# Reaction between *N*-Alkylpyrroles and Alkyl-lithium Reagents.   The Role of Nitrogen Substituent, Solvent, Alkyl-lithium, and Complexing Agents

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Six *N*-alkylpyrroles have been metallated with $Bu^n Li$ under a variety of conditions.   As the bulk of the nitrogen substituent increases, the total yield of lithiopyrroles decreases and the ratio of 2,4- to 2,5-disubstitution increases. Change of solvent from hexane to ethers generally accelerates metallation in the order hexane < diethyl ether < 2,5-dimethyl-THF < 2-methyl-THF < THF, though this is accompanied by increased solvent cleavage, especially at elevated temperatures.   Metallation is also accelerated by the addition of complexing agents, the order of effectiveness being *NNN'N'*-tetramethylethylenediamine > diazabicyclo[2.2.2]octane > tris(dimethylamino)phosphine > 1,4,8,11-tetramethyl-1,4,8,11-tetra-azacyclotetradecane.   Change of lithiating agent from $Bu^n Li$ to $Bu^t Li$ leads to increased overall metallation.

EARLY reports concerning metallation with alkyl-lithium reagents of furan,[1a,b] thiophen,[2] and *N*-methyl-pyrrole [3] describe the formation of α-monolithio-derivatives in relatively low yields.   Our recent reappraisal [4] of such metallations has established that the rate of hydrogen–lithium exchange is profoundly accelerated in solutions containing the chelating ligand *NNN'N'*-tetramethylethylenediamine (TMEDA): [5] it is now possible to prepare 2-lithio- and 2,5-dilithio-derivatives of furan, thiophen, and *N*-methylpyrrole in yields approaching quantitative.   A feature peculiar to the *N*-methyl-pyrrole metallation is the emergence of a 2,4-dilithio-product: [6] this compound is formed at the expense of the 2,5-isomer when an excess of $Bu^n Li$ and extended reaction times are used.   A recent attempt [7] to explore the effect of steric hindrance on the reaction between *N*-alkylpyrroles and $Bu^n Li$, through analysis of the lithio-intermediates by reaction with 2,4,6-trichloro-*s*-triazine has been criticised [8] on the grounds that *N*-alkylpyrroles react directly with the trapping reagent.

This somewhat inadequate approach to the study of *N*-alkylpyrrole metallation, and the observation of the ' anomalous ' 2,4-substitution pattern among the pro-
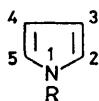
(1) R = Me (4) R = Bu^n
(2) R = Et   (5) R = Bu^t
(3) R = Pr^i (6) R = 1- adamantyl

ducts from *N*-methylpyrrole lithiation together stimulated the present investigation into the factors controlling the extent and orientation of lithiation in *N*-alkylpyrroles.   To this end, five such pyrroles were synthesised and subjected, along with commercially available *N*-methylpyrrole, to a variety of metallation conditions; the mixtures obtained were analysed by conversion of the lithiopyrroles into carboxylic methyl esters whose proportions were deduced from n.m.r. and g.l.c. studies.

RESULTS AND DISCUSSION

Experimental results are presented in Table 1.   All experiments on a particular *N*-alkylpyrrole bear the appropriate compound number (*e.g.* 1 implies *N*-methyl-pyrrole, 2 *N*-ethylpyrrole, and so on), and experiments carried out under identical reaction conditions bear the same Roman numeral.   In the following sections the effects of the nature of the *N*-alkyl group, solvent, organolithium alkyl group, and complexing agent are discussed separately.

(a) *Effect of* N-*Alkyl Group on the Lithiation of* N-*Alkylpyrroles in Hexane.*—The results of experiments (i)—(iv) demonstrate the influence of the *N*-alkyl group on the yields and ratios of lithio-products formed in hexane in the absence [experiment (i)] and presence [experiments (ii)—(iv)] of TMEDA.

Several general conclusions may be drawn from experiment (i).   As the size of the *N*-alkyl group increases (*i*) the yield of each lithio-product and the total yield of lithiated pyrroles decrease substantially, (*ii*) the [2,4] : [2,5] ratio increases rapidly, and (*iii*) the ratio of di- to mono-substituted products remains fairly constant. Effects (*i*) and (*ii*) are attributable to the increasing steric hindrance to formation of both the 2-mono- and 2,5-dilithio-intermediates.   Effect (*iii*) may imply that for constant [$Bu^n Li$] : [substrate] ratio, temperature, and reaction time, introduction of the β-lithio-atom into the α-monolithio-compounds in non-polar solvents is essentially unaffected by the nature of the *N*-alkyl group and depends only on the concentration of the monolithio-species.

