Sterically Hindered *N*-Aryl Pyrroles: Chromatographic Separation of Enantiomers and Barriers to Racemization

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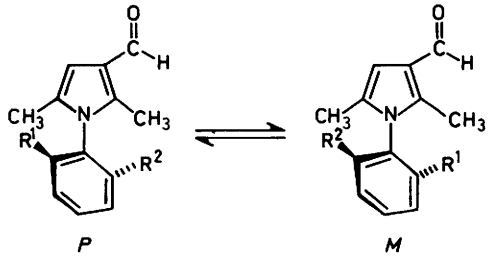
The novel *N*-aryl-2,5-dimethylpyrrole-3-carbaldehydes (**1**)–(**7**) have been synthesized by condensation of hexane-2,5-dione with the appropriate aniline and subsequent Vilsmeier–Haack formylation of the pyrrole ring. Diastereoisomeric association complexes of these racemic pyrroles were studied by ^{1}H n.m.r. spectroscopy chemical shifts and the splittings induced by the optically active auxiliary compound (+)-Eu(hfbc)$_3$. Separation of the enantiomers of (**6**) was achieved by liquid chromatography on triacetylcellulose. The barrier to partial rotation about the C–N bond in (**6**) was determined and their lower limits in (**2**) and (**4**) were estimated by variable temperature ^{1}H n.m.r. spectroscopy.

Our interest in chiral *N*-aryl-substituted heterocyclic compounds and their barriers to partial rotation about the C–N bond[1] led us to prepare sterically hindered *N*-aryl-substituted pyrroles (Scheme). Because of restricted rotation about the C–N bond between the aryl and pyrrole rings the ground state of compounds (**1**)–(**7**) is non-planar, *i.e.* chiral. If the barrier is sufficiently high (> *ca.* 100 kJ mol^{-1} at room temperature[2]) then the separation of enantiomeric rotational isomers should be possible. This study has precedent in the work of Bock and Adams[3] on the separation of enantiomers of *N*-(2-carboxyphenyl)-2,5-dimethylpyrrole-3-carboxylic acid by classical resolution *via* formation of diastereoisomeric salts. The initial aim of this research was to separate enantiomers (**1**)–(**7**) by an alternative, more versatile method which does not require the presence of special functional groups (*e.g.* CO_2H) in the molecule, *i.e.* liquid chromatography on microcrystalline triacetylcellulose,[4] and to determine their barriers to partial rotation about the C–N bond.



	R^1	R^2
(**1**)	Cl	H
(**2**)	CN	H
(**3**)	Me	H
(**4**)	OMe	H
(**5**)	OEt	H
(**6**)	OCH_2Ph	H
(**7**)	Cl	Me

Scheme.

Results and Discussion

Novel *N*-aryl-3-formyl-2,5-dimethylpyrroles were obtained by Knorr–Paal condensation of hexane-2,5-dione with a suitable 2-substituted aniline and subsequent Vilsmeier–Haack formylation of the pyrrole ring. The chirality of compounds (**1**)–(**7**) was confirmed by ^{1}H n.m.r. spectroscopy in the presence of the optically active auxiliary compound (+)-tris[3-(heptafluoropropylhydroxymethylene)camphorato]europium(III) [(+)-Eu(hfbc)$_3$]. Enantiotopic groups in (**1**)–(**7**) become diastereotopic by association with (+)-Eu(hfbc)$_3$ and are anisochronous,[5] *i.e.*, display unequal ^{1}H n.m.r. shifts. A series of five spectra with increasing reagent to substrate ratios was recorded for each substrate in order to distinguish reagent from substrate signals and to assign the latter (Figure 1). A practical consequence of the observed anisochrony and signal splittings is that activation parameters for intramolecular processes, such as restricted bond rotation, can be determined by variable-temperature ^{1}H n.m.r. studies in the presence of chiral solvating agents.[6] The shift difference $\Delta\nu$ in (**2**) and (**4**) decreases with increasing temperature. Although complete coalescence[7] was not observed even at the maximum temperature of 140 °C, a calculation[8] of the lower limits of free enthalpies of activation, $\Delta G^{\ddagger}$, for the interconversion of enantiomers was possible, giving values greater than 99 and 98 kJ mol^{-1} for (**2**) and (**4**) respectively (see Table 1).

