Pivaloylation of N-Methylpyrrole. Formation of a Novel 3,4-Diacylation Product[1]

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The pivaloylation of *N*-methylpyrrole (1) with pivaloyl chloride and tin(IV) chloride in benzene or 1,2-dichloroethane at 20 °C gives mixtures of mono- and dipivaloylated pyrroles. *N*-Methyl-2-pivaloylpyrrole (2) is formed in only trace amounts and the 3-isomer 3 is the predominant monosubstituted product. Substantial amounts of *N*-methyl-2,4-dipivaloylpyrrole (4) and smaller amounts of the 3,4-isomer 5 are also formed. Facile Lewis acid mediated rearrangements of 2 into 3 and of 4 into 5 were demonstrated. The 3,4-disubstituted isomer 5 is the thermodynamically most stable product and all compounds in this study were converted into 5 on treatment with tin(IV) chloride and excess pivaloyl chloride. The pivaloylation of 1 is markedly different from its acetylation. Acetylation takes place to give 2- and 3-acetyl derivatives, and diacetylation gives the 2,5- and/or 2,4-diacetyl derivatives. Fully proton-coupled ^{13}C NMR spectra were obtained for all the acylated pyrroles in this study and complete assignment of chemical shifts and coupling constants was made.

In connection with our studies on the ionic [S_N1 and S_N(AEAE] and radical ($S_{RN}1$) substitution reactions of heteroaryl neopentyl chlorides of the form ArCH(Cl)-*t*-Bu,[2] we needed to prepare the previously unknown 2- and 3-pivaloylated derivatives of *N*-methylpyrrole. Conditions for direct pivaloylation using pivaloyl chloride and a Lewis acid were considered since thiophene[3,4] and furan[5] pivaloylated in the 2-position under similar conditions. It has been stated that "acylation of pyrrole with acyl chlorides in the presence or absence of a Lewis acid catalyst, invariably gives the 2-acylpyrrole".[6] More recent results show that 3-acylpyrroles form when there are substituents, especially bulky ones, on the pyrrole nitrogen.[7] One final complication in reactions involving acylpyrroles is the demonstration that 2- and 3-acylpyrroles give equilibrium mixtures of the two isomers on treatment with strong anhydrous acids and 1-alkyl-2-acylpyrroles are completely converted into the corresponding 3-acyl derivatives under the same conditions.[8]

The pivaloylation of *N*-methylpyrrole, 1, and a reinvestigation of the acetylation and diacetylation of 1 constitute this report.[9]

Results and Discussion

Pivaloylations. The results of the pivaloylation reactions performed on 1 and some related reactions are collected in Table I. The products detected were the 2- and 3-pivaloyl derivatives 2 and 3 and the 2,4- and 3,4-dipivaloylated compounds 4 and 5, respectively. The assignment of constitution to these compounds is discussed in the section on ^{13}C and ^{1}H NMR spectra below. Boron trifluoride etherate was initially used as the Lewis acid catalyst, since it has been shown to successfully catalyze acetylation of 1.[11] The reaction occurred to a negligible extent or only very slowly in benzene (entry 1) and in ether (entry 2). By way of contrast, use of tin(IV) chloride in benzene at 20 °C gave extremely rapid pivaloylation since the incorporation of pivaloyl groups after 10 min and 5 h was virtually identical (see entries 3 and 4). At lower reaction temperatures (entry 5) or after shorter reaction times (4–5 min) in benzene (entry 6) or in 1,2-dichloroethane (entry 7), small amounts of the 2-pivaloyl derivative 2 could be detected. Both the reactions in benzene (entries 3 and 4) and in 1,2-dichloroethane (entries 7 and 8) show similar product distributions. It is apparent that monopivaloylation of 1 and dipivaloylation of the monopivaloylated compounds proceed at a similar rate. Thus direct pivaloylation cannot be used for production of either 2 or 3 in good yield. It appears that after an initial mono-

	R^1	R^2	R^3	R^4
1	H	H	H	H
2	$COBu^t$	H	H	H
3	H	$COBu^t$	H	H
4	$COBu^t$	H	$COBu^t$	H
5	H	$COBu^t$	$COBu^t$	H
10	COMe	H	H	COMe
11	COMe	H	COMe	H
12	COMe	H	H	H

(1) This research was supported by a grant from the Australian Research Grants Scheme (to R.K.N.) and a University of Sydney Postgraduate Scholarship (to M.C.H.).

