Pyrrole Studies. Part 28.[1] The Effect of Steric Hindrance upon the Reaction of 2-Vinylpyrroles with Dimethyl Acetylenedicarboxylate

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Steric interaction between the *N*-substituent and the vinyl substituent of 1-substituted 1-(1-substituted pyrrol-2-yl)ethenes destabilises the *cisoid* conformation (**1b**), thereby inhibiting ($_{\pi}4 + _{\pi}2$) cycloaddition reactions leading to dihydroindoles. Bulky *N*-substituents also sterically inhibit the Michael addition of dimethyl acetylenedicarboxylate at the 5-position of the pyrrole ring.

In previous publications[2,3] we have shown that the mode of addition of dimethyl acetylenedicarboxylate (DMAD) to 1-substituted 2-vinylpyrroles (**1**; R′ = H) was temperature dependent and that both the ($_{\pi}4 + _{\pi}2$) cycloaddition reaction leading to the dihydroindoles (**4**) and the formation of the Michael adducts (**2**) and (**3**) can occur. The requirement of the higher temperatures to effect the preferential formation of the ($_{\pi}4 + _{\pi}2$) cycloadducts arises from the necessity to overcome the energy difference between the unreactive *transoid* diene (**1a**) and the reactive *cisoid* system (**1b**). The relative thermodynamic stabilisation of the two conformations will obviously depend to a large extent upon the steric requirements of the substituents R and R′ (*cf.* ref. 4) and our earlier work [3] has shown that, unlike 1-methyl-2-vinylpyrrole which reacts with DMAD at 20 °C to produce both the Michael adducts and the cycloadduct, 1-phenyl-2-vinylpyrrole yields only the dihydroindole over a wide temperature range. It was postulated [3] that the phenyl group restrains the reactive diene system in the *cisoid* conformation required for the cycloaddition reaction and simultaneously hinders the Michael addition reaction at the 5-position of the pyrrole ring. Conversely, the *N*-methyl group of compound (**1**; R = Me, R′ = H) does not inhibit the Michael reaction and presents little steric hindrance to coplanarity of the diene system in either conformation (**1a**) or (**1b**). The present work confirms that steric factors play an important role in the reaction of 2-vinylpyrroles with DMAD.

Comparison of the data presented in the Table shows that where both the substituents R and R′ are bulky [*e.g.* (**1**; R = Me, R′ = Me or Bu^t)] the dihydroindole (**4**) is not obtained even under reflux conditions, indicating that for such systems the thermodynamic stability of the *transoid* conformer (**1a**) is considerably greater than that of the *cisoid* system (**1b**) with the consequent inhibition of the ($_{\pi}4 + _{\pi}2$) cycloaddition reaction. However, the contrasting modes of reactivity of the isomeric compounds, 1-(1-methylpyrrol-2-yl)-1-phenylethene (**1**; R = Me, R′ = Ph) and 2-(1-phenylpyrrol-2-yl)propene (**1**; R = Ph, R′ = Me) are significant. The reaction of 2-(1-phenylpyrrol-2-