Separation and Racemization of Enantiomers.—Surprisingly, (*MP*)-(**3**) and (*MP*)-(**7**) showed no separation of enantiomers at +20 °C and −20 °C by liquid chromatography on triacetylcellulose. However, almost complete separation of enantiomers was achieved for (*MP*)-(**6**) as can be seen from the analytical chromatogram (Figure 2) showing very slight overlap of the enantiomer peaks. This behaviour may be explained by the presence of an additional phenyl group in (**6**), which obviously increases the retention differences of the enantiomers. This is consistent with the earlier observation that separation of enantiomers is improved by the presence of a phenyl group near the centre of chirality.[4] However it has been observed[9] that chiral diaziridines possessing two phenyl groups show less separation than their monophenyl analogues.[10] Obviously, further studies are needed to gain an understanding of structural effects on the chromatographic behaviour of racemic molecules. The barrier to partial rotation about the C–N bond in (**6**) was determined by thermal racemization of preparatively enriched (+)-(**6**). First-order kinetics were followed by polarimetry during two half-lives. The free enthalpy of activation for

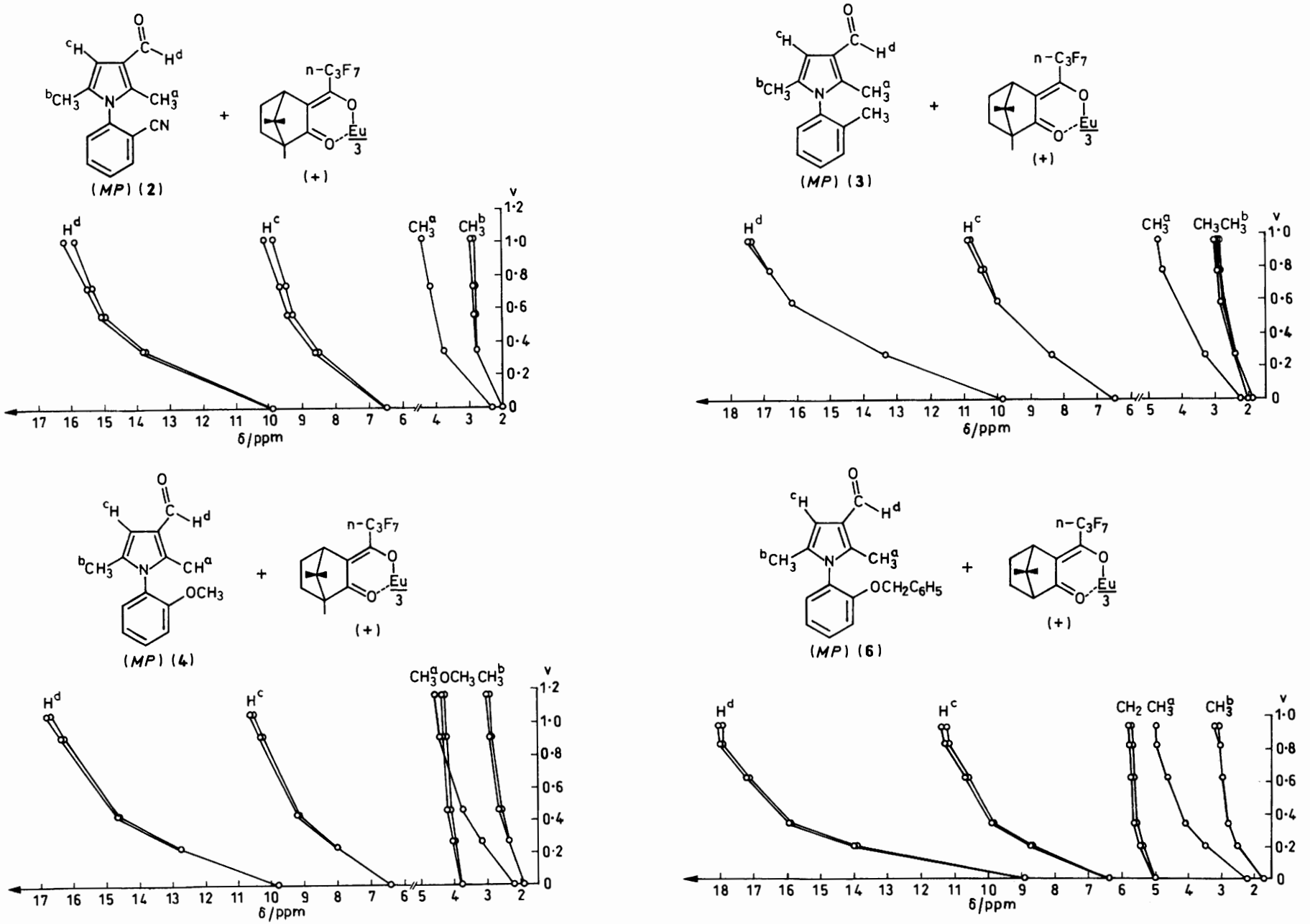


Figure 1. ^{1}H N.m.r. shifts of racemic *N*-arylpyrroles in $CDCl_3$ at 22 °C and 100 MHz as functions of V = [(+)-Eu(hfbc)$_3$]/[*N*-arylpyrrole].

Table 1. Barriers to partial rotation about the C–N bond.

	Method	Solvent	T/°C	Δν/Hz[a]	$\Delta G^{\ddagger}$/kJ mol^{-1}
(*MP*)-(**2**)	^{1}H N.m.r. signal splitting	$(CDCl_2)_2$	140[b]	1.28	>99[c]
(*MP*)-(**4**)	^{1}H N.m.r. signal splitting	$(CDCl_2)_2$	140[b]	1.60	>98[c]
(*MP*)-(**6**)	Polarimetry	Diglyme	108	—	125.2 ± 0.2[d]

[a] Shift difference in the presence of 0.5 equiv. of (+)-Eu(hfbc)$_3$ at 250 Hz for CH_3[b] (**2**) and OCH_3 (**4**), respectively. [b] Highest temperature of measurement. [c] Lower limit for the barrier. [d] Obtained by preparative enrichment of (+)-(**6**).

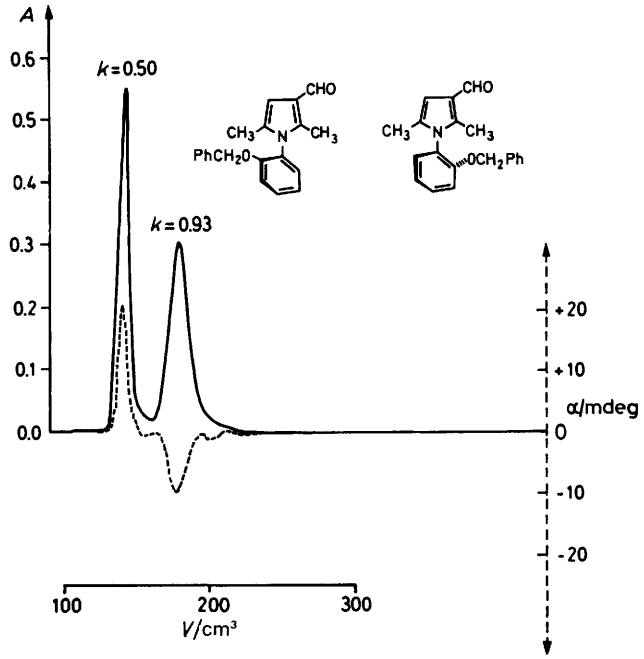
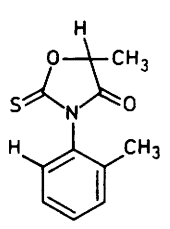
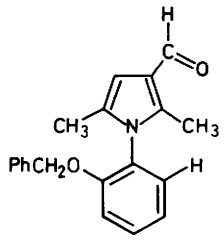


