Identification of a 4*H*-Benz[*f*]indole By-product from the Friedel-Crafts-Based Synthesis of Benzoylpyrrole Calcium Channel Activators

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9,9a-Dihydro-2,9a-dimethyl-4-oxo-4*H*-benz[*f*]indole-3-carboxylic acid, methyl ester was formed in varying amounts from the Friedel-Crafts-based synthesis of benzoylpyrrole calcium channel activators. The structure of this by-product was determined using two-dimensional long-range ^{1}H-^{13}C heteronuclear correlated and INADEQUATE nmr techniques.

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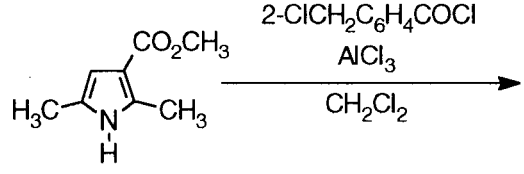
Voltage-dependent L-type calcium channels provide an important pathway for calcium influx into cardiac tissue. A number of clinically useful cardiovascular drugs block calcium influx through these channels. These agents, known collectively as the calcium channel antagonist [1], include 1,4-dihydropyridines such as nifedipine (**1**), benzothiazepines such as diltiazem (**2**), and phenylalkylamines such as verapamil (**3**). While many compounds are known to act as antagonists of L-type calcium channels [2], only a few compounds are known to act predominately as L-channel activators [3]. These agents are structurally related to the 1,4-dihydropyridines and include compounds such as (*S*)-BAY K 8644 (**4**) [4]. Recently, the novel 4-benzoylpyrrole **5** (Ar = C_6H_5, FPL 64176) was described as a potent activator of L-type calcium channels [5-7].

Driven by both a desire to study this interesting lead and a lack of available compound to study, we developed a new, two-step, one-pot synthesis of **5** (Ar = C_6H_5) [8]. Thus, Friedel-Crafts acylation of 2,5-dimethylpyrrole-3-carboxylic acid, methyl ester (**6**) with 2-chloromethylbenzoyl chloride generated 4-(2-chloromethylbenzoyl)pyrrole **7** which was reacted *in situ* with benzene and additional aluminum



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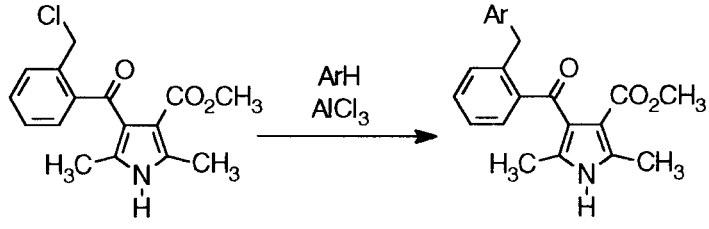
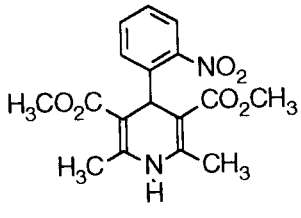


7 **5**



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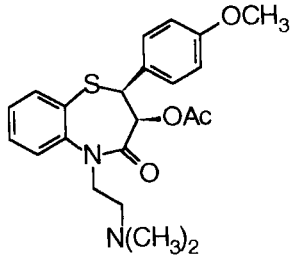

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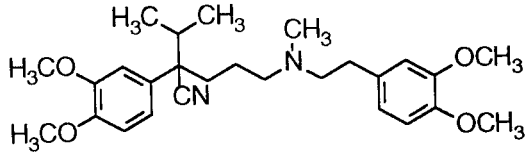

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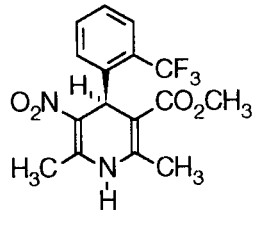

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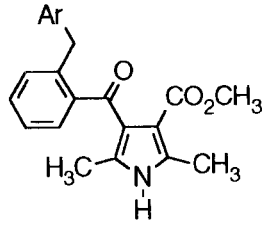

