Regioselective β-Metallations of 2-Substituted Furan and *N*-Methylpyrrole Derivatives Employing the Directing Effect of the Oxazolino Group: Syntheses of 2,3-Disubstituted Furans and *N*-Methylpyrroles

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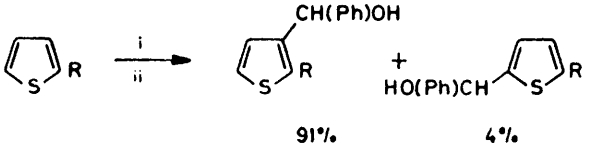
The effects of change of solvent and reaction time, of addition of Li^+-chelating agent, and, in some instances, of change of temperature and metallating agent, on the metallation of 2-(2-furyl)- and 2-(*N*-methylpyrrol-2-yl)-oxazolines by alkyl-lithium reagents are explored. Conditions are thereby established for high-yielding syntheses of lithio-intermediates and for control of regioselectivity of metallation. Syntheses of pure samples of 2-(3-hydroxyphenylmethyl-2-furyl)-, 2-(5-hydroxyphenylmethyl-2-furyl)-, 2-(3-carboxy-*N*-methylpyrrol-2-yl)- and 2-(5-carboxy-*N*-methylpyrrol-2-yl)-4,4-dimethyloxazolines, based on the results of these investigations, are reported.

FURAN, thiophen, and *N*-alkylpyrroles undergo electrophilic substitution and metallation predominantly at α-positions. This reactivity pattern makes the syntheses of the β-substituted derivatives a challenging problem and any new methodology in this connection is therefore valuable. The bias towards α-electrophilic substitution may sometimes be overcome by the introduction of an electron-withdrawing group at one α-position:[1] 2,4-disubstituted derivatives have been prepared by this approach, in favourable cases, but regioselectivity is frequently poor. A second strategy, applicable to pyrroles, requires the use of a bulky *N*-substituent to restrict access to the α-positions: success is achievable, but only with very large substituents (*e.g.* t-butyl) and large electrophiles as in the Vilsmeier reaction.[2] In 1977, Vecchia and Vlattas[3] recognised that the oxazolino group at an α-position in thiophen could be used to direct metallation into the adjacent β-position with high regioselectivity (Scheme 1) thus providing a new route



R = 4,4-dimethyloxazolin-2-yl

SCHEME 1 Vlattas' procedure with the 2-(2-thienyl)oxazoline *Reagents:* i, Bu^nLi, Et_2O, −70—25 °C; ii, PhCHO

to the particularly awkward 2,3-disubstitution pattern. This observation prompted us to explore, as part of our continuing interest in the metallation of furans, thiophens and pyrroles,[4] whether this useful technique could be applied to the 2-(2-furyl) -(1) and 2-(*N*-methylpyrrol-2-yl)-oxazolines (2).

More recently, after the commencement of this work, Vlattas recorded (in a personal communication to a reviewer[5]) a disappointing lack of regioselectivity in the furan case having obtained a 3 : 5 metallation ratio of only 1.4 : 1. In the results presented below, we show that this ratio can be improved to 9.5 : 1 by judicious choice of reaction solvent (and investigate generally the effects of solvent and added Li^+-chelating agent on the course of the reaction).[6] We further demonstrate that high β-selectivity is attainable in the analogous *N*-methylpyrrole derivative (2) although somewhat at the expense of high yields.

(1) (2)

R = 4,4-dimethyloxazolin-2-yl

RESULTS AND DISCUSSION

(*a*) 2-(2-*Furyl*)*oxazoline* (1).—In Table 1 are summarised the results of a range of experiments in which the extent and position of metallation of the oxazoline (1) with n-butyl-lithium, in a range of solvents and for various reaction times and temperatures, have been studied. Proportions of α- and β-metallo-intermediates were deduced *via* work-up with D_2O and integration of n.m.r. ring proton resonances. Most reactions are essentially complete within 15 min and yields approach the quantitative in the majority of cases.