Figure 2. Chromatogram of (*MP*)-(**6**) in ethanol–water (96:4) after chromatography through a column of triacetylcellulose (particle size 0.02–0.03 mm). α: Rotational angle (– – – –) at 365 nm; *A*: absorbance (——) at 278 nm; *V*: volume of eluate; *k*: capacity factors.[4]

interconversion of the enantiomeric rotational isomers of (**6**) was found to be 125.2 ± 0.2 kJ mol^{-1} (Table 1). This barrier may be compared with the reported[11] rotational barrier in 2-thioxo-3-(*o*-tolyl)-1,3-oxazolidin-4-one (**8**) which undergoes enantiomeric inversion *via* transition state (**9**) and possesses a similar skeleton, *i.e.*, a C–N pivotal bond linking two cyclic moieties, two groups at the 2- and 4-positions of the five-membered ring, and one *ortho* substituent on the phenyl ring. The comparison shows that the $\Delta G^{\ddagger}$ value for (**6**) is *ca.* 25 kJ mol^{-1} higher than the corresponding value for (**8**). This difference may be attributed to more severe steric interactions in the transition state (**10**) for the enantiomeric inversion of pyrrole (**6**), than that for (**9**).



(**9**)



(**10**)

Experimental

M.p.s were determined on a Büchi apparatus and are not corrected. I.r. spectra were recorded on a Perkin-Elmer 297 Infracord and u.v. spectra on a Hitachi–Perkin-Elmer 124 spectrophotometer. ^{1}H N.m.r. spectra were recorded on JEOL JNM FX (PFT mode, 8 K addresses, 100 MHz) and Bruker WH 250 (PFT mode, 32 K data points, 250 MHz) spectrometers. The e.i. (electron impact) mass spectra of (**1**)–(**5**) and (**7**) were recorded on a Varian MAT 711 double-focussing mass spectrometer with ionizing energy 80 eV and emission current 0.8 mA. The exact mass measurements were performed by using the same instrument at resolution 10^4 (10% relative value definition). The e.i. mass spectra of (**6**), (**13**), and (**14**) were recorded on a Shimadzu GC MS-QP-1000 spectrometer with ionizing energy 70 eV and emission current 0.2 mA. Elemental analyses were performed by the Central Analytical Service, Institute 'Ruđer Bošković', Zagreb. (+)-Tris[3-(heptafluoropropylhydroxymethylene)camphorato]europium(III) was purchased from Aldrich, Europe Division, Janssen Pharmaceutica N.V., B-2340 Beerse, Belgium.

The *N*-aryl-2,5-dimethylpyrrole-3-carbaldehydes (**1**)–(**7**) were prepared by Vilsmeier–Haack formylation of the corresponding *N*-aryl-2,5-dimethylpyrroles (**11**)–(**17**) according to the procedure given for pyrrole-2-carbaldehyde and *N*-methylpyrrole-2-carbaldehyde[12] which was modified as follows: to a stirred mixture of phosphorus oxychloride (15.3 g, 0.1 mol) and dimethylformamide (DMF) (7.31 g, 0.1 mol) cooled to 0 °C, was added dropwise an equimolar solution of the corresponding *N*-aryl-2,5-dimethylpyrrole dissolved in DMF (15 cm^3). The resulting deep red viscous mixture was heated for 3 h at 40–60 °C, and poured onto crushed ice. The residue was precipitated in aqueous sodium hydroxide (10%, w/v). The crude residue was recrystallized twice to give the pure compound (see Tables 2 and 3); the following compounds were obtained in this way:

N-(2-*Chlorophenyl*)-2,5-*dimethylpyrrole*-3-*carbaldehyde* (**1**). Yield 89%; *m/z* 235 (34%), 234 (42), 233 ($M^{+\bullet}$, 100), 232 (87), 204 (39), 170 (35), and 168 (34) [direct inlet temperature (d.i.t.), 60 °C].