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(9) During the course of this work an independent preparation of 2- and 3-pivaloylpyrrole using the reaction of 1-pyrrolylmagnesium bromide and pivaloyl chloride was developed at The University of Sydney by Ritchie and Mirarchi. Our experimental adaptation of their method has been reported recently by them.[10]

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Table I. Pivaloylation of *N*-Methylpyrrole and 2- and 3-Pivaloylpyrrole[a]

entry	substrate (concn)	[Me_3CCOCl]	[$SnCl_4$]	time, h	products, % yield[b] 2	3	4	5
1	1 (0.15)	0.15	0.3[c]	1				
2[d]	1 (0.3)	0.3	0.6[c]	17	2	3		
3	1 (0.15)	0.15	0.27	0.17		33	11	5
4	1 (0.15)	0.15	0.27	5		31	8	11
5[e]	1 (0.15)	0.15	0.27	0.08	4	26	10	3
6	1 (0.3)	0.3	0.6	0.08	0.5	29	17	6
7[f]	1 (0.3)	0.3	0.6	0.07	0.5	33	17	4
8[f]	1 (0.3)	0.3	0.6	17		40	2	19
9	2 (0.26)	0	0.34	0.08	89	9		
10	2 (0.26)	0	0.34	1		97[g]		
11	2 (0.2)	0.04	0.27	0.06	36	45	19	
12	2 (0.2)	0.04	0.27	0.17	7	70	20	
13	2 (0.2)	0.04	0.27	0.33	0.6	76	20	
14	2 (0.2)	0.04	0.27	1.17		74	18	1
15	2 (0.2)	0.2	0.6	0.08	14	31	54	0.7
16	2 (0.2)	0.3	0.8	0.17	3	33	56	2
17	3 (0.2)	0.04	0.4	0.08		83	11	5
18	3 (0.2)	0.2	0.6	0.17		43	26	30
19[h]	2 (0.2)	0.3	0.8	1.5[i]				72[j]

[a] Unless otherwise stated, reactions were carried out in benzene at 20 °C with benzophenone as internal standard at a concentration approximately one-third that of the substrate; yields were estimated by GLC and are the average of duplicate reactions, which differed by no more than 4% (at 50%). Reactions were performed with 2–3 mmol of substrate. [b] Absence of an entry indicates <0.1% yield. [c] Boron trifluoride etherate. [d] In ether. [e] At 5 °C. [f] In 1,2-dichloroethane. [g] Isolated yield after 2 h. [h] At 80 °C. [i] Worked up after 1.5 h; GLC indicates over 95% conversion of intermediate compound 4 into 5 after 1.0 h. [j] Isolated yield.

and dipivaloylation stage that subsequent reaction merely involves isomerization of **2** into **3** and **4** into **5** without significant exchange of pivaloyl groups between mono- and disubstituted products. Evidence has been presented by other workers that isomerization of acylpyrroles is an intramolecular process involving C-protonated species.[8] It is also apparent that the 3,4-disubstituted compound **5** is the thermodynamically favored isomer among the disubstituted compounds (compare entries 3 and 4, and 7 and 8).

In an attempt to more clearly define the pathways leading from **1** to the products **2–5**, some control experiments were performed. The 2-pivaloyl compound **2** was isomerized into **3** in excellent yield by tin(IV) chloride in benzene in the absence of added pivaloyl chloride (entries 9 and 10). It is reasonable to assume that this reaction is brought about by the inevitable presence of hydrogen chloride in the tin(IV) chloride. The mechanism for this rearrangement reaction presumably is the same as that found when anhydrous acids are used, although the rearrangement of **2** into **3** appears to proceed under milder conditions and in better yield than the rearrangements reported with other acyl groups.[8] Although it is difficult to simulate the reaction conditions, an attempt was made to determine the sequence of formation of products **2–5**. Compounds **2** and **3** were treated with pivaloyl chloride (entries 11–18). The rate of isomerization of **2** into **3** is too slow to be consistent with the formation of **2** as a major monopivaloylation product (compare entry 3 with entries 11–14 and entry 6 with entries 15 and 16). The relative amounts of compounds **4** and **5** formed on pivaloylation of **2** are completely different from those obtained in the pivaloylation of **1** (compare entries 6 and 15) and of **3** (compare entries 11 and 17 and 15 and 18). The isomerization of **4** to give **5** is slow relative to mono- and dipivaloylation reactions under the conditions used in the experiments in Table I (see entries 3, 4, 7, 8, and 11–14).

The results in Table I can be interpreted as shown in Scheme I. The σ-complex **6** formed from **2** must rearrange to give the σ-complex **7** of the 3-isomer **3** more rapidly than it deprotonates to give **2**. Compound **3** then pivaloylates at both the α and β positions to give σ-complexes **8** and **9**, which deprotonate to give **4** and **5**, or equilibrate to a mixture in which **9** predominates.

The remarkable stability of the 3,4-dipivaloyl derivative **5** and the tendency of the system in this study to form **5** are demonstrated by the final experiment in Table I (entry 19) in which treatment of the 2-pivaloyl derivative **2** with excess pivaloyl chloride in benzene under reflux gives a 72% isolated yield of **5** in 1.5 h. Compound **4** is *not* isomerized into **5** by tin(IV) chloride alone even after reflux in benzene for 5 h. Hydrogen chloride, produced in the acylation reactions, appears to be necessary.

