono- and diesters were collected at retention times of 17.5 and 20 min, respectively. The monoester **21a** (0.025 g, 14%) was obtained as an oil which crystallized on standing. After crystallization from methanol, **21a** had the following: mp 88–89 °C; UV (MeOH) 249, 315 nm (ε 7600, 15200); IR (KBr) 1730, 1625, 1575 cm^{-1}; NMR ($CDCl_3$) δ 2.81 (m, 2 H, 2-CH_2), 3.77 (s, 3 H, OCH_3), 3.98 (dd, 1 H, J_{AX} = J_{BX} = 7 Hz, H-1), 4.48 (m, 2 H, 3-CH_2), 6.73 (s, 1 H, H-6), 7.48 (m, 3 H, H-3′,4′,5′), 7.74 (m, 2 H, H-2′,6′).

Anal. Calcd for $C_{16}H_{14}BrNO_3$: C, 55.19; H, 4.05; Br, 22.95; N, 4.02. Found: C, 55.13; H, 4.10; Br, 22.71; N, 3.92.

The diester **21b** was also obtained as an oil (0.164 g, 81%) which crystallized on trituration with ethyl acetate. Recrystallization of this solid from hexane gave material with the following: mp 109–109.5 °C; UV (MeOH) 254, 314 nm (ε 8120, 15500); IR ($CHCl_3$) 1743, 1631, 1604, 1581 cm^{-1}; NMR ($CDCl_3$) δ 3.16 (t, 2 H, J = 6.6 Hz, 2-CH_2), 3.82 (s, 6 H, OCH_3), 4.52 (t, 2 H, J = 6.6 Hz, 3-CH_2), 6.82 (s, 1 H, H-6), 7.48 (m, 3 H, H-3′,4′,5′), 7.78 (m, 2 H, H-2′,6′).

Anal. Calcd for $C_{18}H_{16}BrNO_5$: C, 53.22; H, 2.97; Br, 19.69; N, 3.45. Found: C, 53.32; H, 3.93; Br, 19.43; N, 3.41.

Synthesis of 5-Benzoyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]-pyrrole-1-carboxylic Acid (15a) from Dibromo Diester 20 without Purification of Intermediates. Sodium hydride in mineral oil (0.275 g, 0.0055 mol) was added to a stirred solution of compound **20** (2.44 g, 0.005 mol) in dry DMF (20 mL) maintained in an argon atmosphere. After 25 min the solution was placed in an oil bath at 74 °C where the reaction was maintained for 2.75 h. The reaction was worked up in the manner described above to give a mixture (2.04 g) of **21a** and **21b**. A solution of this mixture, in methanol (100 mL) and water (10 mL) containing sodium hydroxide (0.40 g, 0.010 mol), was heated at reflux temperature in an argon atmosphere for 2 h. The solvent was removed in vacuo and the residue was taken up in 50% aqueous methanol (125 mL) to which magnesium oxide (1.0 g) and 5% palladium on charcoal (0.40 g) were added. The mixture was hydrogenated for 2 h at room temperature and atmospheric pressure, the mixture was filtered through Celite, and the filter cake was washed with methanol and water. The filtrate was then worked up as described previously to give a solid (1.19 g) which was homogeneous by TLC. Recrystallization of this material from dichloromethane–hexane gave the product in two crops, mp 154–154.5 °C (0.699 g) and 149–151.5 °C (0.170 g). Evaporation of the mother liquor, solution of the residue in ethyl acetate, treatment of the solution with charcoal, removal of the solvent, and crystallization of the residue from methanol water gave a further quantity (0.038 g) of the carboxylic acid, mp 148–150 °C. The total yield was 71% (0.907 g) on the basis of the starting uncyclized diester **20**. The carboxylic acid prepared in this manner was spectroscopically indistinguishable from material prepared by the sulfinate displacement route.

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Registry No. **4**, 5617-70-9; **7**, 39095-38-0; **8a**, 80964-97-2; **8b**, 80964-98-3; **9a**, 53391-61-0; **9b**, 80964-99-4; **10a**, 80965-00-0; **10b**, 80965-01-1; **10c**, 80965-02-2; **11**, 80965-03-3; **12**, 80965-04-4; **13a**, 80965-05-5; **13b**, 80965-06-6; **13c**, 80965-07-7; **14a**, 80965-08-8; **14b**, 80965-09-9; **14c**, 80965-10-2; **14e**, 80965-11-3; **15a**, 66635-83-4; **15b**, 66635-90-3; **15c**, 80965-12-4; **16a**, 80965-13-5; **16b**, 80965-14-6; **16c**,-Na, 80965-15-7; **17a**, 80965-16-8; **17b**, 80975-60-6; **18a**, 7697-46-3; **18b**, 50372-61-7; **19**, 80965-17-9; **20**, 80965-18-0; **21a**, 80965-19-1; **21b**, 80965-20-4; dimethyl sulfide, 75-18-3; *N*-chlorosuccinimide, 128-09-6; pyrrole, 109-97-7.

Synthesis of Azaspiro Ketones via Ring Contraction of Heterocyclic Enamino Esters

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Upon treatment by bromine followed by water–triethylamine, six- and seven-membered heterocyclic enamino esters **4a,b** underwent easily ring contraction, giving five- and six-membered azacyclic aldehydes **5a,b**, respectively. The resulted aldehydes **5** were converted to azaspiro ketones **8a,b** in three steps. Starting 3-substituted seven-membered heterocyclic enamino ester **4a** was synthesized by desulfurization of ketene acetal **12** with Raney nickel. 3-(Methoxycarbonyl)-*N*-methylcaprolactam, prepared from *N*-methylcaprolactam [LDA, $CO(OMe)_2$, −70 °C, Et_2O], was converted to the corresponding thio lactam by treatment with P_2S_5 in CS_2, which upon reaction with CH_3I followed by deprotonation with NEt_3 afforded the ketene acetal **12**.

In a previous paper,[2] we reported a method of obtaining spiro heterocycles from bicyclic enamines. Thus the bicyclic enamine **1a** reacted with bromine and aqueous sodium hydroxide to give **2a**. However, attempts to bring

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