The solvent and reaction conditions of experiment (i) are those which Vecchia and Vlattas used to obtain high β-regioselectivity in 2-(2-thienyl)oxazoline: however, in the furan case α-metallation is preferred. Further, in close agreement with Vlattas' later work (*vide supra*), we find that a change of solvent to THF and a reduction in reaction temperature [experiment (vii)] lead to only modest β-selectivity. The use of hexane as solvent is especially disadvantageous for β-metallation [experiment (v)] and addition of TMEDA, whilst diminishing the α-selectivity in this case [experiment (vi)] actually works in the opposite sense when THF is the solvent [experiment (ix)]. A change of solvent to DME leads to a dramatic change in the pattern of selectivity with β-metallation strongly preferred [experiment (x)]. Although reaction temperature and time have some influence on the product ratio they are variables of comparatively minor importance.

TABLE 1

Metallation and deuteriation of 2-(2-furyl)oxazoline (1)

Experiment	Reaction conditions [a] Solvent	Temp. (°C)	Lithiation time (h)	Product ratio α : β	Yield (%)
(i)	Ether	0	0.75 [b]	3 : 1	83
(ii)	Ether	−78	0.25	1 : 1	100
(iii)	Ether	−78	1.0	1.5 : 1	91
(iv)	Ether	−97	0.25	1 : 1	94
(v)	Hexane	−78	0.25	4.5 : 1	73
(vi)	Hexane–TMEDA [c]	−78	0.25	2.5 : 1	93
(vii)	THF [d]	−78	0.25	1 : 1.5	95
(viii)	THF	−97	1.0	1 : 1.5	94
(ix)	THF–TMEDA [c]	−78	0.25	1.5 : 1	92
(x)	DME [e]	−78	0.25	1 : 9.5	100

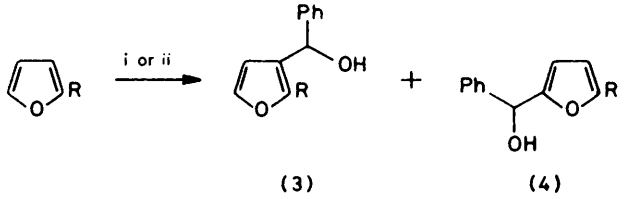
[a] Compound (1) and Bu^nLi were used in equimolar amounts. [b] 0.25 h at −78 °C and 0.5 h at 0 °C. [c] One molar equivalent of *NNN'N'*-tetramethylethylenediamine (TMEDA) with respect to Bu^nLi was used. [d] Tetrahydrofuran. [e] 1,2-Dimethoxyethane.

It is striking that whereas Vlattas found, in the thiophen case, that the use of ether as the solvent favours β-metallation and THF α-metallation, the reverse seems to be true for the analogous furan.

In order to achieve appreciable β-metallation of compound (1), co-ordination of the alkyl-lithium with the oxazoline (probably *via* the nitrogen lone-pair) prior to abstraction of an adjacent hydrogen atom is presumably necessary.[7] Such co-ordination would be expected to lead to partial or complete dissociation of the alkyl-lithium oligomer: a solvent which assists this dissociation should therefore aid β-metallation. This argument is supported by our results of lithiations in various solvents: increasing β-selectivity occurs in the order hexane < ether < THF < DME which is probably also the order of increasing Li^+-complexing ability and hence of 'de-oligomerisation.' It is at first sight surprising, therefore, that a reaction conducted in THF–TMEDA [experiment (ix)] shows poorer β-selectivity than a similar reaction in the absence of TMEDA [experiment (vii)], in view of the latter's powerful Li^+-complexing ability. Presumably, if an added ligating agent (or solvent) competes too successfully for an alkyl-lithium molecule, complex formation with the oxazoline moiety becomes less favourable and β-selectivity is reduced.

