Synthesis and nucleophilic properties of 1,2-dialkyl-3-nitropyrroles and 1,5-dialkyl-4-nitropyrrole-2-carboxylic acid derivatives

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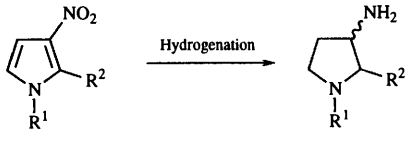
1,2-Dialkyl-3-nitropyrroles 1 are versatile synthetic tools for obtaining substituted pyrrolidines or fused ring heterocycles such as pyrrolopyridines, pyrrolopyrimidines or pyrroloazepines. We have established a method for obtaining compounds related to structure 1 and studied the reactivity as a nucleophile of the benzylic type moiety in the alkyl residue bound to position 2.

The synthesis of 3-amino-1,2-dialkylpyrrolidines **2** by catalytic hydrogenation of the corresponding pyrrole compounds **1** has previously been described[1] (Scheme 1). These saturated



1 **2**

Scheme 1

heterocyclic rings are of interest since such structures occur in drugs with neuroleptic and antipsychotic properties; further these compounds were found to coordinate with nickel, palladium and platinum, the last mentioned being noteworthy since such compounds have been proposed as cytostatic drugs in cancer chemotherapy.[1] In a similar way, fused ring heterocycles could be prepared from compounds **1**, the nitro group being easily reduced to the corresponding primary amine which could then react intramolecularly with a suitable functional group in the 2-alkyl residue on the pyrrole ring. Thus, compounds related to the title structure have potential as synthetic intermediates although little has been published in this connection.[1-3]

We describe here a method for synthesizing compounds **1** with different alkyl substitutions in positions 1 and 2 (Schemes 2 and 3). This method is based on a previously described procedure for obtaining 1,2-dimethyl-3-nitropyrrole **1a**.[2] All the experimental steps were studied and optimized in order to obtain compounds related to structure **1** with a variety of 1- and 2-substituents. We also studied the nucleophilic properties in these systems of the benzylic type moiety in the alkyl residue bound at the 2-position of the pyrrole when the compounds were treated with electrophiles, such as alkyl halides[1] or aldehydes.

The above-mentioned synthetic method starts from a pyrrole compound with an alkyl residue (R^2) at the 2-position. The 1-alkyl group was introduced by alkylation of compound **3** [treatment with alkyl iodide in a dimethyl sulfoxide (DMSO)–KOH system]. The nitro group is linked in the next step. In this operation, an alkoxycarbonyl moiety plays the role of protecting and directing group: it blocks for electrophilic substitution a highly reactive position, directing the attack selectively instead to the desired position. This group can easily be cleaved later by hydrolysis and decarboxylation (Scheme 3).

At first, it appears that the scope of this method is restricted by the availability of the starting 2-alkylpyrroles; fortunately, however, the synthesis of such compounds has been the subject of several reports.[4-6] Nevertheless, we found that the higher homologues could best be synthesized from the corresponding nitro compounds in which R^2 is methyl, to which an electrophilic C_{n-1} residue could be added (see below).

Results and discussion

Results obtained from earlier experiments following the method described[2] showed that although very good yields were obtained when primary alkyl halides were used (Tables 1 and 2), alkylation did not proceed when **3** was treated with a secondary alkyl halide. Treatment of alkylated compounds **4** with 70% HNO_3 at 30 ± 1 °C led to the corresponding nitropyrrole **5** with the exception of **4c** (R^1 = benzyl). Nitration of this compound gave a complex mixture the spectral data for which suggest the presence of a number of nitrated benzene ring products (Table 3). The synthesis of compound **5f** can be achieved using the following alternative method.