The clear result of the investigation into the effect of *N*-alkyl group on the irreversible formation of mono-lithio-species [experiment (ii)] is that the reaction is unaffected by the size of the *N*-alkyl group (the zero yield observed for *N*-1-adamantylpyrrole may be accounted for either by the low solubility of this compound in hexane, or by the possibility that the six protons at the 2-positions of the adamantyl group have an especially hindering effect to reaction).

Experiment (iii) was designed to explore the variation of the 2,4 : 2,5 substitution ratio with change of *N*-alkyl group, since the fall-off in concentration of the 2,5-intermediate in experiment (i) was too great to permit detailed analysis.   Experiment (iv) illustrates the effect of the *N*-alkyl group on the concentration of 2,5-disubstituted product formed under high-yield reaction conditions.[4]   The results of these two experiments will

be discussed together since similar trends are apparent in both. (*i*) As the bulk of the N-alkyl group increases, the total yield of lithiopyrroles once again decreases, though this decrease is not in general so rapid as that found in experiment (i) (TMEDA absent). This necessarily arises from the reaction conditions used in experiments (iii) and (iv) which force rapid and almost quantitative formation of the monolithio-species prior to dilithiation [*cf.* experiment (ii)]. Thus total yields greater than 50% would be expected and were obtained [with the exception of experiment 6(iii) for which special considerations apply]. (*ii*) In both experiments, the concentration of 2,5-diester decreases as the size of the N-alkyl group increases, but the changes in concentration of the 2-mono- and 2,4-di-esters are variable. This effect is illustrated by the decrease in the dilithiation : monolithiation ratio which accompanies the change from a primary to a tertiary N-alkyl group. (*iii*) Both studies show an increase in the 2,4 : 2,5 substitution ratio as the size of the N-alkyl group increases. This arises from a large decrease in concentration of the 2,5-dilithio-species together with only a slight change in concentration of the 2,4-compound.

A comparison of the experiments with and without TMEDA [experiments (i) and (ii)—(iv)] leads to the following general conclusions. (i) When TMEDA is absent, the formation of monolithiopyrrole, and the 2,4 : 2,5 isomer ratio, are more sensitive to change in N-alkyl group than when TMEDA is present. (ii) When TMEDA is present, monolithiation is essentially quanti-tative at room temperature (with the exception of N-adamantylpyrrole), the 2,5-isomer is always favoured over the 2,4-compound at reflux temperature, though the 2,4 : 2,5 ratio increases with increasing bulk of the N-alkyl group, and the extent of dilithiation increases both with increase in reaction time and Bu^nLi : substrate ratio.

(b) *Effect of Ethereal Solvents on the Lithiation of* N-*Alkylpyrroles.*—It was noted soon after the discovery of metallation by organolithium compounds that the rate of the reaction was much greater in ether than in hydro-carbons. The reasons for this solvent effect may include depolymerisation of the organolithium oligomer (Bu^nLi is a tetramer in ether and a hexamer in hexane), increase of carbanion character by solvation of the metal, and dielectric stabilisation of the transition state.[9] This increased reactivity is demonstrated by the results of experiments 1(v) and 1(vi), in which the metallation of N-methylpyrrole to give the 2-monolithio-species with ether as solvent is shown to occur in much greater yield than with hexane under the same condi-tions.