The synthetical utility of this approach to the control of regioselectivity is illustrated by the results of the reactions shown in Scheme 2 in which D_2O is replaced by benzaldehyde as electrophile. In each case, total yields approach the quantitative and the major regioisomer may be separated from the minor contaminant by simple recrystallisation.

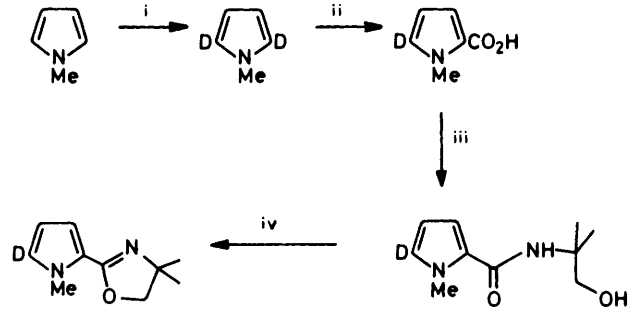
(*b*) 2-(N-*Methylpyrrol-2-yl*)*oxazoline* (2).—In Table 2 are presented, in a similar fashion to Table 1, the results of metallation and deuteriation studies on the pyrrolyl-oxazoline (2). Unfortunately, the n.m.r. ring proton resonances due to H-3 and H-5 (on which reliance is placed for the α : β product ratio determination) are almost coincident. In all the entries in Table 2, therefore, these signals were first resolved by the addition of a small amount of the lanthanide shift reagent $Eu(fod)_3$. Although experience tells us that the resonance due to H-3 should show the greater paramagnetic shift, our assignment was confirmed by an unambiguous synthesis of the 5-deuteriated oxazoline based on our earlier work on the mono- and 2,5-di-lithiation of *N*-methylpyrrole [2d] (Scheme 3).



SCHEME 2 Syntheses of (hydroxyphenylmethyl-2-furyl)-oxazolines

Reagents and yields: i, Bu^nLi, Et_2O, 0.25 h at −78 °C and 0.5 h at 0 °C, then PhCHO gives (3), 21%, and (4), 74%; and ii, Bu^nLi, DME, 0.25 h at −78 °C, then PhCHO gives (3), 87%, and (4), 9%.

The experimental conditions outlined in Table 2 represent a compromise between those previously established [2d] for high-yielding metallation of *N*-methylpyrrole (involving temperatures of ambient or above) and the constraints imposed by the presence of imine functionality in the oxazoline substrate. Thus, reactions conducted at temperatures above 0 °C lead increasingly to complex product mixtures perhaps arising



SCHEME 3 Synthesis of 2-(*N*-methyl-5-deuteriopyrrol-2-yl)-oxazoline

Reagents: i, Bu^nLi (3.5 molar excess), hexane–TMEDA, 3 h, reflux, then D_2O; ii, Bu^nLi (1.5 molar excess), hexane–TMEDA, 0.5 h, 25 °C, then CO_2 and aqueous HCl; iii, Na-salt and $(COCl)_2$, then $H_2NCMe_2CH_2OH$; and iv, $SOCl_2$.

TABLE 2

Metallation and deuteriation of the 2-pyrrolyloxazoline (2)