The anomalous nature of the above reactions, namely the similarity in rate of mono- and diacylation and the preferred formation under thermodynamic control of the 3,4-diacyl derivative, caused us to reexamine the diacetylation of *N*-methylpyrrole, **1**. Heating **1** with acetic anhydride in a sealed tube at 225 °C for 18 h (a literature procedure involves heating **1** with acetic anhydride at 250 °C for about 8 h)[12] gave 7% of the 2,5-diacetyl derivative **10** and 10% of the previously undetected[12] and hitherto unreported 2,4-diacetyl compound **11**. This result parallels that with pyrrole itself.[13] The reaction of 2-acetyl-*N*-methylpyrrole, **12**, with acetyl chloride and tin(IV) chloride in benzene at reflux was followed by GLC. Clean conversion into **11** was observed with a maximum of 0.05% of **10** developing during the course of the reaction. When **12** had completely reacted (about 20 min) workup gave a 41% isolated yield of isomerically pure **11**. When this reaction was repeated and reflux was continued, the amount of **11** decreased (6% after 18 h), but no isomeric diacetyl derivatives could be detected.

When the pivaloylation reactions of **1** in this study are compared with the acetylation reactions in this and earlier work,[11,12] the following differences are apparent. Monopivaloylation unlike monoacetylation takes place preferentially in the 3-position, presumably the result of greater steric hindrance between the pivaloyl group and the *N*-methyl group than betwen the acetyl and *N*-methyl group in the σ-complexes leading to 2-substitution. Disubstitution in the monopivaloylated derivatives **2** and **3** occurs at a comparable rate with monopivaloylation of **1**, pre-

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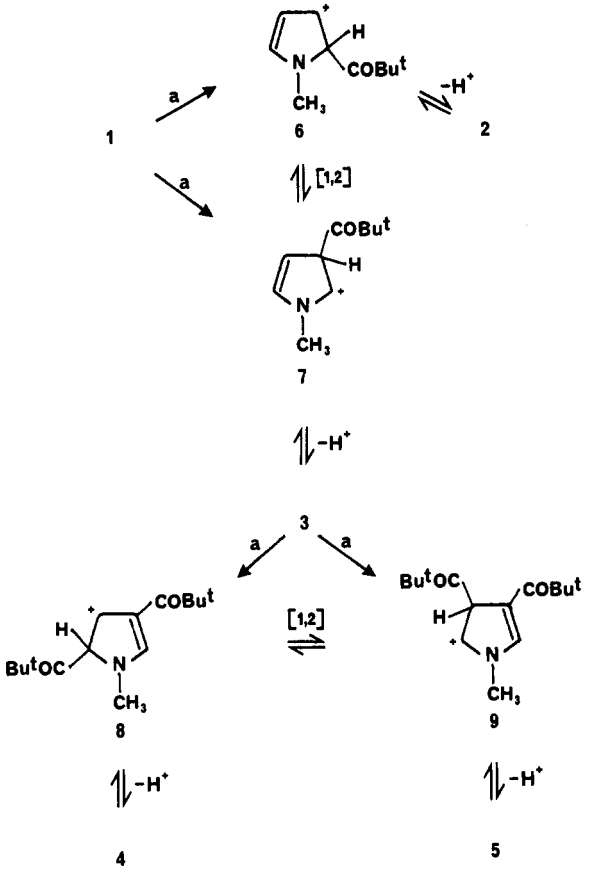
Scheme I[a]



[a] (a) $Me_3CCOCl/SnCl_4$.

sumably the result of the lower deactivating nature of an out-of-plane pivaloyl group compared with an acetyl group.[14] The 2,4-disubstituted derivative **11** appears to be the preferred isomer in diacetylation reactions, but the 3,4-disubstituted derivative **5**, is the most thermodynamically stable product among the dipivaloylated compounds. It can only be assumed that a combination of the well-established higher stability of 3-substituted pyrroles over 2-substituted derivatives[8,15] and the steric interaction between the *N*-methyl group and an α-pivaloyl substituent overcomes the energy penalty involved in having two pivaloyl groups in an ortho relationship. To the best of our knowledge, with the exception of the formation of 1,2-dipivaloylcyclopentadiene on reaction of the cyclopentadienide ion with pivaloyl chloride,[16] formation of *o*-dipivaloyl derivatives in aromatic or heteroaromatic systems by direct acylation appears to be without precedent. This class of derivatives is known but indirect preparative methods have been used. The thiophene analogue of **5** has been prepared by a ring-closure reaction[17] and *o*-dipivaloylbenzenes have been prepared by several methods.[18]