N-(2-*Cyanophenyl*)-2,5-*dimethylpyrrole*-3-*carbaldehyde* (**2**). Yield 84%; *m/z* 224 ($M^{+\bullet}$, 98%), 223 (100), 195 (60), 102 (13), and 50 (18) (d.i.t., 50 °C) (Found: $M^{+\bullet}$, 224.0931. Calc. for $C_{14}H_{12}N_2O$; $M^{+\bullet}$, 224.2616).

N-(2-*Methylphenyl*)-2,5-*dimethylpyrrole*-3-*carbaldehyde* (**3**). Yield 90%; *m/z* 213 ($M^{+\bullet}$, 100%), 212 (33), 198 (32), 184 (20), and 170 (56) (d.i.t., 50 °C).

N-(2-*Methoxyphenyl*)-2,5-*dimethylpyrrole*-3-*carbaldehyde* (**4**). Yield 91%; *m/z* 229 ($M^{+\bullet}$, 100%), 228 (33), 214 (26), 200 (27), and 186 (35) (d.i.t., 50 °C).

N-(2-*Ethoxyphenyl*)-2,5-*dimethylpyrrole*-3-*carbaldehyde* (**5**). Yield 93%; *m/z* 243 ($M^{+\bullet}$, 100%), 228 (24), 214 (29), 200 (41), and 170 (27) (d.i.t., 70 °C).

N-(2-*Benzyloxyphenyl*)-2,5-*dimethylpyrrole*-3-*carbaldehyde* (**6**). Yield 86%; *m/z* 305 ($M^{+\bullet}$, 47%), 200 (19), 186 (26), 91 (100), and 65 (24) (d.i.t., 87 °C).

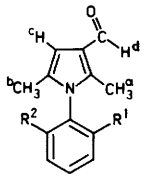
N-(2-*Chloro*-6-*methylphenyl*)-2,5-*dimethylpyrrole*-3-*carb*-

Table 2. Analytical and spectroscopic data.

Compd.	Formula	M.p./°C	Required, % (Found) C	H	N	$\tilde{\nu}_{C=O}$/cm^{-1} [c]	λ_{max}/nm [d] (log ε)
(1)	$C_{13}H_{12}ClNO$	75–77 [a]	66.81 (66.54)	5.18 (5.40)	5.99 (6.21)	1 655(s)	288 (3.94) 249 (4.27)
(2)	$C_{14}H_{12}N_2O$	137–138 [b]	74.98 (74.86)	5.39 (5.68)	12.49 (12.54)	1 645(s)	280 (3.99) 250 (4.26)
(3)	$C_{14}H_{15}NO$	74–75 [a]	78.84 (78.62)	7.09 (7.23)	6.57 (6.93)	1 650(s)	285 (3.99) 250 (4.26)
(4)	$C_{14}H_{15}NO_2$	73–74 [b]	73.34 (73.13)	6.59 (6.56)	6.11 (5.81)	1 645(s)	280 (4.11) 255 (4.18)
(5)	$C_{15}H_{17}NO_2$	65–67 [b]	74.05 (73.97)	7.04 (6.90)	5.76 (5.91)	1 645(s)	280 (4.07) 255 (4.14)
(6)	$C_{20}H_{19}NO_2$	121–122 [b]	78.66 (78.67)	6.27 (6.39)	4.59 (4.33)	1 645(s)	279 (4.02) 255 (4.11)
(7)	$C_{14}H_{14}ClNO$	77–78 [b]	67.88 (68.08)	5.70 (5.65)	5.65 (5.79)	1 650(s)	285 (3.90) 247 (4.22)

[a] From MeOH–H_2O(50:50). [b] From light petroleum (40–70 °C). [c] In KBr. [d] In MeOH.

Table 3. Values of δ_H and J/Hz (in $CDCl_3$ at 22 °C) [a] for protons a–d.