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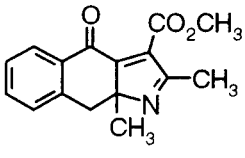
chloride to yield **5** (Ar = C_6H_5) in 60% overall yield. We have subsequently employed this synthesis to prepare a number of substituted derivatives of **5**. As we monitored the course of these reactions by thin-layer chromatography, we often noticed the formation of a by-product spot which, while varying in intensity, occurred at the same R_f in the chromatograms of each reaction. In the case where the Lewis acid-catalyzed alkylation was attempted on 1,3-dichlorobenzene, this spot appeared to be the major spot in the reaction. Indeed, from this reaction we isolated only a 19% yield of the desired **5** (Ar = 2,4-$Cl_2C_6H_3$). Instead, the product corresponding to this new spot was isolated as the major reaction product. Characterization of this product by a combination of elemental analysis and routine spectral analysis indicated that it resulted from the intramolecular cyclization of **7**. Such a cyclization could in principle yield the three isomeric pyrrole derivatives **8-10**.



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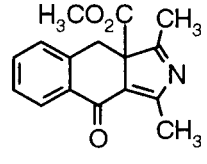

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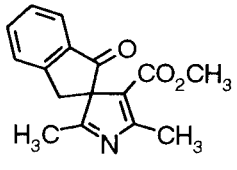

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Initially, mass spectrometry was used in an attempt to differentiate between these three tricyclic isomers. Since all three proposed structures were expected to have similar fragmentation patterns, attempts were made to determine the structure of this material by examination of fragment ion intensities. A summary of the major ions with relative intensities and ion assignments is shown in Table I.

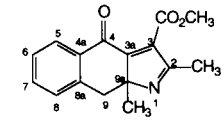
Table I

Mass Spectrometry Data

Ion m/z (Relative Intensity)	Ion Assignment
269 (15)	$M^{+\cdot}$
254 (3)	$M^{+\cdot}$ - $\cdot CH_3$
241 (18)	$M^{+\cdot}$ - CO
238 (13)	$M^{+\cdot}$ - $\cdot OCH_3$
237 (5)	$M^{+\cdot}$ - $HOCH_3$
222 (6)	$M^{+\cdot}$ - $HOCH_3$ - $\cdot CH_3$
210 (100)	$M^{+\cdot}$ - $\cdot CO_2CH_3$
209 (24)	$M^{+\cdot}$ - HCO_2CH_3
182 (59)	$M^{+\cdot}$ - CO- $\cdot CO_2CH_3$

Table II

^{13}C NMR Data



Chemical Shift (ppm)	T1 (seconds)	T1 x/Cr(acac)$_3$ (seconds)	Assignment
182.61	16.3	0.4	4
168.99	12.7	0.4	2
166.48	15.0	0.4	3a
163.34	20.5	0.4	ester carbonyl
141.65	10.0	0.3	8a
134.15	1.2	0.2	7
133.52	13.3	0.2	4a
131.38	18.3	0.4	3
129.62	1.5	0.2	8
127.70	1.4	0.2	5
127.47	1.3	0.2	6
82.32	11.8	0.4	9a
52.28	4.0	0.2	-OCH_3
42.28	0.8	0.2	9
19.35	0.8	0.2	9a-CH_3
17.80	3.2	0.3	2-CH_3

The molecular ion was observed at m/z 269 and the base peak was m/z 210 which corresponds to the loss of a carbomethoxy radical. Of the three possible structures it was postulated that **9** was most likely to have the carbomethoxy radical loss as the base peak since a stable tertiary carbonium ion would be formed. Similarly, for **8** it was postulated that the loss of a methyl radical would be a significant ion since it would also lead to a stable tertiary carbonium ion. Only a 3% ion intensity was observed for this loss. Both **8** and **10** were expected to show a more significant loss of methanol and methoxy radical from the molecular ion than was observed. Therefore, based on the intensities of these fragment ions, isomer **9** was postulated. This was, however, not supported by nmr data.