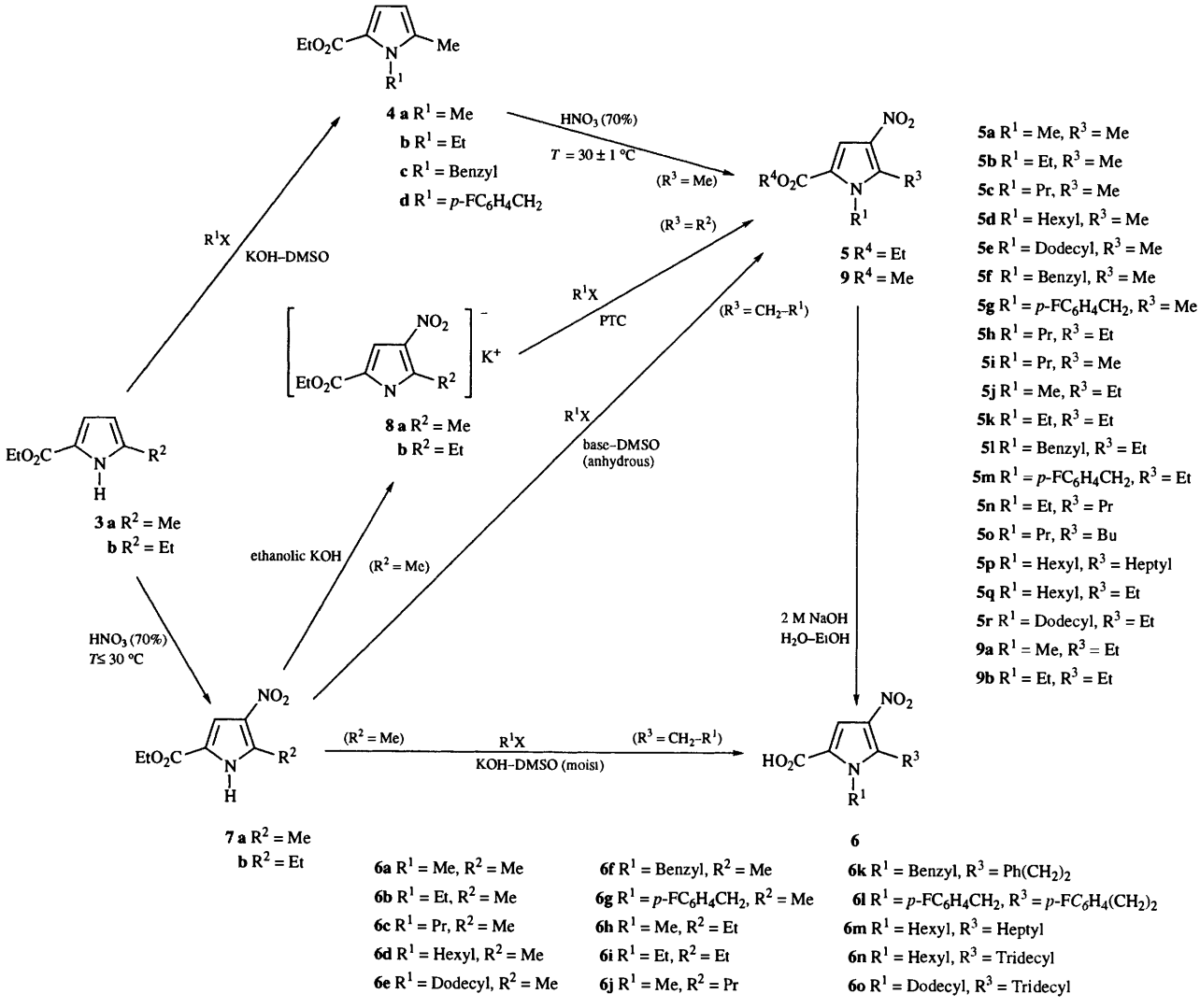
The synthetic path was modified to transpose the nitration and alkylation procedures. The synthesis of compounds **7** was carried out by treatment of **3** with 70% nitric acid at 30 ± 1 °C. In the alkylation step, we found that treatment of **7a** (R^2 = Me) with alkyl halides in KOH–DMSO gave doubly alkylated compounds. The *N*-alkylated compound initially formed reacted with further alkyl halide, and a second alkylation was observed on the methyl group at position 5. This kind of reactivity for methyl groups bound to the vicinal position of a nitro moiety in a heterocyclic ring has previously been described by Frydman *et al.*[7] for 2-alkoxy-4-methyl-5-nitropyridines. In our pyrrole system, this reactivity is explicable in terms of the high degree of acidity of the hydrogens as a result of stabilization of the conjugated base, caused by the electron-withdrawing effects of the nitro and carbonyl substituents on the pyrrole ring. The excess of base present in the medium would then induce a second deprotonation, now on the methyl group, to form the carbanion which could react with the excess of alkyl halide. In addition, hydrolysis of the ester group was observed in some cases, probably as a result of atmospheric moisture absorption by the DMSO; this was minimized by using anhydrous solvent under an argon atmosphere.