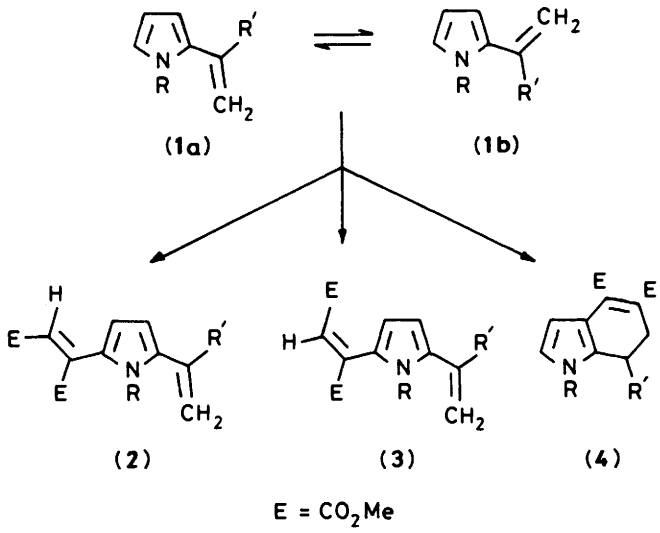

Table. Reactions of 1-substituted 2-vinylpyrroles with DMAD in $CHCl_3$

Pyrrole (**1**) R	R′	Reaction temp. (°C)	Reaction time	% Yields of isolated products (**2**)	(**3**)	(**4**)
Me	H[a]	20	4 days	20	9	21
		60	3 h	0	0	70
Me	Me	20	3 days	22	17	0
		60	3 h	30	41	0
Me	Bu^t	20	20 days	26	18	0
		60	6 h	39	16	0
Me	Ph	20	7 days	35	27	38
		60	9 h	7	10	32
Ph	H[a]	20	4 days	0	0	65
		60	3 h	0	0	80
Ph	Me	20	10 days	0	0	25[b]
		60	5 days	0	0	39

[a] Data taken from ref. 3. [b] Dimethyl 7-methyl-1-phenylindole-4,5-dicarboxylate (4%) also isolated.

yl)propene with DMAD is analogous to that of 1-phenyl-2-vinylpyrrole[3] and always leads to the exclusive formation of the cycloadduct (**4**; R = Ph, R′ = Me), whereas 1-(1-methylpyrrol-2-yl)-1-phenylethene produces both the Michael adducts and the ($_{\pi}4 + _{\pi}2$) cycloadducts in a ratio of 1.6:1 at 20 °C changing to 0.5:1 at 60 °C. These observations suggest that, although steric hindrance by the *N*-phenyl substituent to the coplanarity of the *cisoid* conformation of the propenyl group contributes to the lower reactivity of compound (**1**; R = Ph, R′ = Me), compared with 1-phenyl-2-vinylpyrrole, it is the inhibitory effect of the *N*-phenyl group on the Michael addition at the 5-position of the pyrrole ring which creates the greater influence upon the reaction pathway. In contrast, the *N*-methyl group of compound (**1**; R = Me, R′ = Ph) presents no steric or electronic influence upon the Michael addition pathway, whilst the phenyl ring can twist out of the plane of the vinyl group, thereby minimising the energy difference between the two conformations (**1a**) and (**1b**). Consequently, the rates of the Michael addition and the cycloaddition reactions at 20 °C are comparable, whilst the effect of the increased temperature on the product ratio is in accord with earlier observations.[3]

The stereochemistry of the Michael adducts was confirmed by an examination of the $^{3}J_{CO,H}$ coupling constants of the carbonyl group ^{13}C resonance signals.[3,5]

Experimental

^{1}H and ^{13}C N.m.r. chemical shifts downfield from the internal standard (Me_4Si) were measured for *ca.* 0.3M solutions in $CDCl_3$ using a JEOL FX-100 spectrometer operating, respectively, at 100 and 25.05 MHz.* I.r. spectra were measured as liquid films or as solutions in $CHBr_3$ using a Perkin-Elmer 297 spectrophotometer and electronic spectra were recorded for *ca.* 10^{-5}M solutions in EtOH using a Unicam SP8-200 spectrophotometer.

Unless otherwise stated, t.l.c. analyses and preparative t.l.c. separations of the products were conducted on Kieselgel HF_{254} using hexane–diethyl ether (4:3) as the eluant.