The ^1H nmr spectrum of this product suggested structure **8** but did not permit conclusive structural assignment. A methyl signal was observed at 1.31 ppm most consistent with **8** with a methyl on an aliphatic quaternary carbon. By contrast, for **9** or **10** both non-ester methyls are on sp2 carbons and would be expected farther downfield. Similarly, the ester methyl was observed at 3.92 ppm, most consistent with attachment of the ester carbonyl to an sp2 carbon (**8** or **10**) leading to a greater deshielding of the ester methyl signal than would be predicted for **9**. It could not be ruled out, however, that for these tricyclic systems that unusual shifts could be observed. We therefore desired a more definitive proof of structure without having to resort to an alternate synthesis.

This was accomplished by two separate approaches us-

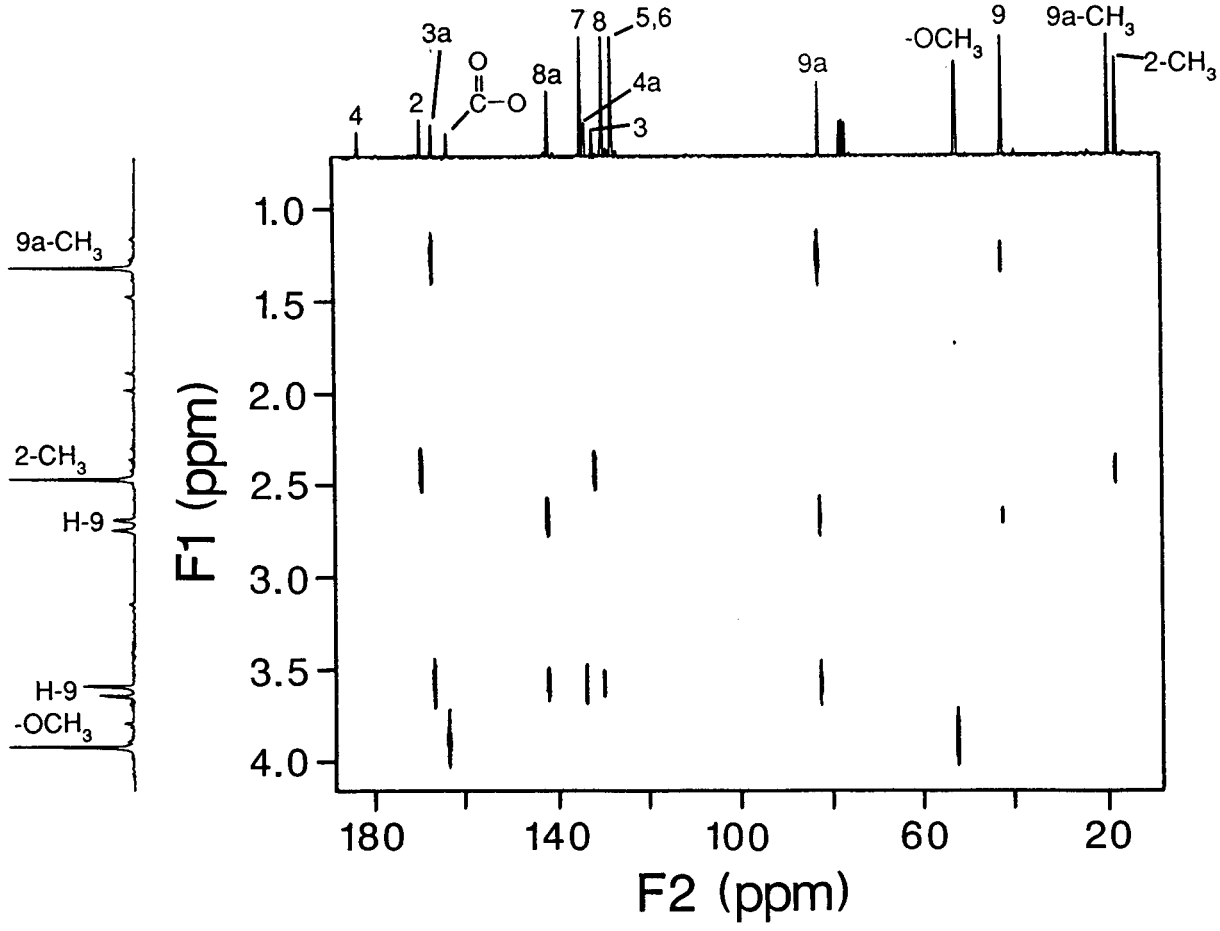


Figure 1. Long-range HETCOR spectrum of the product of intramolecular cyclization. The 1D ^{1}H and ^{13}C nmr spectra are shown on the side and top, respectively.

ing 2D nmr spectroscopy. The first approach was a series of two-dimensional ^{1}H-^{13}C heteronuclear correlated (HETCOR) spectra. HETCOR spectra were obtained with the pulse sequence adjusted for one-bond (140 Hz) and longer-range (9.5 Hz and 6 Hz) ^{1}H-^{13}C couplings. The first, in conjunction with chemical shifts, ^{1}H-^{1}H COSY and NOESY data, was used to aid in peak assignments. The ^{13}C nmr assignments thus made are shown in Table II. For the latter two the 9.5 and 6.0 Hz values were