Selective 1-alkylation of compound **7a** was achieved by converting compounds **7** into the corresponding potassium salts **8** followed by treatment of these with R^1X in the presence of a phase transfer catalyst (PTC). Treatment of compounds **7a** and

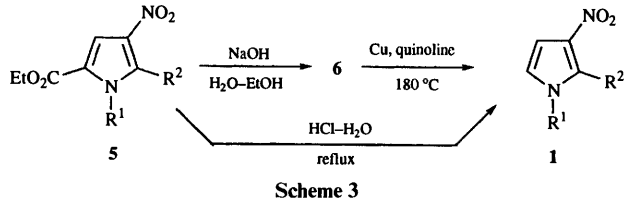
Table 1 Analytical data for 5-alkylpyrrolecarboxylic esters **3** and for 1,5-dialkylpyrrolecarboxylic esters **4**

Compound (formula)	R^1	R^2	Yield (%)	ν_{max}/cm^{-1} (C=O)	Mp (°C)	Bp (°C) [mmHg]	Found (%) (required) C	H	N
3a ($C_8H_{11}NO_2$)	H	Me	76	1685[b]	100–101[a]	—	62.7 (62.73)	7.3 (7.24)	9.2 (9.14)
3b ($C_9H_{13}NO_2$)	H	Et	68	1685[b]	46–47	—	64.6 (64.64)	7.9 (7.83)	8.4 (8.37)
4a ($C_9H_{13}NO_2$)	Me	Me	92	1695[c]	—	108–110 [10][a]	64.7 (64.64)	7.8 (7.83)	8.4 (8.37)
4b ($C_{10}H_{15}NO_2$)	Et	Me	93	1700[c]	—	71–83 [3]	66.2 (66.27)	8.35 (8.34)	7.7 (7.73)
4c ($C_{15}H_{17}NO_2$)	Benzyl	Me	89	1700[c]	48–49	106–109 [0.3]	74.15 (74.05)	7.1 (7.04)	5.75 (5.76)
4d ($C_{15}H_{16}FNO_2$)	p-$FC_6H_4CH_2$	Me	90	1695[c]	—	117–123 [0.3]	69.2 (68.95)	6.1 (6.17)	5.2 (5.36)

[a] Compounds **3a** and **4a** were found in the literature (refs. 11 and 2, respectively). The reported data are: **3a** mp: 100 °C and **4a** bp: 108–109 °C (10 mmHg). [b] Also **3a**: 3320 cm^{-1} (KBr) and **3b**: 3305 cm^{-1} (molten, on NaCl); NH st. [c] Excepting compound **4c**, sample preparation: liquid film on NaCl, **4c**: molten, on NaCl.



Scheme 2



Scheme 3

7b with potassium hydroxide in absolute ethanol yielded products **8a** and **8b**, respectively, as light-brown solids. Their IR spectra showed no absorption at 3500 cm^{-1} (lack of NH stretching) with displacement to lower wavenumbers of the C=O stretching and nitro group bands [1665 cm^{-1} (CO), 1505 and 1305 cm^{-1} (NO_2)]. Treatment with different alkyl halides using hexadecyl(tributyl)phosphonium bromide as PTC catalyst led to the corresponding compounds **5**; the results are shown in Tables 3 and 4. This method gave lower yields for compounds where R^1 was a secondary alkyl group (*i.e.* Pr^i).

The nucleophilicity of the benzylic type moiety in the 2-alkyl residue in compounds **5a–g** and **7a** was studied in order to see whether it was possible to obtain compounds in which the carbon chain attached at the 2-position was $>C_1$ (Scheme 4). With such a method, a single precursor **7a** only would be needed

Table 2 ^{1}H NMR spectral data for 5-alkylpyrrolecarboxylic esters **3** and for 1,5-dialkylpyrrolecarboxylic esters **4**; δ_H(80 MHz; $CDCl_3$; Me_4Si)

Compd.	R^1	R^2	$CH_3CH_2O^a$	$CH_3CH_2O^b$	H-3	H-4	$CH_xC(5)^c$	CH_xN	Other
3a	H	Me	1.20	4.30	6.70 (1 H, d, *J* 4)	5.90 (1 H, d, *J* 4)	2.21	—	8.70 (1 H, br, NH)
3b	H	Et	1.32	4.28	6.7–6.9 (1 H, m)	5.9–6.0 (1 H, m)	2.63 (2 H, q, *J* 7)	—	1.24 [3 H, t, *J* 7, $CH_3CH_2C(5)$], 8.80 (1 H, br, NH)
4a	Me	Me	1.35	4.29	6.90 (1 H, d, *J* 4)	5.91 (1 H, d, *J* 4)	2.26	3.87 (3 H, s)	—
4b	Et	Me	1.29	4.26	6.89 (1 H, d, *J* 4)	5.88 (1 H, d, *J* 4)	2.26	4.31 (2 H, q, *J* 7)	1.33 (3 H, t, *J* 7, CH_3CH_2N)
4c	Benzyl	Me	1.25	4.18	6.8–7.3 (1 H, m)[d]	5.97 (1 H, d, *J* 4)	2.14	5.60 (2 H, s)	6.8–7.3 (5 H, m, Ar)[d]
4d	*p*-$FC_6H_4CH_2$	Me	1.25	4.18	6.8–7.4 (1 H, m)[d]	5.96 (1 H, d, *J* 4)	2.13	5.53 (2 H, s)	6.8–7.4 (4 H, m, Ar)[d]