A comparison of yields of lithio-products obtained in the reactions of N-alkylpyrroles and Bu^nLi in ether [experiment (v)] with the yields obtained in hexane [experiment (i)] leads to the following general conclusions. (*i*) The total amount of lithium incorporated into primary and secondary N-alkylpyrroles is greater in ether than in hexane; the reverse is, however, true for metallation of

N-t-butylpyrrole. (*ii*) In both solvents, the total yield decreases as the size of the N-alkyl group increases, but the effect is more pronounced in ether. The con-centration of dilithio-intermediate in ether appears to be insensitive to the nature of the N-alkyl group; the rapid decrease in concentration of *total* lithio-product is caused by the rapid fall-off in concentration of monolithio-compound (from 50 to 1%). This effect differs from that observed in hexane where, because the amount of monolithio-species present is so small, it is the variation in concentration of the dilithio-compounds which dominates the decrease in total concentration of lithio-pyrrole. These effects are demonstrated by the dilithi-ation : monolithiation ratio which, with increasing bulk of the N-alkyl group, increases rapidly in the case of ether, but remains fairly constant in the case of hexane. (*iii*) As the yields of lithiopyrrole obtained in ether are of the same order as or greater than those obtained in hexane, and since the boiling points of ether and hexane are **36** and **69**° respectively, it may be concluded that the reactivity of alkyl-lithium compounds is greater in ether than in hexane, as expected. (*iv*) The very small amount of dilithiation which occurs with ether as solvent may be due solely to the effect of temperature: the low yields obtained mean that little can be said about the significance of the 2,4 : 2,5 product ratio since small errors in the concentration measurements are greatly magnified in the ratios.

The best solvents for deprotonation reactions at low temperatures are found to be those containing ethers [10] of which ether–THF (80 : 20) [11] and Trapp's mixture [ether–THF–light petroleum (4 : 4 : 1)] [12] are perhaps the most effective. At higher temperatures, however, cleavage of ethers by organolithium compounds becomes a competitive reaction, *e.g.* diethyl ether is itself decom-posed to ethylene and lithium ethoxide.[13] Similarly, THF undergoes cleavage to ethylene and the lithium enolate of acetaldehyde.[14a,b]

It was the half-lives of such cleavage processes [14a,15] that led to the choice of reaction conditions for experi-ments (vii)—(xiv) in which the effects of different solvents and different reaction temperatures on the lithiation of N-methylpyrrole were studied.

The conclusion to be drawn from experiments (vii)—(x) is that THF accelerates the metallation. This result agrees with the view that an increase in the sol-vating power of the medium would enhance the basicity of the organometallic compound.

The data in experiments (vii) and (x)—(xii) show that the yield of monolithio-material obtained increases in the order of solvent: ether < 2,5-dimethyl-THF < 2-methyl-THF < THF. This series bears an inverse relationship to that for the half-lives of Bu^nLi in these solvents: it therefore seems reasonable to suppose that activation of the alkyl-lithium by solvent will be reflected both in a reduction of half-life (attack on solvent) and in an increase in the yield of monolithiopyrrole (attack on substrate). The differences observed for sub-stituted tetrahydrofuran derivatives arise from the

reduced solvating ability of 2- and 2,5-alkylated THFs compared with THF itself: this may be due to steric hindrance to lithium complexing.

In experiments (xii)—(xiv) the effect of temperature on the reaction in 2,5-dimethyl-THF was studied. This solvent was chosen because (i) it has the longest half-life of the cyclic ethers studied, (ii) it gave better yields of monolithiopyrrole at 19° than did ether, and (iii) its high boiling point (91°) permitted high-temperature studies. The following conclusions may be drawn. At 36°, the extent of lithiation observed in 2,5-dimethyl-THF [experiment 1(xiii)] and ether [experiment 1(v)] was comparable. This implies that solvent cleavage becomes an increasingly important side-reaction above room temperature. Increase in reaction temperature to that of 2,5-dimethyl-THF boiling under reflux allowed only a

small amount of further pyrrole lithiation to occur. It follows that at such an elevated temperature all the Bu^{n}Li must have been consumed by solvent before much further reaction with N-methylpyrrole could occur. Very little dilithiation was observed at this temperature (7% 2,5-diester) which may mean that the monolithio-intermediate is preferentially stabilised by this solvent compared with the dilithio-compound.