chosen as typical two- and three-bond ^{1}H-^{13}C coupling constants [9]. The HETCOR spectra obtained optimized for these values showed all the same correlations. The 9.5 Hz HETCOR is shown in Figure 1. Important correlations observed include 9a-CH_3 to C-9a, 9a-CH_3 to C-9, and 9a-CH_3 to C-3a. These are consistent with two/three-bond couplings and structure **8**. Structures **9** and **10** were rejected because the correlation between the upfield methyl protons and the methylene carbon would be a four-bond coupling, which is unlikely.

As a definitive structure proof an INADEQUATE (Incredible Natural Abundance Double Quantum Transfer Experiment) spectrum was obtained [10]. This experiment, based on spin-spin couplings between adjacent ^{13}C atoms, yields carbon-carbon connectivities and therefore definitive proof of structure. To obtain this spectrum the spin-lattice relaxation times for each carbon were first obtained using a standard inversion-recovery experiment. The T1 values obtained are given in Table II and range from less than one to greater than 20 seconds. Since this would have required an excessively long delay between pulses in the INADEQUATE experiment, 30 mg of chromium acetylacetonate ($Cr(acac)_3$) were added to the solution of 300 mg of compound in 1 ml of deuteriochloroform. This resulted in approximately a five-fold loss in signal-to-noise in a single transient ^{13}C spectrum due to line-broadening, but resulted in a significant reduction in T1 values as shown in Table II. The INADEQUATE spectrum was then obtained