Constitution and NMR Properties of Acylated *N*-Methylpyrroles. The constitution of the monosubstituted compounds **2** and **3** (and their unmethylated precursors—see Experimental Section) and the disubstituted compounds **4** and **11** were readily assigned by ^1H NMR spectroscopy on the basis of the magnitude of coupling constants in pyrroles[19a] and chemical shift and substituent effects in pyrroles and related heteroaromatic systems.[19b] Assignment of structure to **5** was less straightforward, since both **5** and the isomeric 2,5-dipivaloyl-*N*-methylpyrrole would have similar ^1H NMR spectra, namely three singlets for the *tert*-butyl, *N*-methyl, and aromatic protons in the ratio 9:3:2. ^{13}C NMR spectroscopy proved a simple means of distinguishing these two isomers. Fully proton-coupled ^{13}C NMR spectra were recorded for all the acylated pyrroles in this study (see Experimental Section) and a self-consistent set of assignments for the carbon resonances was obtained by the usual methods.[20] Thus the quaternary aromatic carbons bearing acyl substituents were easily identified by the absence of a large direct coupling (^1J). The α and β aromatic carbons without acyl substituents in compounds **2** and **3** (and their unmethylated precursors) and in **4**, **10**, and **11** were assigned on the basis of the difference in the direct coupling constants, $^1J_{C\alpha,H\alpha}$ (183–186 Hz) and $^1J_{C\beta,H\beta}$ (171–174 Hz).[21] Since the direct coupling in **5** is 185.5 Hz, clearly **5** is a 3,4-disubstituted compound. The chemical shift data for the acylpyrroles forms a self-consistent set. Comparing the ^{13}C shifts for **2** and **3** with that for **1**[22] reveals that a pivaloyl group in the 2-position deshields C3 by 10.2 ppm, shields C4 by 1.2 ppm, and deshields C5 by 7.7 ppm and a pivaloyl group in the 3-position deshields C2 by 5.1 pm, deshields C4 by 2.2 ppm, and has no effect on the shift of C5. If additivity of these effects is assumed, the actual and calculated (in parentheses) shifts for **4** and **5** can be compared. For **4**, C3 was at δ 120.0 (120.3) and C5 was at δ 133.0 (134.4). For **5**, C2 and C5 resonated at δ 122.4 (125.5), whereas the calculated value, if it were the 2,5-dipivaloyl derivative, for C3(C4) would have been δ 117.0. Nearly identical substituent effects are observed for the acetyl group and, indeed, the shift for C3(C4) in the 2,5-diacetyl derivative **11** is δ 117.1. Two final pieces of evidence unambiguously allow assignment of constitution to **5**. First, the ^{13}C satellites of the aromatic signal at δ 6.82 for H2(H5) consisted of a doublet of doublets ($^1J_{C,H}$ = 185.5 Hz, J = 1.75 Hz), in which the magnitude of the smaller splitting is nearer that for $J_{2,5}$ (2.2 Hz) than that for $J_{3,4}$ (3.4 Hz) in pyrroles.[19a] Secondly, NOE difference experiments were performed on **5**. Irradiation of the *tert*-butyl hydrogens gave an 18% NOE of the aromatic protons at δ 6.82 but did not lead to enhancement of the *N*-methyl group. Irradiation of the *N*-methyl group gave an 11% NOE of the aromatic protons and left the intensity of the *tert*-butyl group unaffected.

Experimental Section

Melting points were determined thermoelectrically on a Reichert hot-stage melting point apparatus and are uncorrected. ^1H NMR spectra were determined on a Varian Associates EM-390 or a Bruker WM-400 spectrometer on ca. 10% w/v solutions in $CDCl_3$. ^{13}C NMR spectra were recorded on a JEOL FX-60Q

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spectrometer on ca. 30% w/v solutions in $CDCl_3$ and are proton-coupled. Both ^{13}C and ^1H chemical shifts are quoted in ppm downfield of internal $SiMe_4$. Infrared spectra were recorded in $CHCl_3$ or as liquid films on a Perkin-Elmer 221 spectrophotometer, and ultraviolet spectra were recorded on Perkin-Elmer 402 and Hitachi 150-20 spectrophotometers. Mass spectra were recorded on an A.E.I. MS-902 spectrometer at 70 eV. Analyses were carried out at the Australian Microanalytical Service, Melbourne.

This layer chromatography (TLC) was performed on Merck Kieselgel $HF_{254+366}$ (type 60). Flash chromatography[23] was performed on Merck silica gel 60 (230–240 mesh). Light petroleum refers to the fraction of bp 65–70 °C.

Acylation Reactions. These reactions were carried out in the solvents and under the conditions (scale, substrate concentrations, temperatures, and times) specified in Table I. In each experiment, a solution of the Lewis acid catalyst was added to a solution containing the substrate, benzophenone (the internal standard), and pivaloyl chloride in the appropriate solvent. All solutions were equilibrated at the appropriate temperature prior to mixing. Reactions became inhomogeneous after mixing. Stirring of reaction mixtures caused no significant changes in reaction rate or product distribution. Reaction mixtures were quenched by addition of excess sodium hydroxide solution (3 M) and the organic phase was then separated and dried (Na_2SO_4). The organic phase was subjected to GLC analysis on 3% OV-17 on GAS-CHROM Q (100–120 mesh) (4 mm × 1.5 m) with a Hewlett Packard HP-5890 instrument using a FID detector employing a temperature program [initial temperature 140 °C (2 min), final temperature 190 °C (6 min), rate (8°/min)].

Materials. All chemicals were purchased from Aldrich Chemical Co. unless otherwise noted. *N*-Methylpyrrole was redistilled (bp 112–113 °C), while 2-acetyl-*N*-methylpyrrole was used without further purification. Tin(IV) chloride and boron trifluoride etherate were distilled under vacuum from tin and calcium hydride, respectively, and stored under nitrogen. Pivaloyl chloride was prepared from pivalic acid and redistilled (bp 105–106 °C). Acetyl chloride, acetic anhydride, and 1,2-dichloroethane were used without further purification. AR Benzene and ether were dried over sodium.