[a] Multiplicity of signals is 3 H, t, *J* 7. [b] 2 H, q, *J* 7. [c] Unless otherwise specified, multiplicity of signals is 3 H, s. [d] Signals corresponding to H-3 and Ar are overlapped.

Table 3 Analytical data for 1,5-dialkyl-4-nitropyrrole-2-carboxylic ethyl esters **5**, methyl esters **9** and for 5-alkyl-4-nitropyrrole-2-carboxylic ethyl esters **7**

Compound (formula)	R^1	R^2	Method[a]	Yield (%)	ν_{max}/cm^{-1}(KBr) C=O	ν_{max}/cm^{-1}(KBr) NO_2	Mp (°C)	Found (%) (required) C	H	N
5a ($C_9H_{12}N_2O_4$)	Me	Me	A	65	1720	1520, 1325	79–80[b]	50.9 (50.94)	5.8 (5.70)	13.2 (13.20)
			B	86						
5b ($C_{10}H_{14}N_2O_4$)	Et	Me	A	65	1715	1510, 1310	102–104	53.0 (53.09)	6.3 (6.24)	12.3 (12.38)
			B	83						
5c ($C_{11}H_{16}N_2O_4$)	Pr	Me	B	87	1715	1510, 1320[c]	—[b,c]	55.2 (54.99)	6.8 (6.71)	11.65 (11.58)
5d ($C_{14}H_{22}N_2O_4$)	Hexyl	Me	B	93	1715	1510, 1320[c]	—[b,c]	59.8 (59.55)	7.9 (7.85)	10.0 (9.92)
5e ($C_{20}H_{34}N_2O_4$)	Dodecyl	Me	B	83	1715	1510, 1320[c]	—[b,c]	65.6 (65.54)	9.45 (9.35)	7.6 (7.63)
5f ($C_{15}H_{16}N_2O_4$)	Benzyl	Me	A	22[d]	1710	1510, 1320	101–102	62.4 (62.49)	5.6 (5.59)	9.7 (9.72)
			B	77						
5g ($C_{15}H_{15}FN_2O_4$)	*p*-$FC_6H_4CH_2$	Me	A	65	1710	1515, 1320	124–126	58.9 (58.82)	4.95 (4.94)	9.15 (9.15)
			B	77						
5h ($C_{12}H_{18}N_2O_4$)	Pr	Et	B	91	1715	1510, 1315[c]	*c*	56.7 (56.68)	7.3 (7.13)	10.95 (11.02)
5i ($C_{11}H_{16}N_2O_4$)	Pr^i	Me	B	40	1720	1515, 1320	61–64	55.2 (54.99)	6.6 (6.72)	11.8 (11.66)
5j ($C_{10}H_{14}N_2O_4$)	Me	Et	B	70	1720	1515, 1310	68–69	53.15 (53.09)	6.2 (6.24)	12.25 (12.38)
5k ($C_{11}H_{16}N_2O_4$)	Et	Et	B	99	1715	1510, 1315[c]	—[c]	55.1 (54.99)	6.8 (6.71)	11.4 (11.66)
5l ($C_{16}H_{18}N_2O_4$)	Benzyl	Et	B	55	1715	1510, 1315	55–58	63.6 (63.56)	6.0 (6.00)	9.3 (9.27)
5m ($C_{16}H_{17}FN_2O_4$)	*p*-$FC_6H_4CH_2$	Et	B	93	1715	1510, 1315	83–85	60.1 (59.99)	5.6 (5.35)	8.6 (8.75)
5n ($C_{12}H_{18}N_2O_4$)	Et	Pr	C	76	1715	1510, 1320[c]	—[c]	56.8 (56.68)	7.2 (7.13)	10.9 (11.02)
5o ($C_{14}H_{22}N_2O_4$)	Pr	Bu	C	30	1715	1510, 1300[c]	—[c]	59.6 (59.56)	7.9 (7.85)	9.8 (9.92)
5p ($C_{20}H_{34}N_2O_4$)	Hexyl	Heptyl	C	30	1710	1510, 1310[c]	—[c]	65.7 (65.54)	9.5 (9.35)	7.4 (7.64)
5q ($C_{15}H_{24}N_2O_4$)	Hexyl	Et	B	90	1715	1510, 1315[c]	—[c]	60.9 (60.79)	8.2 (8.16)	9.4 (9.45)
5r ($C_{21}H_{36}N_2O_4$)	Dodecyl	Et	B	76	1715	1510, 1315[c]	—[c]	66.4 (66.28)	9.7 (9.54)	7.2 (7.36)
7a ($C_8H_{10}N_2O_4$)	H	Me	—	61	1690	1515, 1320	175–178	48.6 (48.49)	5.1 (5.09)	14.25 (14.14)
7b ($C_9H_{12}N_2O_4$)	H	Et	—	55	1685	1515, 1320	148–150	50.95 (50.94)	5.75 (5.70)	13.2 (13.20)
9a ($C_9H_{12}N_2O_4$)	Me[e]	Et[e]	C	54	1715	1510, 1310	70–72	51.2 (50.94)	5.75 (5.70)	13.15 (13.20)
9b ($C_{10}H_{14}N_2O_4$)	Et[e]	Et[e]	C	88	1715	1510, 1315[c]	—[c]	53.2 (53.09)	6.2 (6.24)	12.2 (12.38)