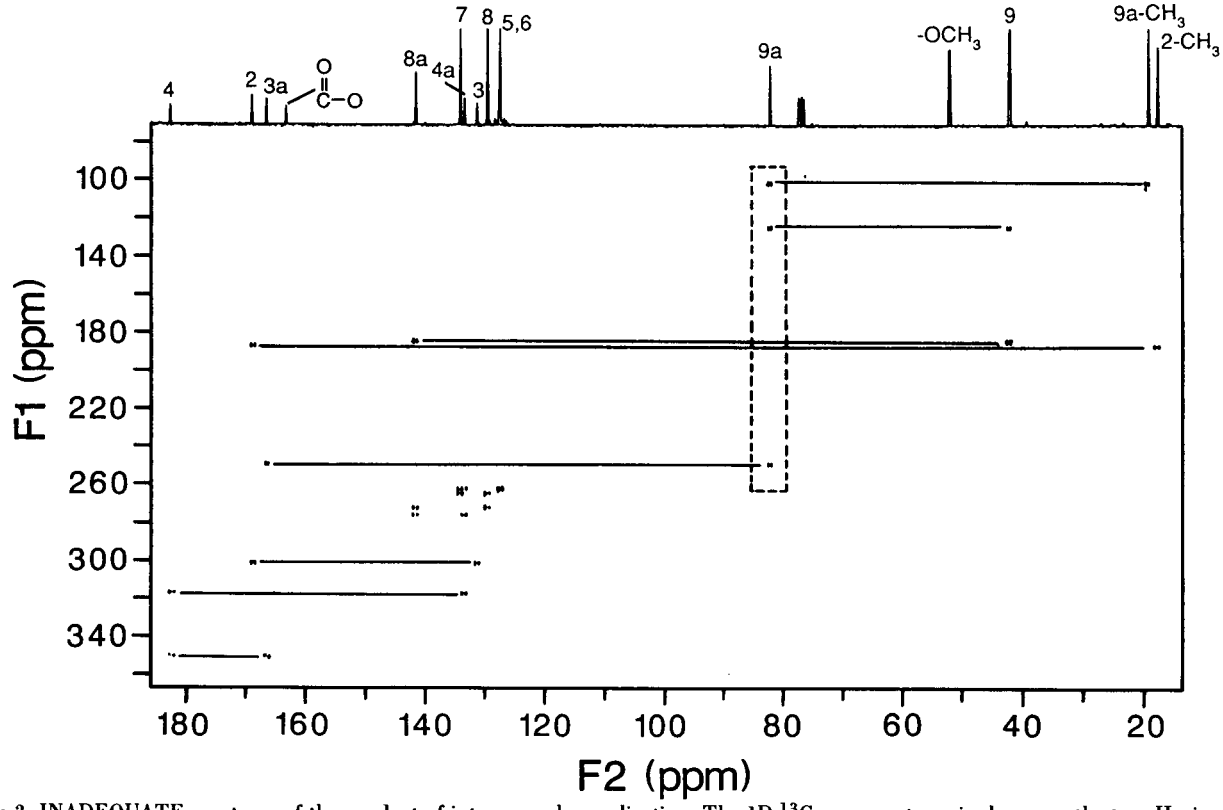


Figure 2. INADEQUATE spectrum of the product of intramoecular cyclization. The 1D ^{13}C nmr spectrum is shown on the top. Horizontal lines represent connectivities. Due to congestion connectivities were not drawn in aromatic region. The boxed region is expanded in Figure 3.