(c) *Effect of the Alkyl Group in the Organolithium Compound on the Lithiation of N-Alkylpyrroles.*—The yields of lithiopyrroles obtained when Bu^{n}Li and Bu^{t}Li were used under the same reaction conditions [experiments (vi) and (xv)] illustrate that Bu^{t}Li is the more effective metallating agent, which is in agreement with previous work on the metallation of dibenzofuran [16] and triphenylmethane.[17] This may be due either to the

TABLE 1

Reactions with N-alkylpyrroles

Expt. no.	C$_4$H$_4$NR [a]	BuLi (n = normal, t = tertiary)	Solvent [b]	BuLi : C$_4$H$_4$NR (n : 1)	Complexing agent [c]	Temp. (°C or Re = reflux, Am = ambient)	Time (h)	Mono-ester	Di-esters 2,4	Di-esters 2,5	Total	[Di]/[Mono]	[2,4]/[2,5]
1 (i)	Me	n	1	1	X	Re	3	3	17	10	30	9	1.7
2 (i)	Et	n	1	1	X	Re	3	1	12	1	14	13	12.0
3 (i)	Bu^n	n	1	1	X	Re	3	1	11	1	13	12	11.0
4 (i)	Pr^i	n	1	1	X	Re	3	0.7	7	0.4	8	10	17.5
5 (i)	Bu^t	n	1	1	X	Re	3	0.5	5	0.5	6	11	10.0
6 (i)	Ad	n	1	1	X	Re	3	0	5	0	5	L	L
1 (ii)	Me	n	1	2.5	A	Am	0.5	91	0	0	91	0	0
2 (ii)	Et	n	1	2.5	A	Am	0.5	77	0	0	77	0	0
3 (ii)	Bu^n	n	1	2.5	A	Am	0.5	85	0	0	85	0	0
4 (ii)	Pr^i	n	1	2.5	A	Am	0.5	87	0	0	87	0	0
5 (ii)	Bu^t	n	1	2.5	A	Am	0.5	88	0	0	88	0	0
6 (ii)	Ad	n	1	2.5	A	Am	0.5	0	0	0	0	0	0
1 (iii)	Me	n	1	2.5	A	Re	0.5	37	5	46	88	1.38	0.11
2 (iii)	Et	n	1	2.5	A	Re	0.5	32	5	50	87	1.72	0.10
3 (iii)	Bu^n	n	1	2.5	A	Re	0.5	31	6	51	88	1.84	0.12
4 (iii)	Pr^i	n	1	2.5	A	Re	0.5	52	3	26	81	0.56	0.12
5 (iii)	Bu^t	n	1	2.5	A	Re	0.5	50	3	16	69	0.38	0.19
6 (iii)	Ad	n	1	2.5	A	Re	0.5	0	3	9	12	L	0.33
1 (iv)	Me	n	1	4.5	A	Re	3	0	0	95	95	L	0
2 (iv)	Et	n	1	4.5	A	Re	3	3	6	72	81	26.0	0.08
3 (iv)	Bu^n	n	1	4.5	A	Re	3	4	7	70	81	19.3	0.10
4 (iv)	Pr^i	n	1	4.5	A	Re	3	5	4	64	73	13.6	0.06
5 (iv)	Bu^t	n	1	4.5	A	Re	3	9	8	52	69	6.7	0.15
6 (iv)	Ad	n	1	4.5	A	Re	3	0	10	52	62	L	0.16
1 (v)	Me	n	2	1	X	Re	3	50	0.2	5	55	0.10	0.04
2 (v)	Et	n	2	1	X	Re	3	26	2	9	37	0.42	0.22
4 (v)	Pr^i	n	2	1	X	Re	3	27	3	6	36	0.33	0.50
5 (v)	Bu^t	n	2	1	X	Re	3	1	0	2	3	2.00	0
1 (vi)	Me	n	1	1	X	36	3	1	0	0	1	0	0
1 (vii)	Me	n	2	1	X	Am	1	9	0	0	9	0	0
1 (viii)	Me	n	3	1	X	Am	1	16	0	0	16	0	0
1 (ix)	Me	n	4	1	X	Am	1	36	0	0	36	0	0
1 (x)	Me	n	5	1	X	Am	1	57	0	0	57	0	0
1 (xi)	Me	n	6	1	X	Am	1	48	0	0	48	0	0
1 (xii)	Me	n	7	1	X	Am	1	24	0	0	24	0	0
1 (xiii)	Me	n	7	1	X	36	3	50	0	0	50	0	0
1 (xiv)	Me	n	7	1	X	91	3	43	0	7	50	0.16	0
1 (xv)	Me	t	8	1	X	Re	3	3	1	3	7	1.33	0.33
5 (xvi)	Bu^t	t	8	2.5	A	Am	0.5	24	2	3	38 f	0.27	0.66
1 (xvii)	Me	n	1	2.5	B	Re	0.5	61	0	3	64	0.05	0
1 (xviii)	Me	n	1	2.5	C	Re	0.5	35	0	0	35	0	0
1 (xix)	Me	n	1	2.5	D	Re	0.5	12	12	16	40	2.33	0.75
1 (xx)	Me	n	1	4.5	D	Re	3	5	13	34	52	9.40	0.38