Isolation or Independent Synthesis of Acylated Pyrroles. 1-(1-Methyl-1*H*-pyrrol-2-yl)-2,2-dimethyl-1-propanone (2) and 1-(1-Methyl-1*H*-pyrrol-3-yl)-2,2-dimethyl-1-propanone (3). Pyrrole (11.5 g, 0.17 mol) was converted to the bromomagnesium derivative and pivaloylated[10] and the product mixture separated by flash chromatography with 20% ethyl acetate/light petroleum to yield the less polar component, 1-(1*H*-pyrrol-2-yl)-2,2-dimethyl-1-propanone (18.3 g, 71%): mp 46–48 °C (lit.[10] mp 46–48 °C); ^{13}C NMR δ 28.4 (q septet, CMe_3, ^1J = 127 Hz, ^3J = 4.9 Hz), 42.5 (decet, CMe_3, ^3J = 3.9 Hz), 110.0 (dtd, C4, $^1J_{C4,H4}$ = 172.4 Hz, $^3J_{C4,NH}$ = $^2J_{C4,H5}$ = 8 Hz, $^2J_{C4,H3}$ = 2.9 Hz), 116.0 (dtd, C3, $^1J_{C3,H3}$ = 171.2 ± 0.3 Hz, $^3J_{C3,H5}$ = $^3J_{C3,NH}$ = 6 Hz, $^2J_{C3,H4}$ = 4 Hz), 123.3 (dtd, C5, $^1J_{C5,H5}$ = 185.5 Hz, $^3J_{C5,H3}$ = $^2J_{C5,H4}$ = 7.8 Hz, $^2J_{C5,NH}$ = 3.9 Hz), 129.0 (m, C2), 196.7 (m, C=O). The more polar component was obtained as a brown solid (4.6 g), which on recrystallization (light petroleum) gave **1-(1*H*-pyrrol-3-yl)-2,2-dimethyl-1-propanone** (3.2 g, 12%), white crystals, mp 98–100 °C: ^1H NMR δ 1.35 (s, 9 H, *t*-Bu), 6.72 (m, 2 H, H4 and H5), 7.46 (m, 1 H, H2), 9.15 (m, 1 H, N-H); ^{13}C NMR δ 22.2 (q septet, CMe_3, ^1J = 127 Hz, ^3J = 4.9 Hz), 43.6 (decet, CMe_3, ^3J = 3.9 Hz), 109.9 (dq, C4, $^1J_{C4,H4}$ = 172.9 Hz, $^2J_{C4,H5}$ = $^3J_{C4,H2}$ = $^3J_{C4,NH}$ = 8 Hz), 118.6 (dtd, C5, $^1J_{C5,H5}$ = 187.0 ± 0.5 Hz, $^2J_{C5,H4}$ = $^2J_{C5,NH}$ = 7.8 Hz, $^3J_{C5,H2}$ = 2.9 Hz), 122.5 (m, C3), 124.1 (ddt, C2, $^1J_{C2,H2}$ = 187.0 Hz, $^2J_{C2,NH}$ = $^3J_{C2,H4}$ = $^3J_{C2,H5}$ = 6 Hz), 203.3 (m, C=O); IR ($CHCl_3$) 1639, 1368, 1095, 909 cm^{-1}; UV (EtOH) 212 nm (ϵ 5.4 × 10^3), 247 (7.3 × 10^3), 270 sh (5.2 × 10^3); mass spectrum, *m/z* (relative intensity) 151 (M^+, 18), 95 (9), 94 (100), 66 (9), 57 (5), 39 (18).

Anal. Calcd for $C_9H_{13}NO$: C, 71.5; H, 8.7; N, 9.3. Found: C, 71.7; H, 8.5; N, 9.5.