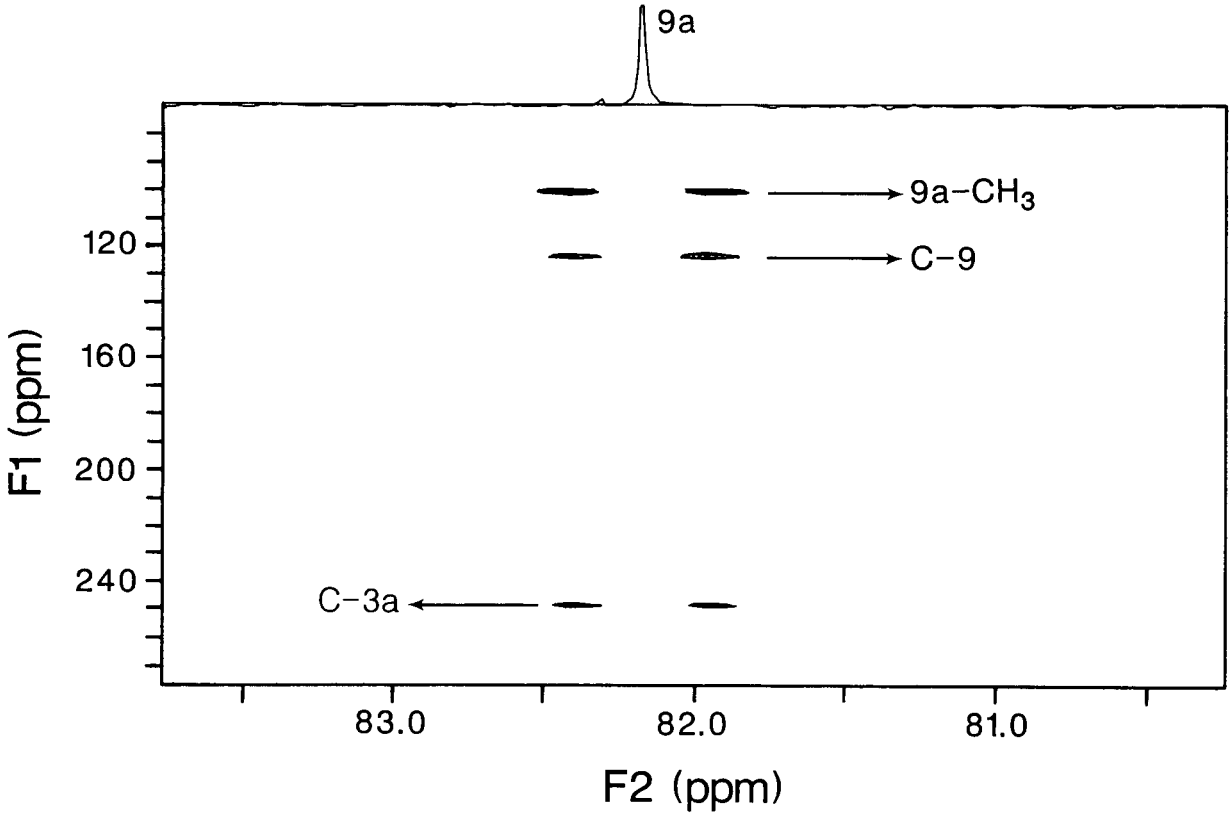


Figure 3. Expansion of the INADEQUATE spectrum with the 1D ^{13}C nmr spectrum shown on top.

with a 0.4 second recycle delay with the pulse sequence set for 40 Hz ^{13}C-^{13}C couplings. In the resulting spectrum signals were produced from molecules containing two adjacent ^{13}C atoms (*ca.* one molecule in 10,000 at natural abundance). These signals appear as two sets of antiphase doublets in F2, centered at the chemical shift of the coupled ^{13}C nuclei and separated by the ^{13}C-^{13}C coupling constant. In F1 the signals are observed at their double-quantum frequency which is equal to the sum of the two chemical shifts.

The resulting 2D contour plot is shown in Figure 2 with connectivity between carbons demonstrated with horizontal lines. All connectivities are observed except the ester carbonyl to C-3 and C-2 to C-3. These carbons have the longest T1's and may have larger coupling constants [11] so these signals are most likely lost in the noise in this spectrum. The important connectivities are 9a-CH_3 to the aliphatic quaternary carbon C-9a, C-9a to the methylene carbon C-9, and C-9a to C-3a. An expansion of the INADEQUATE spectrum showing the antiphase doublets for these connectivities at the chemical shift for C-9a is shown in Figure 3. These connectivities are only consistent with **8** definitively establishing the structure.

EXPERIMENTAL

Melting points were determined in open capillaries on a Thomas Hoover apparatus and are uncorrected. Mass spectra were obtained on a Finnigan MAT TSQ-700 mass spectrometer system. Ir spectra were obtained on a Mattson Galaxy 5020 FT-IR spectrophotometer. The nmr spectra were recorded at 25° on a Varian Unity-300 spectrometer. The chemical shifts are given in parts per million from tetramethylsilane. All 2D spectra were recorded using the Varian supplied pulse sequence. The minimum sweep widths required to observe all appropriate proton and carbon resonances were used. The long-range HETCOR spectra were obtained in the absolute value mode with final delays set for 9.5 or 6.0 Hz. The spectra were obtained with 128 time increments of 256 transients each zero-filled to give a final 256 by 2048 data matrix. The INADEQUATE spectrum was obtained with the delay time τ set to ¼ x $J_{c,c}$ where $J_{c,c}$ = 40 Hz. A repetition interval of 0.4 seconds for 220 increments of 1216 transients each was used. The data matrix was zero-filled to 4096 by 1024 and Fourier transformed after gaussian multiplication in F1 and F2. Elemental analysis data were obtained using a Perkin-Elmer Model 2400 elemental analyzer. Water content was determined by thermogravimetric analysis using a Perkin-Elmer TGA-7 Thermogravimetric Analyzer.