[a] Ad = adamantyl. [b] Solvents 1, hexane; 2, ether; 3, ether–THF (4 : 1); 4, Trapp's solvent; 5, THF; 6, 2-methyltetrahydrofuran; 7, 2,5-dimethyltetrahydrofuran; 8, pentane. [c] The presence (in 1 : 1 molar ratio with BuLi) of complexing agent is denoted by an alphabetical label. A is TMEDA, B is DABCO, C is TMTATD, D is TDMAP. X represents the absence of complexing agent. [d] Mole % yields are based on the initial amount of N-alkylpyrrole present and are quoted to the nearest integer except when yields were less than 1%. [e] L represents a large (>50) mole ratio. [f] 3-Monoester (6%) and 2,3-diester (3%) were also formed.

greater basicity of the t-butyl carbanion or to the inherently different oligomeric structures of the two organolithium compounds (Bu^{t}Li is a tetramer in hydrocarbon solvents).

TABLE 2

New compounds

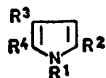| R^1	R^2	R^3	R^4	M.p. [B.p. (bath temp.] (°C)	Analytical figures (%)		C	H	N	N.m.r. (τ values) ^{a}	Abundance (%) of M^+
Et	CO$_2$Me	H	H	[40—42 (0.5 mmHg)]	Found C$_8$H$_{11}$NO$_2$ requires		62.9 62.7	7.2 7.2	8.9 9.1	3.12 (dd, J 2.0 and 4.0, 3-H) 3.22 (dd, J 2.0 and 3.1, 5-H) 3.97 (dd, J 3.1 and 4.0, 4-H) 5.71 (q, NCH$_2$) 6.27 (s, OCH$_3$) 8.68 (t, CCH$_3$)	100
Et	CO$_2$Me	CO$_2$Me	H	62—64	Found C$_{10}$H$_{13}$NO$_4$ requires		57.1 56.9	6.2 6.2	6.6 6.6	2.52 (d, J 1.8, 5-H) 2.78 (d, J 1.8, 3-H) 5.64 (q, NCH$_2$) 6.21 (s, OCH$_3$) 6.23 (s, OCH$_3$) 8.62 (t, CCH$_3$)	53
Et	CO$_2$Me	H	CO$_2$Me	46—48	Found C$_{10}$H$_{13}$NO$_4$ requires		57.0 56.9	6.1 6.2	6.6 6.6	3.22 (s, 3- and 4-H) 5.17 (q, NCH$_2$) 6.18 (s, OCH$_3$) 8.64 (t, CCH$_3$)	100
Bu^n	CO$_2$Me	H	H	[103—105 (2 mmHg)]	Found C$_{10}$H$_{15}$NO$_2$ requires		65.8 66.3	8.1 8.3	7.5 7.7	3.07 (dd, J 1.8 and 4.0, 3-H) 3.18 (dd, J 1.8 and 2.6, 5-H) 3.90 (dd, J 2.6 and 4.0, 4-H) 5.68 (t, NCH$_2$) 6.20 (s, OCH$_3$) 8.23 (m, NCH$_2$CH_2) 8.71 (m, NC$_2$H$_4$CH_2) 9.08 (t, NC$_3$H$_6$CH_3)	45
Bu^n	CO$_2$Me	CO$_2$Me	H	49—50	Found C$_{12}$H$_{17}$NO$_4$ requires		60.4 60.2	7.2 7.2	5.7 5.85	2.55 (d, J 1.8, 5-H) 2.72 (d, J 1.8, 3-H) 5.68 (t, NCH$_2$) 6.19 (s, OCH$_3$) 6.19 (s, OCH$_3$) 8.26 (m, NCH$_2$CH_2) 8.71 (m, NC$_2$H$_4$CH_2) 9.07 (t, NC$_3$H$_6$CH_3)	26
Bu^n	CO$_2$Me	H	CO$_2$Me	23—25	Found C$_{12}$H$_{17}$NO$_4$ requires		60.5 60.2	7.2 7.2	5.9 5.85	3.14 (s, 3- and 4-H) 5.15 (t, NCH$_2$) 6.14 (s, OCH$_3$) 8.24 (m, NCH$_2$CH_2) 8.60 (m, NC$_2$H$_4$CH_2) 9.05 (t, NC$_3$H$_6$CH_3)	33
Pr^i	CO$_2$Me	H	H	[80—82 (14 mmHg)]	Found C$_9$H$_{13}$NO$_2$ requires		64.35 64.65	8.0 7.8	8.1 8.4	2.98 (dd, J 1.9 and 2.8, 5-H) 3.05 (dd, J 1.9 and 4.0, 3-H) 3.86 (dd, J 2.8 and 4.0, 4-H) 4.53 (septet, CH) 6.19 (s, OCH$_3$) 8.57 (d, CCH$_3$)	49

