The Conformational Preferences of *N*-Alkylpyrrole Mono- and Di-Esters: an Infrared and Nuclear Magnetic Resonance Study

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The conformational preferences of 19 *N*-alkylpyrrole 2- and 3-mono-, and 2,3-, 2,4-, and 2,5-di-esters have been investigated by i.r. and (in two cases) n.m.r. spectrometry. The 2-mono-esters are thought to exist in solution in only one rotameric form, probably *syn-s-trans*, whereas two rotational isomers may be present in the 3-mono-ester case. In the di-esters, the doublet i.r. carbonyl absorptions exhibited by the 2,5-compounds can best be rationalised in terms of a mixture of *syn-syn* and *anti-syn* conformers; 2,4-di-esters display asymmetric singlet i.r. carbonyl bands, ascribed to an equilibrium between *syn-cisoid* and *syn-transoid* forms; in the 2,3-di-ester case, the well-separated i.r. carbonyl doublet is thought to arise from *anti-cisoid* and *anti-transoid* isomers, although the possibility of interactions between adjacent substituents makes the interpretation more problematic.

2,5-Dimethoxycarbonyl-*N*-t-butyl- and -*N*-adamantyl-pyrrole have been examined by variable-temperature proton and carbon-13 n.m.r. spectrometry for evidence of rotational isomerism due to restricted rotation about either the *N*-alkyl group bond or the ring-carbonyl group bonds.

2-ACYL-DERIVATIVES of furan and thiophen adopt essentially planar conformations in which the carbonyl function is disposed in a *syn* or *anti* orientation with respect to the ring heteroatom (unless severe steric interactions are involved). I.r. and n.m.r. spectrometry have been especially useful in the study of the resulting rotameric equilibria (Figure 1), and reliable thermodynamic parameters have been obtained in favourable cases.[1]

In the present study, i.r. and n.m.r. approaches are used to investigate the occurrence of rotational isomerism in a range of *N*-alkylpyrrole mono- and di-esters [compounds (1)–(19)] and, where possible, to determine the relative stabilities of rotameric forms.

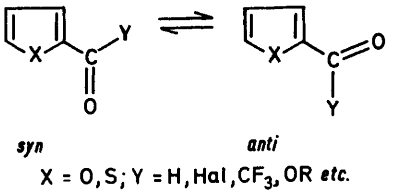
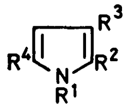


FIGURE 1



Compound	R^1	R^2	R^3	R^4
(1)	Me	CO_2Me	H	H
(2)	Et	CO_2Me	H	H
(3)	Bu^n	CO_2Me	H	H
(4)	Pr^i	CO_2Me	H	H
(5)	Bu^t	CO_2Me	H	H
(6)	Bu^t	H	CO_2Me	H
(7)	Me	CO_2Me	H	CO_2Me
(8)	Et	CO_2Me	H	CO_2Me
(9)	Bu^t	CO_2Me	H	CO_2Me
(10)	Pr^i	CO_2Me	H	CO_2Me
(11)	Bu^t	CO_2Me	H	CO_2Me
(12)	1-adamantyl	CO_2Me	H	CO_2Me
(13)	Me	H	CO_2Me	CO_2Me
(14)	Et	H	CO_2Me	CO_2Me
(15)	Bu^n	H	CO_2Me	CO_2Me
(16)	Pr^i	H	CO_2Me	CO_2Me
(17)	Bu^t	H	CO_2Me	CO_2Me
(18)	1-adamantyl	H	CO_2Me	CO_2Me
(19)	Bu^t	CO_2CH_3	CO_2Me	H

Simple esters usually adopt an *s-trans* conformation: the rare *s-cis* form is only observed when R is small and R′ bulky (*e.g.* t-butyl formate [2]) (Figure 2). The maximum number of possible rotamers is therefore two for *N*-alkylpyrrole 2- and 3-mono-esters, three for the 2,5-, and four for the 2,3- and 2,4-diesters (Figure 3).

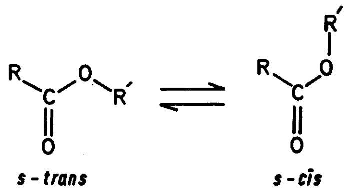


FIGURE 2

RESULTS AND DISCUSSION

Infrared Investigations.—The positions of the i.r. carbonyl fundamental and overtone absorptions for the 19 pyrrole esters are summarised in Table 1.