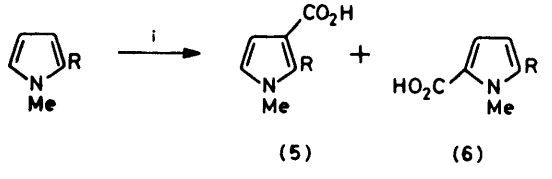
Experiment	RLi, R= [a]	Ratio RLi : (2)	Solvent	TMEDA [b]	Temp. (°C)	Time (h)	Product ratio [c] α : β	Yield (%)
(i)	Bu^n	1 [d]	Ether	×	0 [e,f]	0.5	No reaction	0
(ii)	Bu^n	1	Ether	√	0	0.67	1.8 : 1	100
(iii)	Bu^n	1	DME	×	−78	0.5	1 : 2.0	16
(iv)	Bu^n	1	DME	×	−78	2.0	1 : 2.1	42
(v)	Bu^n	1	DME	×	0	0.5	1 : 2.7	65 [g]
(vi)	Bu^n	2	DME	×	0	0.5	1 : 2.2	95
(vii)	Bu^n	2	DME	×	0	2.75	1 : 2.1	100
(viii)	Bu^n	1	DME	√	0	0.5	1 : 1.4	59
(ix)	Bu^n	1	DME	√	0	4.0	1 : 5.0	11
(x)	Bu^n (D)	2	DME	×	0	0.58	1 : 2.3	73
(xi)	Bu^n (D)	2	DME	×	0	4.0	1 : 15	46
(xii)	Bu^n	1	THF	×	0	0.5	1.5 : 1	100
(xiii)	Bu^n	1	THF	√	0	0.5	2.1 : 1	100
(xiv)	Bu^n	1	Hexane	√	0	0.5	1 : 1.1	94
(xv)	Bu^n	1	Hexane	√	0	4.0	1 : 1.6	100
(xvi)	Bu^t (P)	1	DME	×	−60 [h]	0.5	1.3 : 1	43
					−40 [i]	0.5	1 : 1.6	42
(xvii)	Me (E)	1	DME	×	0	4.0 [j]	Only β	15
(xviii)	Me (D)	4	DME	×	0 [h]	4.0 [j]	1 : 1.7	51
					25	0.5	1 : 1.8	70

[a] RLi as a solution in hexane except where indicated by (D) DME, (P) pentane, and (E) diethyl ether. [b] X means TMEDA absent, √ means TMEDA present in equimolar ratio with respect to RLi. [c] Determined with respect to the n.m.r. pyrrole ring H-4 integral. [d] A ' 1 ' in this column in fact implies a ratio of approximately 1.1 : 1. [e] No reaction was observed in a similar experiment at −78 °C. [f] Decomposition was observed in a similar experiment at 25 °C. [g] No significant improvement in yield was observed when the reaction time was extended to 4 h. [h] The second entry in these cases implies the same reaction mixture was used in a continuing experiment at the higher temperature. [i] Decomposition was observed to occur at −20 °C. [j] No reaction was detected after 0.5 h.

from nucleophilic attack at the imine carbon atom and subsequent oxazoline ring opening; extension of reaction time beyond 4 h at 0 °C also generally seems disadvantageous owing to side-product formation.

As in the analogous furan, regioselectivity is profoundly solvent dependent. However, it is not possible to make the straightforward comparison of Table 1 because reactions carried out with hexane or ether as solvent, in the absence of TMEDA, give only minimal yields. Once again, DME seems to be the solvent of choice, although high β-selectivity can only be achieved at the cost of lowered yields [experiments (xi) and (xvii)].

In order to explore the synthetical utility of these reactions, D_2O was replaced by CO_2 as electrophile in a reaction based on the high-yielding experiment (vi) (Scheme 4). Separation of the regioisomers proved



R = 4,4-dimethyloxazolin-2-yl

SCHEME 4 Synthesis of (carboxy-*N*-methylpyrrol-2-yl)-oxazolines

Reagents and yields: i, Bu^nLi (1 molar excess), DME, 0 °C, 1 h, then CO_2 followed by aqueous HCl gives (5) 56% and (6) 9%.

straightforward since the 3-acid (5) is soluble in, and extracts into, chloroform whereas isolation of the 5-acid (6) requires ethyl acetate extraction. One recrystallisation, in each case, gave material of analytical purity and free from the other isomer as judged by ^1H n.m.r. spectroscopy. That the products were isolated in only moderate yields is probably due to their generally rather low solubility in organic solvents and apparently appreciable solubility in water.