TABLE 2 *(Continued)*

R¹	R²	R³	R⁴	M.p. [B.p. bath temp.] (°C)	Analytical figures (%)		C	H	N	N.m.r. (τ values) [a]	Abundance (%) of M^+
Prⁱ	CO₂Me	CO₂Me	H	72—74	Found		58.8	6.65	6.3	2.34 (d, J 1.8, 5-H)	51
					C₁₁H₁₅NO₄ requires		58.65	6.7	6.2	2.68 (d, J 1.8, 3-H)	
										4.55 (septet, CH)	
										6.20 (s, OCH₃)	
										6.22 (s, OCH₃)	
										8.54 (d, CCH₃)	
Prⁱ	CO₂Me	H	CO₂Me	53—55	Found		58.8	6.7	6.15	3.14 (s, 3- and 4-H)	21
					C₁₁H₁₅NO₄ requires		58.65	6.7	6.2	4.15 (septet, CH)	
										6.15 (s, OCH₃)	
										8.40 (d, CCH₃)	
Buᵗ	CO₂Me	H	H	[122—124 (11 mmHg)]	Found		66.5	8.4	7.9	2.90 (dd, J 2.0 and 3.6, 3-H)	22
					C₁₀H₁₅NO₂ requires		66.3	8.3	7.7	2.91 (dd, J 2.0 and 3.1, 5-H)	
										3.98 (dd, J 3.1 and 3.6, 4-H)	
										6.21 (s, OCH₃)	
										8.28 (s, CCH₃)	
Buᵗ	H	CO₂Me	H	41—43	*b*					2.54 (dd, J 1.8 and 2.4, 2-H)	34 [c]
										3.24 (dd, J 2.4 and 3.0, 5-H)	
										3.43 (dd, J 1.8 and 3.0, 4-H)	
										6.22 (s, OCH₃)	
										8.48 (s, CCH₃)	
Buᵗ	H	CO₂Me	CO₂Me	*d*	*b*					3.22 (dd, J 3.2, 5-H)	27 [e]
										3.52 (dd, J 3.2, 4-H)	
										6.10 (s, OCH₃)	
										6.23 (s, OCH₃)	
										8.41 (s, CCH₃)	
Buᵗ	CO₂Me	CO₂Me	H	117—119	Found		60.2	7.1	5.8	2.30 (d, J 1.8, 5-H)	13
					C₁₂H₁₇NO₄ requires		60.2	7.2	5.85	2.48 (d, J 1.8, 3-H)	
										6.17 (s, OCH₃)	
										6.17 (s, OCH₃)	
										8.26 (s, CCH₃)	
Buᵗ	CO₂Me	H	CO₂Me	36—38	Found		60.5	7.3	5.9	3.44 (s, 3- and 4-H)	4
					C₁₂H₁₇NO₄ requires		60.2	7.2	5.85	6.24 (s, OCH₃)	
										8.29 (s, CCH₃)	
Ad	H	H	H	95—97	Found		83.5	9.5	7.0	3.14 (pseudo-t, 2- and 5-H)	55
					C₁₄H₁₉N requires		83.5	9.5	7.0	3.85 (pseudo-t, 3- and 4H)	
										7.79—8.24 (m, C₁₀H₁₅)	
Ad	CO₂Me	CO₂Me	H	88—90	Found		68.2	7.3	4.2	2.27 (d, J 1.9, 5-H)	12
					C₁₈H₂₃NO₄ requires		68.1	7.3	4.4	2.49 (d, J 1.9, 3-H)	
										6.19 (s, OCH₃)	
										6.19 (s, OCH₃)	
										7.75—8.23 (m, C₁₀H₁₅)	
Ad	CO₂Me	H	CO₂Me	132—133	Found		68.1	7.3	4.5	3.35 (s, 3- and 5-H)	11
					C₁₈H₂₃NO₄ requires		68.1	7.3	4.4	6.15 (s, OCH₃)	
										7.56—8.30 (m, C₁₀H₁₅)	