TABLE 1

N-Alkylpyrrole ester carbonyl absorptions (cm^{-1})

	C=O Fundamental region				C=O Overtone region	
Compd.	CCl_4		MeCN		CCl_4	
(1)	1 713		1 709		3 409	
(2)	1 712		1 707		3 414	
(3)	1 709 *		1 707		3 404	
(4)	1 704 *		1 702		3 391	
(5)	1 713 *		1 710		3 410	
(6)	1 717 *		1 709 *		*a*	
(7)	1 735	1 712	1 731	1 709	3 458	3 412
(8)	1 733	1 710	1 730	1 707	3 458	3 404
(9)	1 733	1 709	1 726	1 706	3 455	3 405
(10)	1 734	1 710	1 730	1 708	3 459	3 408
(11)	1 731	1 715	1 725	1 713	3 457	3 422
(12)	1 735	1 716	1 723	1 712	3 451	3 416
(13)	1 726 †	1 715	1 721 †	1 713	3 418 *	
(14)	1 728 †	1 712	1 722 †	1 711	3 417 *	
(15)	1 725 †	1 712	1 720 †	1 710	3 416 *	
(16)	1 726 †	1 711	1 718 †	1 709	3 409 *	
(17)	1 724 †	1 715	1 722 †	1 711	3 423 *	
(18)	1 726 †	1 713	1 722 †	1 711	3 418 *	
(19)	1 737	1 722	1 735	1 713	*a*	

* Broadening to high-wavenumber side of the band.
† Estimated shoulder position.

[a] Insufficient sample for analysis.

*2-Methoxy-carbonyl-*N*-alkylpyrroles* (1)—(5). *N*-Methyl- (1) and *N*-ethyl-pyrrole (2) monoesters display symmetric singlet carbonyl bands in the fundamental region whereas those of the *N*-n-butyl- (3), *N*-isopropyl (4), and *N*-t-butyl- (5) esters appear as asymmetric singlets. Change of solvent from carbon tetrachloride to acetonitrile removes the asymmetry. By contrast, 2-alkoxycarbonyl-furans display well-separated i.r. carbonyl doublets [1b] (separation *ca.* 30 cm^{-1}) arising from rotational isomerism between *syn-s-trans* and *anti-s-trans* forms: the relative intensities of the doublet component bands are only slightly affected by change of solvent dielectric constant. It seems unlikely, therefore, that *syn-* and *anti*-conformers in the *N*-alkylpyrrole analogues would have essentially the same carbonyl absorption frequencies: we are thus led to the conclusion that 2-mono-esters of *N*-alkylpyrroles exist in solution in only one form, probably *syn-s-trans*, *syn* being the preferred conformation of *N*-alkylpyrrole-2-carbaldehydes and of certain -2-ketones.[3] [The band asymmetry in esters (3)—(5) may owe its origin to Fermi resonance,[4] a not uncommon phenomenon in 2-oxo-furans and -thiophens which can usually be reliably diagnosed by change of solvent, variation in solution concentration, overtone, and (in obstinate cases) isotopic-labelling studies.]