1-(1*H*-Pyrrol-2-yl)-2,2-dimethylpropanone (18.86 g, 0.12 mol) dissolved in dry *N,N*-dimethylformamide (30 ml) was added dropwise to a solution of sodium hydride (4.8 g, 0.2 mol) in dry *N,N*-dimethylformamide (20 mL) and the light brown viscous solution was stirred for 0.5 h. Methyl iodide (21.3 g, 0.15 mol) was added dropwise, and the reaction mixture was allowed to stand for 0.5 h and was then worked up by slow addition of ethanol (20 mL) followed by water (300 mL). The mixture was extracted with ether and the combined ether extracts were washed with water and brine and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield a crude oil (16.6 g) which was distilled at 180 °C/0.4 mmHg (Kugelrohr) to yield **2** (15.2 g, 74 %), a clear oil, bp 225–226 °C: ^1H NMR δ 1.36 (s, 9 H, *t*-Bu), 3.89 (d, 3 H, N-Me, $J_{Me,5}$ = 0.39 Hz), 6.10 (dd, 1 H, H4, $J_{3,4}$ = 4.18 Hz, $J_{4,5}$ = 2.54 Hz), 6.73 (ddq, 1 H, H5, $J_{,5}$ = 2.54 Hz, $J_{3,5}$ = 1.69 Hz, $J_{Me,5}$ = 0.39 Hz), 7.01 (dd, 1 H, H3, $J_{3,4}$ = 4.18 Hz, $J_{3,5}$ = 1.69 Hz); ^{13}C NMR δ 28.6 (q septet, CMe_3, ^1J = 127 Hz, ^3J = 4.9 Hz), 38.1 (qd, N-Me, $^1J_{Me,H}$ = 139.1 Hz, $^3J_{Me,H5}$ = 3 Hz), 43.3 (decet, CMe_3, ^3J = 5 Hz), 106.8 (ddd, C4, $^1J_{C4,H4}$ = 173.8 Hz, $^3J_{C4,H5}$ = 7.8 Hz, $^2J_{C4,H3}$ = 2.9 Hz), 118.2 (ddd, C3, $^1J_{C3,H3}$ = 170.9 Hz, $^3J_{C3,H5}$ = 6.8 Hz, $^2J_{C3,H4}$ = 2.9 Hz), 128.2 (m, C2), 129.3 (dm, C5, $^1J_{C5,H5}$ = 183.6 Hz), 197.1 (m, C=O); IR ($CHCl_3$) 1638, 1474, 1457, 1403, 1363, 1224, 1089, 957, 743 cm^{-1}; UV (EtOH) 201 nm (ϵ 5.4 × 10^3), 290 (1.36 × 10^4), 270 (5.2 × 10^3); mass spectrum, *m/z* (relative intensity) 165 (M^+, 19), 108 (100), 80 (5).

Anal. Calcd for $C_{10}H_{15}NO$: C, 72.7; H, 9.2; N, 8.5. Found: C, 72.4; H, 9.2; N, 8.9.

1-(1*H*-Pyrrol-3-yl)-2,2-dimethyl-1-propanone (1.08 g, 7 mmol) was methylated by the procedure described above to yield a crude product (1.24 g), which was distilled at 150 °C/17 mmHg (Kugelrohr) to yield **3** (0.92 g, 77%), a clear oil: ^1H NMR δ 1.31 (s, 9 H, *t*-Bu), 3.64 (t, 3 H, N-Me, $J_{Me,H2}$ = $J_{Me,H5}$ = 0.45 Hz), 6.53 (ddq, 1 H, H5, $J_{4,H5}$ = 3.0 ± 0.2 Hz, $J_{2,5}$ = 2.1 ± 0.3 Hz, $J_{Me,5}$ = 0.8 Hz), 6.60 (dd, 1 H, H4, $J_{4,5}$ = 3.0 ± 0.2 Hz, $J_{2,4}$ 1.8 ± 0.2 Hz), 7.26 (ddq, 1 H, H2, $J_{2,5}$ = 2.1 ± 0.3 Hz, $J_{2,4}$ = 1.8 ● 0.2 Hz, $J_{Me,2}$ = 0.8 Hz); ^{13}C NMR δ 27.7 (q septet, CMe_3, ^1J = 127 Hz, ^3J = 4.9 Hz), 35.8 (qm, N-Me, $^1J_{Me,H}$ = 140.6 Hz), 42.9 (decet, CMe_3, ^3J = 3.9 Hz), 110.2 (dt, C4, $^1J_{C4,H4}$ = 172.9 Hz, $^2J_{C4,H5}$ = $^3J_{C4,H2}$ = 7 Hz), 121.6 (dm, C5, $^1J_{C5,H5}$ = 185.5 Hz), 122.2 (m, C3, *J* = 3 Hz), 126.7 (dm, C2, $^1J_{C2,H2}$ = 185.5 Hz), 200.6 (m, C=O); IR ($CHCl_3$) 1642, 1526, 1405, 1207, 922, 773 cm^{-1}; UV (EtOH) 213 nm (ϵ 1.01 × 10^4), 257 (8.4 × 10^3); mass spectrum, *m/z* (relative intensity) 165 (M^+, 8), 108 (100), 39 (7).

Anal. Calcd for $C_{10}H_{15}NO$: C, 72.7; H, 9.2; N, 8.5. Found: C, 72.4; H, 9.2; N, 8.6.