Vinylpyrroles.—2-(1-Methylpyrrol-2-yl)propene (R_F 0.92, hexane–diethyl ether, 2:1), b.p. 38 °C at 2 mmHg, 3,3-dimethyl-2-(1-methylpyrrol-2-yl)but-1-ene (R_F 0.83), b.p. 68 °C at 3 mmHg, and 1-(1-methylpyrrol-2-yl)-1-phenylethene (R_F 0.92, hexane–diethyl ether, 3:1), b.p. 87 °C at 1.2 mmHg, were prepared according to procedures described in the literature.[1]

2-(1-Phenylpyrrol-2-yl)propene.—1-Phenylpyrrole (2.86 g, 0.02 mol), acetic anhydride (2.26 g, 0.02 mol), and magnesium perchlorate (0.44 g, 0.002 mol) were stirred at room temperature for 1 h. Water (20 ml) and diethyl ether (20 ml) were added and the mixture was neutralised with solid sodium carbonate. The ether layer was separated and the aqueous layer was extracted with diethyl ether (3 × 10 ml). The combined ether extracts were washed with water (2 × 10 ml) and evaporated to give 2-acetyl-1-phenylpyrrole (2.14 g, 58%) (R_F 0.40), b.p. 130—135 °C at 15 mmHg (lit.,[6] b.p. 147—150 °C at 12 mmHg).

Sodium hydride (0.6 g, 0.025 mol) was stirred with a suspension of methyltriphenylphosphonium bromide (3.57 g, 0.01 mol) in dry tetrahydrofuran (THF) (30 ml) under nitrogen at 20 °C for 2 h. 2-Acetyl-1-phenylpyrrole (1.67 g, 0.009 mol) in dry THF (8 ml) was added and the mixture heated under reflux with stirring for 3 h and then cooled to 20 °C. After 12 h at 20 °C, the mixture was filtered, the residual solid washed with hexane (4 × 15 ml), and the combined organic phases were evaporated to give 2-(1-*phenylpyrrol-2-yl*)*propene* (0.71 g, 41%) (R_F 0.54), b.p. 50 °C at 10^{-3} mmHg (Found: C, 84.8; H, 7.2; N, 7.4. $C_{13}H_{13}N$ requires C, 85.2; H, 7.15; N, 7.65%).

General Procedure for the Reaction of the Vinylpyrroles with Dimethyl Acetylenedicarboxylate.—DMAD (0.56 g, 0.004 mol) was added to the vinylpyrrole (0.004 mol) and hydroquinone (5 mg) in chloroform (5 ml) and the reaction mixture was either stirred at 20 °C or heated under reflux with stirring for the times indicated in the Table. Evaporation of the solvent and preparative t.l.c. purification of the residue gave analytically pure samples of the products.

Products of the Reaction of 2-(1-*Methylpyrrol-2-yl*)*propene.*—The following compounds were obtained. *Dimethyl* (1-*methyl-5-propen-2-ylpyrrol-2-yl*)*fumarate* (R_F 0.34) had m.p. 78 °C (Found: C, 63.5; H, 6.5; N, 5.2. $C_{14}H_{17}NO_4$ requires C, 63.9; H, 6.5; N, 5.3%); δ_C 165.7 (=CHCO) and 166.7 ($^{3}J_{CO,H}$ 6.8 Hz, =CCO); ν_{CO} 1 730 cm^{-1}; $\lambda_{max.}$ 266 (log ε 3.71) and 390 nm (log ε 3.21); *dimethyl* (1-*methyl-5-propen-2-ylpyrrol-2-yl*)*maleate* (R_F 0.17) as an oil (Found: C, 63.4; H, 6.3; N, 5.4%); ν_{CO} 1 720 cm^{-1}; $\lambda_{max.}$ 238 (log ε 3.96) and 355 nm (log ε 4.21).