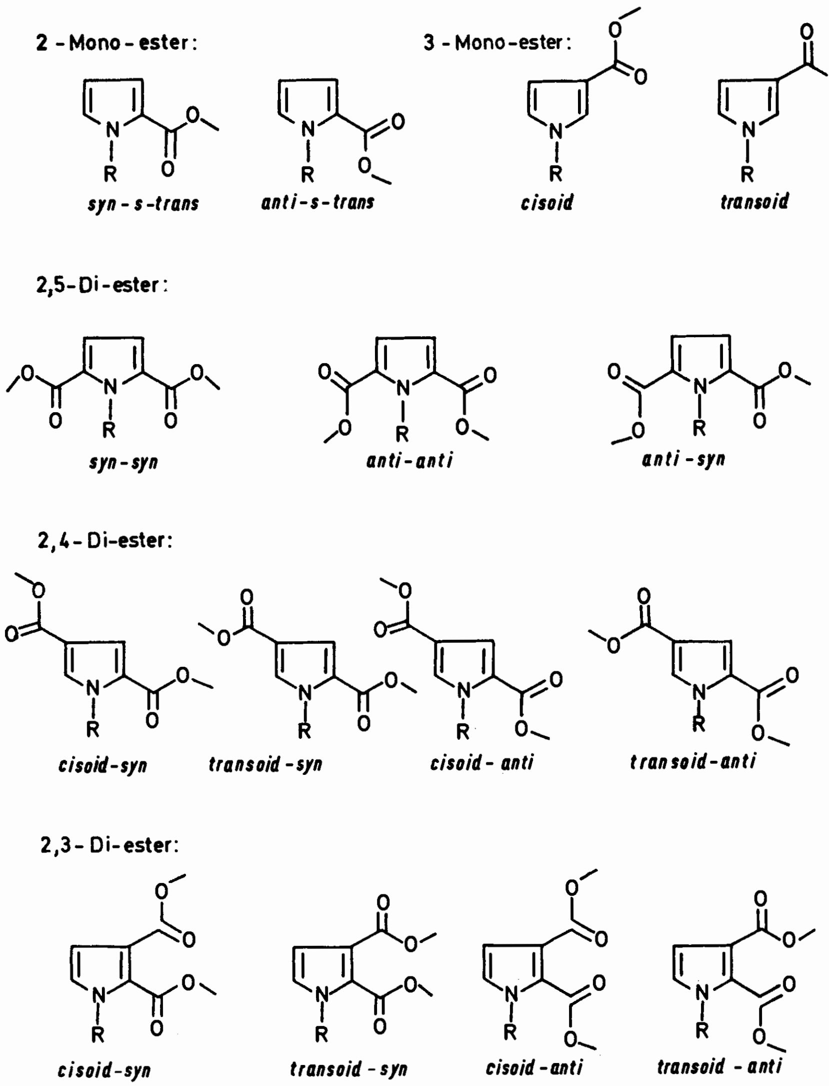


FIGURE 3 Possible conformations of esters

The greater stability of the *syn* over the *anti*-rotamer for pyrrole-2-carbaldehydes and -ketones in low-polarity solvents [1a,3] is due to its lower dipole moment: the moments of the pyrrole ring (with the positive pole located on the nitrogen atom [5]) and the oxo-group are mutually opposed. Similar considerations should obtain for the -2-esters in which the *syn-s-trans*-rotamer is expected to have a much lower dipole moment than the *anti*-rotamer. Steric effects appear to be of little consequence, there being no systematic change in either band structure or absorption frequency on variation in the bulk of the *N*-alkyl group.

*3-Methoxycarbonyl-*N*-t-butylpyrrole* (6). The asymmetric singlet i.r. band observed in the carbonyl region is open to two interpretations: the molecule exists either in one rotameric form (with the band asymmetry perhaps arising from Fermi resonance) or as a mixture of rotamers with approximately equal carbonyl absorption frequencies. From n.m.r. evidence, an equilibrium between *cisoid* and *transoid* forms is known to exist in 3-oxo-*N*-alkylpyrroles[3] (although this does not lead to i.r. carbonyl band doubling). It seems likely, therefore, that both conformers are in equilibrium in the ester case but that the field effects experienced by the ester functions in the two conformations are not sufficiently different for doubling of i.r. carbonyl bands to occur.

2,5-*Dimethoxycarbonyl*-N-*alkylpyrroles* (7)—(12). All the 2,5-di-esters display well-separated i.r. carbonyl doublets (*ca.* 20 cm^{-1} apart) in which the lower wavenumber components are at approximately the same positions as the carbonyl absorptions of the corresponding 2-mono-esters.