1,1′-(1-Methyl-1*H*-pyrrole-2,4-diyl)bis(2,2-dimethyl-1-propanone) (4). Flash chromatography (15% ethyl acetate/light petroleum) of crude reaction mixtures containing **4** (Table I, entries 3–7 and 11–18) followed by recrystallization (ethanol/water) gave **4**: fine white needles, mp 72–72.5 °C: ^1H NMR δ 1.31 (s, 9 H, 2-*t*-Bu), 1.35 (s, 9 H, 4-*t*-Bu), 3.87 (s, 3 H, N-Me), 7.35 (dm, 1 H, H5, $J_{3,5}$ = 1.69 Hz), 7.43 (d, 1 H, H3, $J_{3,5}$ = 1.69 Hz); ^{13}C NMR δ 28.0 and 28.6 (q septet, 2 × CMe_3, ^1J = 127 Hz, ^3J = 4 Hz), 38.9 (qd, N-Me, $^1J_{Me,H}$ = 141.1 Hz, $^3J_{Me,H5}$ = 2.9 Hz), 43.6 and 43.9 (m, 2 × CMe_3), 120.0 (dd, C3, $^1J_{C3,H3}$ = 173.5 Hz, $^3J_{C3,H5}$ = 6.5 Hz), 120.4 (dd, C4, $^2J_{C4,H5}$ = 6.8 Hz, $^2J_{C4,H3}$ = 2.0 Hz), 128.4 (m, C2), 133.0 (ddq, C5, $^1J_{C5,H5}$ = 185.5 Hz, $^3J_{C5,H3}$ = 6.8 Hz, $^3J_{C5,Me}$ = 3.9 Hz), 198.2 and 200.6 (m, 2 × C=O); IR ($CHCl_3$) 1642, 1529, 1457, 1416, 1317, 1276, 1097, 1048, 961, 921 cm^{-1}; UV (EtOH) 240 nm (ϵ 1.85 × 10^4), 292 (1.24 × 10^4); mass spectrum, *m/z* (relative intensity) 249 (M^+, 2), 206 (4), 192 (100), 107 (7), 57 (7), 41 (12).

Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.3; H, 9.3; N, 5.6. Found: C, 72.0; H, 9.2; N, 5.7.

1,1′-(1-Methyl-1*H*-pyrrole-3,4-diyl)bis(2,2-dimethyl-1-propanone) (5). Chromatography (15% ethyl acetate/light petroleum) of the crude product from pivaloylation of **2** (Table I, entry 19) followed by recrystallization of the appropriate fraction (light petroleum) gave **5**: fine white needles, mp 70–71 °C; ^1H NMR δ 1.26 (s, 18 H, 2 × *t*-Bu), 3.61 (s, 3 H, N-Me), 6.82 (s, 2 H, H2 and H5);[24] ^{13}C NMR δ 27.5 (q septet, 2 × CMe_3, ^1J = 127.0 Hz, ^3J = 4.4 Hz), 36.4 (qt, N-Me, $^1J_{Me,H}$ = 139.6 Hz $^3J_{Me,H2(5)}$ = 2.0 Hz), 44.0 (decet, 2 × CMe_3, ^3J = 3.9 Hz), 122.4 (ddq, C2 and C5, $^1J_{C5(2)}$ = 185.5 Hz, $^3J_{C2(5),H5(2)}$ = 4 Hz, $^3J_{C2(5),Me}$ = 3 Hz), 124.5 (br t, C3 and C4, $^2J_{C3(4),H2(5)}$ = $^3J_{C3(4),H5(2)}$ = 7 Hz), 205.3 (m, 2 × C=O); IR ($CHCl_3$) 1680, 1644, 1539, 1521, 1479, 1461, 1407, 1324, 1199, 1000, 927 cm^{-1}; UV (EtOH) 222 nm (ϵ 5.1 × 10^3), 265 (7.1 × 10^3); mass spectrum, *m/z* (relative intensity) 249 (M^+, 0.4), 234

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(24) The ^{13}C satellites of these aromatic protons consisted of a doublet of doublets ($^1J_{C,H}$ = 185.5 Hz, $J_{2,5}$ = 1.75 Hz).

(2), 193 (17), 192 (100), 177 (24), 121 (7), 107 (8), 42 (15).

Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.3; H, 9.3; N, 5.6. Found: C, 72.1; H, 9.7; N, 5.5.

1,1′-(1-Methyl-1*H*-pyrrole-2,4-diyl)bis(ethanone) (11). 2-Acetyl-1-methylpyrrole (12) (0.56 g), acetyl chloride (0.47 g), and tin(IV) chloride (3.12 g) were refluxed in anhydrous benzene (15 mL) for 20 min. The reaction mixture was quenched with sodium hydroxide (3 M) and extracted with ether in the usual manner to give a yellow solid which was recrystallized (light petroleum) to yield 11 (0.31 g, 41%): white needles, mp 86–87 °C; ^{1}H NMR δ 2.43 (s, 3 H, $COCH_3$(2)), 2.47 (s, 3 H, $COCH_3$(4)), 3.97 (d, 3 H, N-Me, $J_{Me,5}$ = 0.5 Hz), 7.34 (d, 1 H, H3, $J_{3,5}$ = 1.9 Hz), 7.39 (dq, 1 H, H5, $J_{3,5}$ = 1.9 Hz, $J_{Me,5}$ = 0.5 Hz); ^{13}C NMR δ 26.9 (q, 2 × $COCH_3$, ^1J = 127 Hz), 38.0 (qd, N-Me, ^1J = 140.6 Hz, $^3J_{Me,H5}$ = 2.9 Hz), 118.8 (dd, C3, $^1J_{C3,H3}$ = 172.9 Hz, $^3J_{C3,H5}$ = 6.5 Hz), 124.1 (m, C4), 131.5 (m, C2), 133.2 (ddd, C5, $^1J_{C5,H5}$ = 185.5 Hz), 188.9 and 192.3 (m, 2 × C=O); IR ($CHCl_3$) 3015, 1658, 1547, 1391, 1261, 1202, 1192 cm^{-1}; UV (EtOH) 236 nm (ϵ 2.33 × 10^4), 288 (1.50 × 10^4); mass spectrum, m/z (relative intensity) 165 (M^+, 80), 150 (100), 108 (16), 43 (15).