4-[2-[(2,4-Dichlorophenyl)methyl]benzoyl]-2,5-dimethyl-1*H*-pyrrole-3-carboxylic Acid, Methyl Ester (**5**, Ar = 2,4-Cl_2-C_6H_3) and 9,9a-Dihydro-2,9a-dimethyl-4-oxo-4*H*-benz[*f*]indole-3-carboxylic Acid, Methyl Ester (**8**).

To a stirred solution of 2-chloromethylbenzoyl chloride (3.45 g, 18.3 mmoles) in dichloromethane (10 ml) was added in one portion aluminum chloride (2.45 g, 18.4 mmoles). After one minute, a solution of 2,5-dimethylpyrrole-3-carboxylic acid, methyl ester (2.82 g, 18.4 mmoles) in dichloromethane (15 ml) was added over a 5 minute period. Immediately following the addition of the pyrrole derivative, additional aluminum chloride (2.45 g, 18.4 mmoles) was added. This addition should be done carefully since it causes a very vigorous reaction. The reaction was stirred for one hour, at which time 1,3-dichlorobenzene (10 ml) and aluminum chloride (2.45 g, 18.4 mmoles) were added in succession. After stirring for 2 hours, the reaction was poured onto crushed ice. The aqueous mixture was stirred one hour before being extracted with dichloromethane (3 x 150 ml). The dichloromethane extracts were combined and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration and the filtrate was evaporated at reduced pressure. The concentrate was purified by flash chromatography [12] (37% ethyl acetate/hexane) affording two distinguishable products. The first product (R_f = 0.26) to elute from the column crystallized from methanol affording 1.44 g (19%) of **5** (Ar = 2,4-$Cl_2C_6H_3$) as colorless prisms, mp 155-158°; ^1H nmr (deuteriochloroform): δ 8.89 (bs, 1H), 7.44-7.01 (m, 7H), 4.32 (s, 2H), 3.25 (s, 3H), 2.37 (s, 3H), 2.14 (s, 3H); ms: (70 eV) m/z (%) 415 (21), 417 (12), 400 (32), 402 (21), 368 (100), 370 (60), 227 (35), 210 (26); ir (potassium bromide): 1715, 1604, and 1455 cm^{-1}.

Anal. Calcd. for $C_{22}H_{19}Cl_2NO_3$: C, 63.47; H, 4.60; N, 3.36. Found: C, 63.25; H, 4.71; N, 3.33.

The second product (R_f = 0.12) to elute from the column crystallized from acetone/hexane affording 2.94 g (60%) of **8** as beige prisms, mp 88-90°; ^1H nmr (deuteriochloroform): δ 8.18 (dd, 1H, J = 7.7 and 1.2 Hz), 7.59 (td, 1H, J = 7.4 and 1.4 Hz), 7.44 (tm, 1H, J = 7.6 Hz), 7.39 (dm, 1H, J = 7.6 Hz), 3.92 (s, 3H), 3.60 (d, 1H, J = 15.4 Hz), 2.71 (d, 1H, J = 15.4 Hz), 2.46 (s, 3H), 1.31 (s, 3H); ^{13}C nmr (deuteriochloroform): see text; ms: (70 eV) see text; ir (potassium bromide): 1730, 1670, and 1267 cm^{-1}.

Anal. Calcd. for $C_{16}H_{15}NO_3 \cdot 0.1H_2O$: C, 70.88; H, 5.65; N, 5.17. Found: C, 70.86; H, 5.65; N, 5.09.

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