If, as a first approximation, the two ester groups are considered independently of one another, then the observed doubled carbonyl bands may be attributed to mixtures of conformers containing *syn*- and *anti*-ester functions, in which the lower-wavenumber bands arise from the *syn*-function (in agreement with the previous 2-monoester assignment) and the higher-wavenumber bands from the *anti*-function. The emergence of this *anti*-conformation (unobserved for 2-mono-esters) can be rationalised by consideration of the relative magnitudes of ester group and pyrrole dipole moments. The *anti-syn*-conformer (Figure 3) is expected to have a lower dipole moment than the *syn-syn*-conformer, with the *anti-anti*-conformer having the highest moment. On this basis, the higher wavenumber absorption of a 2,5-di-ester carbonyl doublet results from the *anti*-ester component of the *anti-syn*-form, and the lower wavenumber absorption from the *syn*-ester components of both the *syn-syn*- and *anti-syn*-forms. In agreement with this assignment, the intensity of the carbonyl band at lower wavenumber increases relative to that of the band at higher wavenumber for all the compounds studied here as the dielectric constant of the solution is increased, either by change of solvent from carbon tetrachloride to acetonitrile or by increase in substrate concentration necessary for the overtone studies. We rationalise this as being a consequence of the increased stabilisation of the more-polar *syn-syn*-form over the less-polar *anti-syn*-form, and hence a decrease in the percentage of *anti*-conformation present.

TABLE 2

Variable-temperature i.r. studies

The ester carbonyl absorptions in the fundamental region were resolved into three bands of areas A_1, A_2, and A_3, normalised so that the total area, A_T, of the low-temperature contour was 100%

Compound	T/K	A_1	A_2	A_3	A_T
(8)	258	49.4	17.6	33.0	100
	348	42.3	10.0	28.5	80.8
(9)	258	20.6	48.8	30.6	100
	348	29.2	26.2	32.3	87.7
(10)	259	60.1	14.1	25.8	100
	351	51.6	10.0	28.4	90.0
(11)	258	26.3	39.1	34.6	100
	348	19.5	33.8	29.3	82.6
(12)	256	29.1	26.8	44.1	100
	344	6.5	30.3	32.9	69.7

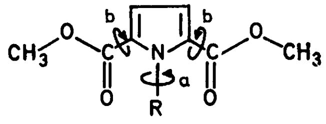
A study of the temperature-dependence of the areas of the doublet components in an attempt to derive thermodynamic parameters (Table 2) gave inconclusive results since three bands were required to achieve acceptable fits to the observed band contours. The validity of the assumption that the ester groups are essentially independent may thus be in doubt since, if there were an electronic interaction through the ring between the ester groups, then the energy of a *syn*-ester carbonyl vibration in the *anti-syn*-conformer might not be the same as that of a *syn*-ester carbonyl vibration in the *syn-syn*-conformer. Furthermore, the possibility of anhydride-like vibrational coupling between the carbonyl groups cannot be excluded, even though the degree of such coupling is known to fall off rapidly as group separation increases (the carbonyl band separation in anhydrides is *ca.* 60 cm^{-1} whereas that in peroxides is only *ca.* 25 cm^{-1}).[6] Both these effects would tend to complicate the observed band profiles in an unpredictable manner.

2,4-*Bismethoxycarbonyl*-N-*alkylpyrroles* (13)—(18). The 2,4-di-ester carbonyl absorptions display only single maxima, but the bands bear distinct shoulders to the high-wavenumber side. The position of the major component of each absorption is close to that of the corresponding 2-mono-ester. This, together with the absence of well-separated carbonyl bands, implies that the 2-ester group is conformationally fixed in the *syn*-form: the 4-ester group can then be *cisoid* or *transoid*. There are thus two possible conformations for the 2,4-di-esters: *syn-cisoid* and *syn-transoid*. The origin of the i.r. band asymmetry can then be ascribed either to (*a*) slightly different carbonyl absorption frequencies of the 4-ester group in the *transoid*- and *cisoid*-forms arising either from a slight intrinsic difference in field effects experienced by the ester group in the two conformations (as discussed for the 3-mono-ester case) or from an electronic interaction between the 2- and 4-ester groups along the lines discussed in the 2,5-di-ester case, or to (*b*) anhydride-like coupling.

2,3-*Bismethoxycarbonyl*-N-*t*-*butylpyrrole* (19). The compound displays well-separated i.r. carbonyl doublets in carbon tetrachloride and acetonitrile.