EXPERIMENTAL

Tables 1 and 2 summarise the experimental results. General procedures for the preparation of heterocyclic lithio-derivatives and their carboxylation have been published previously.[4] ^1H N.m.r. spectra were recorded on P.E. R12 (60 MHz) and R34 (220 MHz) instruments, and mass spectra on an A.E.I. MS-902. Melting-points are corrected. Throughout, ether refers to diethyl ether.

Preparation of the Furan Oxazoline (1).—Meyers' general approach to oxazoline synthesis was followed.[8] Commercial furan-2-carboxylic acid (20 g, 0.18 mol) and thionyl chloride (43 g, 0.36 mol) (freshly-distilled from quinoline) were boiled under reflux for 0.5 h. The excess of thionyl chloride was removed by distillation and the residue distilled *in vacuo* (75 °C, 15 mmHg) to give the acid chloride (23 g, 82%) as a colourless liquid.

A solution of commercial 2-amino-2-methylpropan-1-ol (30.3 g, 0.34 mol) in dichloromethane (124 ml) was added dropwise to a solution of the acid chloride (22.2 g, 0.17 mol) in dichloromethane (45 ml), with the reaction temperature held below 20 °C. The mixture was stirred for 2 h, washed (H_2O), dried ($MgSO_4$) and evaporated, giving the crude amide, *N*-(1,1-dimethyl-2-hydroxyethyl)furan-2-carboxamide, as a colourless, viscous oil which was used without further purification. δ ($CDCl_3$) 1.34 (6 H, s, CH_3), 3.63 (2 H, s, OCH_2), 6.45 (1 H, dd, *J* 1.8 and 3.6 Hz, furan H-4), 7.05 (1 H, dd, *J* 1.0 and 3.6 Hz, furan H-3) and 7.39 (1 H, dd, *J* 0.8 and 1.8 Hz, furan H-5).

The amide (18 g, 0.098 mol) was suspended in benzene (120 ml) and thionyl chloride (47 g, 0.39 mol) was added dropwise with stirring, with the reaction temperature held

below 30 °C. Stirring was continued for 12 h at 25 °C, the benzene then removed by distillation and the residue taken up into water (60 ml). The solution was basified (1M NaOH solution; *ca.* 100 ml) and the product extracted with ether. The combined extracts were washed (H_2O), dried ($MgSO_4$), and the solvent removed to leave the crude product as a yellow oil; this was distilled (69 °C, 13 mmHg) to give 4,4-*dimethyl*-2-(2-*furyl*)*oxazoline* (1) (12.3 g, 76%) as a colourless, waxy solid, m.p. 36.5—37.5 °C (Found: C, 65.2; H, 6.6; N, 8.6. $C_9H_{11}NO_2$ requires C, 65.44; H, 6.71; N, 8.48%), δ ($CDCl_3$) 1.36 (6 H, s, CH_3), 4.09 (2 H, s, OCH_2), 6.46 (1 H, dd, *J* 1.8 and 3.5 Hz, furan H-4), 6.92 (1 H, dd, *J* 0.7 and 3.5 Hz, furan H-3), and 7.52 (1 H, dd, *J* 0.7 and 1.8 Hz, furan H-5); *m/z* 165 (M^+, 24%) and 150 (100).