Anal. Calcd for $C_9H_{11}NO_2$: C, 65.4; H, 6.7; N, 8.5. Found: C, 65.3; H, 6.5; N, 8.7.

1,1′-(1-Methyl-1*H*-pyrrole-2,5-diyl)bis(ethanone) (10). 1-Methylpyrrole (1) (2.0 g, 24.7 mmol) and acetic anhydride (20 g, 0.2 mol) were heated in an autoclave for 18 h at 225 °C. The reaction mixture was worked up with ether in the ususal manner to give a crude product (1.21 g), which was purified by chromatography on silica using 20% ethyl acetate/light petroleum as eluent. The products in order of polarity were **10** (0.29 g, 7%) (recrystallized from light petroleum) [mp 132–134 °C (lit.[12] mp 133–134 °C); ^{1}H NMR δ 2.43 (s, 6 H, 2 × $COCH_3$), 4.10 (s, 3 H, N-CH_3), 6.77 (s, 2 H, H3(4)); ^{13}C NMR δ 28.2 (q, $COCH_3$, ^1J = 127.5 Hz), 35.0 (q, N-Me, $^1J_{Me,H}$ = 142 Hz), 117.1 (dd, C3(4), $^1J_{C3(4),H3(4)}$ = 173.9 Hz, $^2J_{C3(4),H4(3)}$ = 2.9 Hz), 134.7 (m, C2(5)), 190.0 (q, 2 × C=O, $^2J_{CO,Me}$ = 5.9 Hz); UV (EtOH) 232 nm (ϵ 9.10 × 10^3), 304 (2.16 × 10^4)] and **11** (0.42 g, 10%).

Four Novel Phenyldithienoindole Isomers from the Oxidative Photocyclization of Dithienylpyrroles

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The Stetter reaction with thiazolium catalysis was used to prepare diones **20** and **22–24** in high yield. From these were prepared the four isomeric 2,3-dithienyl-1-methyl-5-phenylpyrroles **1**, **7**, **9**, and **11**. From **20** were prepared phenylterthiophene **5** and furan **3**. The diarylpyrroles are the first reported to undergo oxidative photocyclization, forming four novel phenyldithienoindole isomers, **2**, **8**, **10**, and **12**. However, neither **3** nor **5** (in contrast to the unsubstituted terthiophene **6**) would undergo photocyclization; it is suggested that this anomaly has its origin in perturbation of the underlying hexatriene MOs.

Interest in the phototoxic properties of polythiophenes such as α-terthienyl[2] has led us to the synthesis of the substituted terthiophene **5**, the related furan **3**, and the *N*-methylpyrroles **1**, **7**, **9**, and **11** (Scheme I) and to the study of their photoreactivity. We report that the pyrroles undergo oxidative photocyclization to form the novel phenyldithienoindoles **2**, **8**, **10**, and **12**. An examination of Mallory's exhaustive review[3] and of the more recent literature indicates that these are the first oxidative photocyclizations of diarylpyrroles to be reported. The four dithieno-fused indole ring systems formed in these cyclizations are likewise unprecedented and are of further interest because of their similarity to several compounds recently synthesized by Cava as thiophene congeners of two phosphodiesterase inhibitors related to antitumor agent CC-1065.[4] (However, Cava's palladium photocyclization protocol did not improve yields with our compounds.[5])

In surprising contrast to **1**, the analogous thiophene **5** and furan **3** are photoinert. A still more striking contrast in photoreactivity is afforded by **5** and its unsubstituted parent terthiophene **6**, whose synthesis in this laboratory was recently reported:[6] whereas **5** is inert, **6** readily undergoes oxidative photocyclization under the same conditions as **1** to form the as-yet unreported benzotrithiophene **4**[7] in good yield (72%).

This pattern of reactivity gives rise to several mechanistic considerations. All cyclizations proceed upon irradiation of a benzene solution with 350-nm light in the presence of air, with yields improved when a catalytic quantity of iodine is present as well: these are the standard conditions for the oxidative photocyclization of *o*-terphenyl to triphenylene. There is extensive evidence[3] that the latter reaction, as well as analogous photocyclizations of diaryl heteroaromatics like **1**, **7**, **9**, and **11**, proceeds by a concerted conrotatory process from the lowest excited singlet state to form a *trans*-dihydrotriphenylene intermediate. This intermediate must be trapped by an effective oxidant such as iodine if the desired product is to be formed, since it can otherwise readily revert to the starting material by either a thermal or a photochemical process, thereby regenerating three aromatic rings.[8]

When one or both of the cyclizing aryl groups is 3-thienyl, as in **7**, **9**, and **11**, considerations advanced by Wynberg would suggest that the yield of cyclized product

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