On the basis of the previous discussion, the position of the higher-wavenumber component would imply the presence of the 2-ester group in an *anti*-conformation. Change of solvent from carbon tetrachloride to acetonitrile causes a shift to low wavenumber for both component bands, as expected. The magnitude of the shift for the lower-frequency component is larger than that observed for the 2-ester group in the 2-mono-, 2,4-di- and 2,5-di-esters studied here (2—4 cm^{-1}) and is comparable to the shift in 3-methoxycarbonyl-*N*-t-butylpyrrole (8 cm^{-1}). It appears, therefore, that the lower-wavenumber component may owe its origin to the 3-ester group. The possible conformations are then *anti-cisoid* and *anti-transoid*. It should, however, be borne in mind that steric interactions are likely to be especially significant in a 1,2,3-trisubstituted pyrrole. Resulting out-of-planarity of ester groups and the pyrrole ring will lead to anomalous i.r. carbonyl band positions and solvent-induced shifts, thereby exacerbating the band-assignment problem.

Nuclear Magnetic Resonance Investigations.—Two esters, 2,5-dimethoxycarbonyl-*N*-t-butyl- (11) and -*N*-adamantyl-pyrrole (12) were examined by variable-temperature proton and carbon-13 n.m.r. spectrometry for evidence of rotational isomerism due to restricted rotation about either (*a*) the *N*-alkyl group bond or (*b*) the ring-carbonyl group bonds (Figure 4).



R = Bu^t or 1-adamantyl

FIGURE 4

The carbon-13 n.m.r. spectra of (11) and (12) show little change on cooling of the deuterodichloromethane solutions to −70 °C: the proton spectra, however, show significant broadening of the ester-methyl and *N*-alkyl signals (although not of the aromatic signals) at this temperature. Although the results are inconclusive, the absence of appreciable broadening of the aromatic protons at −70 °C would seem to suggest that hindrance to rotation mode (a) is responsible for the observed changes. This implies a very low energy barrier for rotation mode (b) (certainly lower than those barriers measured for *N*-alkylpyrrole-2-carbaldehydes, E_a *ca.* 45 kJ mol^{-1},[7] and pyrrole-2,5-dicarbaldehyde, E_a *ca.* 39 kJ mol^{-1} [8]) and is compatible with results obtained for furan-2-esters in which no coalescence phenomenon in either the carbon-13 or proton n.m.r. spectra is observed even at −90 °C.[9] This may be a consequence of reduced π-electron donation from the heteroaromatic ring into the carbonyl bond when the carbonyl carbon atom bears an additional group capable of π-donation.

EXPERIMENTAL

The i.r. spectra were recorded on a Perkin-Elmer 521 spectrometer, purged continuously with dry air, at a spectral slit width of 1–2 cm^{-1} and a scanning rate of 10 cm^{-1} min^{-1}: calibration was to 0.5 cm^{-1}. Variable-temperature spectra were obtained on dilute solutions in carbon tetrachloride with an R.I.I.C. VLT-2 probe and TEM-1 controller: temperature stability was to within 1 °C. Curve resolution was carried out on a Du Pont 310 Curve Resolver. Solvents (analytical grade) were dried over pre-heated molecular sieves (B.D.H. type 3A) prior to use. The preparation of the pyrrole esters has been described elswhere:[10] their purity was checked by g.l.c. Results are summarised in Tables 1 and 2.

N.m.r. spectra were recorded on Perkin-Elmer R32 (proton data; 90 MHz) and Brücker WH90 (carbon-13 data; 22.63 MHz) spectrometers: temperature control was to 1 °C. The chemical shifts (p.p.m.) of the carbon-13 n.m.r. signals for 1M-solutions in CD_2Cl_2 at 298 K (internal $SiMe_4$ reference) are assigned as: (11); 31.3 $C(\mathit{C}H_3)_3$, 52.3 $(CO_2\mathit{C}H_3$, 61.6 $\mathit{C}(CH_3)_3$, 116.9 C-3 and C-4, 132.5 C-2 and C-5, and 163.6 $-\mathit{C}O_2CH_3$: (12); 31.1 C-4′, 36.2 C-3′, 42.4 C-2′, 52.3 $-CO_2\mathit{C}H_3$, 63.4 C-1′, 117.2 C-3 and C-4, 132.2 C-2 and C-5, and 163.9 $-\mathit{C}O_2CH_3$.

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