2-(5-*Hydroxyphenylmethyl*-2-*furyl*)-4,4-*dimethyloxazoline* (4).—The oxazoline (1) (1 g, 6.06 mmol) was dissolved in dry ether (25 ml) and n-butyl-lithium in hexane (6.06 mmol) was added dropwise, with stirring, under nitrogen at −78 °C. The mixture was stirred at −78 °C for 15 min and at 0 °C for 30 min, after which benzaldehyde (0.64 g, 6.1 mmol) was added and the whole was allowed to warm to room temperature and then poured into water. Extraction (Et_2O), washing of the extracts (H_2O), drying ($MgSO_4$), and evaporation gave a white solid which on recrystallisation from hexane afforded the 5-*substituted oxazoline* (4) (1.2 g, 74%), m.p. 118.5—119.5 °C (Found: C, 70.8; H, 6.3. $C_{16}H_{17}NO_3$ requires C, 70.83; H, 6.32%), δ ($CDCl_3$) 1.31 (6 H, s, CH_3), 3.58 (1 H, broad s, OH) 4.04 (2 H, s, OCH_2), 5.93 (1 H, s, PhC*H*), 6.10 (1 H, d, *J* 2.9 Hz, furan H-4), 6.83 (1 H, d, *J* 3.6 Hz, furan H-3), and *ca.* 7.35 (5 H, m, phenyl-H's); *m/z* 271 (M^+, 33%) and 256 (100).

2-(3-*Hydroxyphenylmethyl*-2-*furyl*)-4,4-*dimethyloxazoline* (3).—The oxazoline (1) (1 g, 6.06 mmol) was dissolved in dry DME (25 ml) and n-butyl-lithium in hexane (6.06 mmol) was added dropwise, with stirring, under nitrogen at −78 °C. The mixture was stirred at −78 °C for 15 min then benzaldehyde (0.64 g, 6.06 mmol) was added and the whole worked up as above to yield a colourless oil which was recrystallised at low temperature from hexane; this gave the 3-substituted oxazoline (3) (1.4 g, 87%) as a colourless oil, δ ($CDCl_3$) 1.29 and 1.33 (6 H, 2s, 2 × CH_3), 4.08 (2 H, s, OCH_2), 5.83 (1 H, s, PhC*H*), 6.09 (1 H, d, *J* 1.9 Hz, furan H-4), and *ca.* 7.32 (m, phenyl H's and furan H-5); *m/z* 271 (M^+ 100%) and 199 (94).

Preparation of the N-*Methylpyrrolyloxazoline* (2).—Sodium hydride (80%; 2.1 g, 70 mmol) was stirred for 10 min with commercial *N*-methylpyrrole-2-carboxylic acid (3.83 g, 30.6 mmol) in benzene (150 ml). Oxalyl chloride (10 ml, 115 mmol) was added and the mixture boiled under reflux for 15 min. After evaporation of the excess of oxalyl chloride and benzene, dry ether (150 ml) was added, followed by a solution of commercial 2-amino-2-methylpropan-1-ol (5.75 g, 64.5 mmol) in ether (20 ml) dropwise during 10 min. The mixture was stirred for 15 min and then boiled under reflux for 2 h. The mixture was washed (H_2O), dried ($MgSO_4$), and evaporated to yield crude (*N*-1,1-dimethyl-2-hydroxyethyl)-*N*-methylpyrrole-2-carboxamide as a yellow solid. A further sample of the amide was obtained by extraction of the aqueous washings with chloroform, giving, *in toto*, 5.69 g (95%) of product, m.p. 89—91 °C, which was used without further purification. A sample for analysis was recrystallised as flakes from $CHCl_3/C_6H_{14}/Et_2O$ affording the pure amide, m.p. 91—92 °C (Found: C, 60.9; H,8.3; N, 14.2. $C_{10}H_{16}N_2O_2$ requires C, 61.20; H, 8.22; N, 14.28%); δ ($CDCl_3$) 1.37 (6 H, s, CH_3), 3.66 (2 H, s, OCH_2), 3.94 (3 H, s, N-CH_3), 5.23 (1 H, broad s, OH), 6.05 (1 H, broad s, NH), 6.10 (1 H, dd, *J* 2.7 and 3.8 Hz, pyrrole H-4), 6.55 (1 H, dd, *J* 1.7 and 3.8 Hz, pyrrole H-3) and 6.74 (1 H, dd, *J* 1.7 and 2.7 Hz, pyrrole H-5); *m/z* 196 (M^+, 18%) and 108 (100).