Products of the Reaction of 1-(1-*Methylpyrrol-2-yl*)-1-*phenylethene.*—The following compounds were obtained. *Dimethyl* [1-*methyl-5-*(1-*phenylethenylpyrrol-2-yl*]*fumarate* (R_F 0.36) as an oil (Found: C, 69.7; H, 5.6; N, 4.0. $C_{19}H_{19}NO_4$ requires C, 70.1; H, 5.9; N, 4.3%); δ_C 165.5 (=CHCO) and 166.6 ($^{3}J_{CO,H}$ 6.6 Hz, =CCO); ν_{CO} 1 720 cm^{-1}; $\lambda_{max.}$ 240 nm (log ε 3.95); *dimethyl* [1-*methyl-5-*(1-*phenylethenyl*)*pyrrol-2-yl*]*maleate* (R_F 0.23) as an oil (Found: C, 69.7; H, 5.9; N, 4.25%); δ_C 165.3 (=CHCO) and 168.0 ($^{3}J_{CO,H}$ 12.1 Hz, =CCO); ν_{CO} 1 720 and 1 735 cm^{-1}; $\lambda_{max.}$ 235 (log ε 4.17) and 352 nm (log ε 4.26); and *dimethyl* 6,7-*dihydro-1-methyl-7-phenylindole-4,5-dicarboxylate* (R_F 0.10), m.p. 126 °C (Found: C, 69.6; H, 5.7; N, 4.1. $C_{19}H_{19}NO_4$ requires C, 70.1; H, 5.9; N, 4.3%); ν_{CO} 1 730 cm^{-1}; $\lambda_{max.}$ 245 nm (log ε 4.08).

Products of the Reaction of 3,3-*Dimethyl-2-*(1-*methylpyrrol-2-yl*)*but-1-ene.*—The following compounds were obtained. *Dimethyl* 5-(3,3-*dimethylbut-1-en-2-yl*)-1-*methylpyrrol-2-yl*)-*fumarate* (R_F 0.37) as an oil (Found: C, 67.3; H, 7.9; N, 4.3. $C_{17}H_{23}NO_4$ requires C, 66.9; H, 7.6; N, 4.6%); δ_C 165.8 (=CHCO) and 166.8 ($^{3}J_{CO,H}$ 6.8 Hz, =CCO); ν_{CO} 1 740 and 1 720 cm^{-1}; $\lambda_{max.}$ 380 nm (log ε 3.03) and *dimethyl* 5-(3,3-*dimethylbut-1-en-2-yl*)-1-*methylpyrrol-2-ylmaleate* (R_F 0.20) as an oil (Found: C, 66.5; H, 7.8; N, 4.45%); δ_C 166.1 (=CHCO) and 168.4 ($^{3}J_{CO,H}$ 12 Hz, =CCO); ν_{CO} 1 730 cm^{-1}; $\lambda_{max.}$ 346 nm (log ε 4.21).

Products of the Reaction of 2-(1-*Phenylpyrrol-2-yl*)*propene.*—The following compounds were obtained. *Dimethyl* 6,7-*dihydro-7-methyl-1-phenylindole-4,5-dicarboxylate* (R_F 0.27) as a thermally unstable oil (Found: 69.5; H, 5.6; N, 4.2%; M^+ 325.1320. $C_{19}H_{19}NO_4$ requires C, 70.1; H, 5.9; N, 4.3%. M^+ 325.1313); ν_{CO} 1 775 and 1 740 cm^{-1}; $\lambda_{max.}$ 235 (log ε 3.60) and 290 nm (log ε 2.83); and *dimethyl* 7-*methyl-1-phenylindole-4,5-dicarboxylate* (R_F 0.26), m.p. 85 °C (Found: C, 70.2; H, 5.5; N, 3.95; M^+ 323.1171. $C_{19}H_{17}NO_4$ requires C, 70.6; H, 5.3; N, 4.3%; M^+ 323.1157); ν_{CO} 1 730 and 1 710 cm^{-1}; $\lambda_{max.}$ 214 (log ε 4.43) and 248 nm (log ε 3.74).

* Full ^{1}H and ^{13}C n.m.r. spectroscopic data are listed in a Supplementary Publication (SUP No. 56065, 4 pp.). For details of the Supplementary Publications Scheme see Instructions for Authors (1984) in *J. Chem. Soc., Perkin Trans. 1*, 1984, Issue 1.

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