	R^1	R^2	a	b	c	d	Ph
(1)	Cl	H	2.23	1.94 ^4J = 0.9	6.41 ^4J = 0.9	9.88	7.24–7.67
(2)	CN	H	2.30	2.00 ^4J = 0.9	6.43 ^4J = 1.2	9.89	7.29–7.93
(3)	Me 1.96	H	2.19	1.90 ^4J = 0.6	6.41 ^4J = 0.6	9.87	7.11–7.39
(4)	OMe 3.80	H	2.23	1.94 ^4J = 0.9	6.40 ^4J = 0.9	9.82	7.04–7.48
(5)	OEt CH_2CH_3, 4.04 (J = 7) CH_2CH_3, 1.28 (J = 7)	H	2.27	1.93 ^4J = 0.9	6.37 ^4J = 0.9	9.86	6.99–7.53
(6)	OCH_2Ph 5.08	H	2.23	1.95 ^4J = 0.9	6.42 ^4J = 0.9	9.83	7.07–7.32
(7)	Cl	Me 2.0	2.18	1.90 ^4J = 0.9	6.46 ^4J = 0.9	9.89	7.27–7.38

[a] The digital resolution ±0.29 Hz in 8 K addresses and 1 200 Hz sweep width.

aldehyde (**7**).—Yield 79%; *m/z* 249 (35%), 248 (30), 247 ($M^{+\cdot}$, 100), 246 (49), and 204 (33) (d.i.t., 50 °C).

The *N*-aryl-2,5-dimethylpyrroles (**11**)–(**15**), were prepared by Knorr–Paal condensation of hexane-2,5-dione with the corresponding aniline (dissolved in benzene) and phosphoryl chloride, according to the general method.[13] The products were purified either by distillation or by recrystallization and the following compounds were obtained in this way:

N-(2-*Chlorophenyl*)-2,5-*dimethylpyrrole* (**11**). Yield 90%; b.p. 143–145 °C/34 Torr (lit.,[14] 135 °C/15 Torr).

N-(2-*Cyanophenyl*)-2,5-*dimethylpyrrole* (**12**). Yield 68%; m.p. 83–85 °C (methanol); δ_H($CDCl_3$; 22 °C) 2.02 (6 H, s, Me), 5.95 (2 H, s, pyrrole-H), and 7.29–7.84 (4 H, m, phenyl).

N-(2-*Methylphenyl*)-2,5-*dimethylpyrrole* (**13**). Yield 82%; b.p. 122–124 °C/17 Torr (lit.,[14] 123–125 °C/22 Torr; lit.,[13] 78 °C/2 Torr[13]).

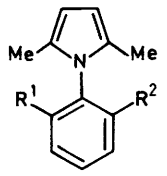
N-(2-*Methoxyphenyl*)-2,5-*dimethylpyrrole* (**14**). Yield 76%; m.p. 65–67 °C (methanol) (lit.,[14] 65 °C).

N-(2-*Chloro*-6-*methylphenyl*)-2,5-*dimethylpyrrole*[15] (**15**). Yield 83%; b.p. 131–132 °C/37 Torr (lit.,[15] 146–148 °C/15 Torr); δ_H($CDCl_3$; 22 °C) 1.90 (6 H, s, pyrrole-CH_3), 1.97 (3 H, s, phenyl-CH_3), 5.94 (2 H, s, pyrrole-H), and 7.19–7.32 (3 H, m, phenyl-H).

N-(2-*Ethoxyphenyl*)-2,5-*dimethylpyrrole* (**16**) *and* N-(2-*benzyloxyphenyl*)-2,5-*dimethylpyrrole* (**17**).—These were obtained by alkylation of *N*-(2-hydroxyphenyl)-2,5-dimethylpyrrole[13,16] with the corresponding alkyl bromide according to the procedure given in the literature.[17]

(**16**), *m/z* 215 (100%), 200 (42), 186 (23), 170 (53), and 156 (19) (d.i.t., 30 °C).

(**17**), *m/z* 277 ($M^{+\cdot}$, 11%), 108 (11), 91 (100), 65 (16), and 43 (22) (d.i.t., 51 °C).



	R^1	R^2
(11)	Cl	H
(12)	CN	H
(13)	Me	H
(14)	MeO	H
(15)	Cl	Me
(16)	EtO	H
(17)	$PhCH_2O$	H

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