The amide (1.5 g, 7.7 mmol) was suspended in benzene (60 ml) and thionyl chloride (5 ml, 69 mmol) was added dropwise, with stirring, whilst the reaction temperature was held below 25 °C. Stirring was continued for 16 h at 25 °C after which time benzene and the excess of thionyl chloride were removed by distillation to yield a solid; sodium hydrogencarbonate (3 g) and water (10 ml) were added to this. Extraction with ether afforded the crude product as a yellow oil which was distilled to give 4,4-*dimethyl*-2-(N-*methylpyrrol*-2-*yl*)*oxazoline* (2) (1.3 g, 95%) as a colourless oil, b.p. 55 °C at 0.3 mmHg (Found: C, 67.4; H, 8.3; N, 15.9. $C_{10}H_{14}N_2O$ requires C, 67.38; H, 7.92; N, 15.72%), δ ($CDCl_3$) 1.32 (6 H, s, CH_3), 3.93 (3 H, s, N-CH_3), 3.95 (2 H, s, OCH_2), 6.12 (1 H, dd, *J* 2.4 and 3.8 Hz, pyrrole H-4), and 6.73 (2 H, m, pyrrole H-3 and H-5); *m/z* 178 (M^+, 27%) and 135 (100).

Carboxylation of 4,4-*Dimethyl*-2-(N-*methylpyrrol*-2-*yl*)*oxazoline*.—The oxazoline (2) (0.85 g, 4.8 mmol) in dry DME (8 ml) was cooled to −78 °C and n-butyl-lithium in hexane (9.5 mmol) was added with stirring under nitrogen. The mixture was stirred at 0 °C for 1 h and then poured into a slurry of solid carbon dioxide–ether. The lithium salts were taken up into water (20 ml) and separated from the residual hexane which was extracted with water (2 × 10 ml). The combined aqueous solutions were washed with ether (3 × 30 ml), acidified to pH 2 with 2M aqueous hydrochloric acid and extracted with chloroform (9 × 30 ml). Drying ($MgSO_4$) and removal of solvent gave a solid which recrystallised as rods from chloroform–hexane to yield the 3-*carboxylated pyrrole derivative* (5) (0.59 g, 56%), m.p. 142—144 °C (Found: C, 59.3; H, 6.6; N, 12.9. $C_{11}H_{14}N_2O_3$ requires C, 59.45; H, 6.35; N, 12.60%), δ [$^2H_6$]acetone 1.40 (6 H, s, CH_3), 3.93 (3 H, s, N-CH_3), 4.38 (2 H, s, OCH_2), 6.75 (1 H, d, *J* 2.8 Hz, pyrrole H-4), and 6.97 (1 H, d, *J* 2.8 Hz, pyrrole H-5); *m/z* 222 (M^+, 35%) and 163 (100).

Subsequent extraction of the acidified, aqueous solution of lithium-salts from above with ethyl acetate (10 × 30 ml), drying of the extracts ($MgSO_4$), and removal of solvent gave a solid which recrystallised as white needles from acetone–hexane to yield the 5-*carboxylated pyrrole derivative* (6) (0.09 g, 9%), m.p. 163—164 °C (Found: C, 59.5; H, 6.5; N, 12.8. $C_{11}H_{14}N_2O_3$ requires C, 59.45; H, 6.35; N, 12.60%), δ [$^2H_6$]acetone 1.30 (6 H, s, CH_3), 4.00 (2 H, s, OCH_2), 4.27 (3 H, s, N-CH_3), 6.64 (1 H, d, *J* 4.2 Hz, pyrrole H-4), and 6.91 (1 H, d, *J* 4.2 Hz, pyrrole H-3); *m/z* 222 (M^+, 87%) and 207 (100).

[1/1657 *Received*, 26*th October*, 1981]

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