[a] Recorded on dilute solutions in CDCl₃ (100% D) at 90 MHz with Me₄Si as internal standard (J in Hz). [b] Sample purified by g.l.c.; insufficient material for microanalysis. [c] m/e 181.1102 (M^+; C₁₀H₁₅NO₂ requires m/e 181.1103). [d] Insufficient material for b.p. measurement. [e] m/e 239.1157 (M^+; C₁₂H₁₇NO₄ requires m/e 239.1157).

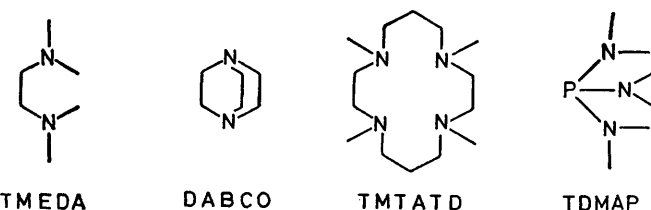The reaction between *N*-t-butylpyrrole and BuᵗLi under relatively mild conditions [experiment 5(xvi)] gave a mixture of five esters, including the previously un- observed 3-mono- and 2,3-di-esters. The formation of the 3-lithiated compounds may be solely a consequence of the steric bulk of the organolithium reagent; their

presence in the product mixture suggests that the postulated system of reactions for N-alkylpyrrole metallation [4] may be more complicated than at first thought.

(d) *Effect of Complexing Agent on the Lithiation of* N-*Methylpyrrole.*—Experiments 1(iii) and 1(xvii)—(xx) demonstrate the role of complexing agents in the lithiation of N-methylpyrrole.

The total yields obtained with TMEDA [experiment 1(iii)] and diazabicyclo[2.2.2]octane [DABCO, experi-

TMEDA   DABCO   TMTATD   TDMAP

ment 1(xvii)] compare favourably with previous work in which the order of reactivity for metallation of benzene in the presence of tertiary amines was shown [18] to be TMEDA > $NNN'N'$-tetramethylpropane-1,2-diamine > DABCO and 2-methyltriethylenediamine > $NNN'N'$-tetramethylbutane-1,4-diamine $\gg$ $NNN'N'$-tetramethylmethylenediamine and N,N'-dimethylpiperazine.

1,4,8,11-Tetramethyl-1,4,8,11-tetra-azacyclotetradecane (TMTATD) readily forms complexes with Ni^{2+} and Cu^{2+} cations.[19] As these cations and Li^+ are of roughly comparable size it might be expected that strong complexation of an alkyl-lithium would occur. Use of this complexing agent in the metallation procedure [experiment 1(xviii)] gave a relatively low yield of monolithioproduct (35%). This may be due either to weak coordination (resulting in reduced reaction rate) or to strong complexation leading to metallation of the chelate.

Results of experiments with tris(dimethylamino)phosphine (TDMAP) [1(xix) and 1(xx)] show that it is not as effective a complexing agent as DABCO or TMEDA.

EXPERIMENTAL

The method of Elming and Clauson-Kaas [20] (reaction between a primary amine and 2,5-dimethoxy-THF in the presence of glacial acetic acid) was used, with minor modifications, for the preparation of the N-alkylpyrroles required in the present study. Ethereal solutions of Bu^nLi were prepared at $-70°$ by the slow addition of ethereal solvent to hexane-free Bu^nLi (the solvent was removed from commercially available hydrocarbon solutions by gentle distillation *in vacuo*). General procedures (preparation of heterocyclic lithio-derivatives, carboxylic acids, and methyl esters) are given in an earlier paper.[4] The experimental results are given in Table 1 and physical data for new compounds are summarised in Table 2.

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