[a] Method A: nitration of the corresponding *N*-alkylpyrrole-2-carboxylic ester **4**. Method B: alkylation of the potassium salt of ethyl 5-alkyl-4-nitropyrrole-2-carboxylate **8** in a PTC system. Method C: Treatment of the corresponding ethyl 5-methyl-4-nitropyrrole-2-carboxylate **5** with an alkyl halide in anhydrous DMSO–base system. [b] Compounds **5a**, **5c**, **5d**, **5e**, were found in the literature. The reported mp are **5a**: 79–80 °C (ref. 2), **5c–e**: yellow oils (ref. 1). [c] These compounds were not solid at room temperature. IR: liq. film on NaCl. [d] A complex mixture was obtained. Yield calculated based on the recovered amount of product after isolation by column chromatography. [e] Methyl ester.

to synthesize any compound in this series. The results shown in Table 5 demonstrate that the relative amount of both base and alkylating agent, *vs.* substrate **7a** has a great influence both on the compounds obtained and the yields; furthermore, the final reaction product could be conditioned by the presence of small amounts of moisture in the medium. With a high molar excess of methyl iodide as alkylating agent the isolated compound was the corresponding methyl ester **9a** rather than the ethyl ester **5a**. This formal transesterification can be explained by the high reactivity of methyl iodide as alkylating agent. Thus, the carboxylate intermediate induced by the KOH present in the medium could react with it to yield the corresponding methyl ester. With a high molar ratio of MeI *vs.* substrate there would be a shift of the equilibrium in the direction of methyl ester formation.

The presence of unreacted material **7a** in the products from reactions with a 1.1 molar ratio of alkyl halide (entries 3, 5 and 6), and the simultaneous presence of doubly alkylated compounds suggest that *C*-alkylation and *N*-alkylation occur at a similar rate. Nevertheless, the absence of compounds resulting from monoalkylation of the methyl group, suggests that *C*-alkylation is only possible when *N*-alkylation has taken place.

The results for the reaction of compounds **5** with electrophiles (Scheme 5) are also shown in Table 5. Except for experiments in which highly reactive alkyl halides were used, yields were low. Use of a large molar excess of methyl iodide gave a good yield of the corresponding methyl ester **9**, as described above. Use of long chain alkyl halides gave problems of isolation because of the lipophilicity of the products. In spite of the poor yield (*ca.* 30%), this method is appropriate for synthesizing long chain derivatives ($> C_{12}$) substituted at the 2-position of the pyrrole, even though optimization of the isolation method is necessary for each product.

Reactions carried out with exposure to the atmosphere gave large amounts of a product having a hydroxy group bound to the benzylic type methylene moiety (Table 5, entry 14; synthesis of compound **12**). This product arises as a result of oxidation of the alkylated compound by atmospheric oxygen.[8,9] In the same way, the alcohol **13** was obtained by passing air through a solution of compound **5j** (R^1 = Me, R^2 = Et) in KOH–DMSO in the absence of an alkylating agent; no products of further oxidation were detected.

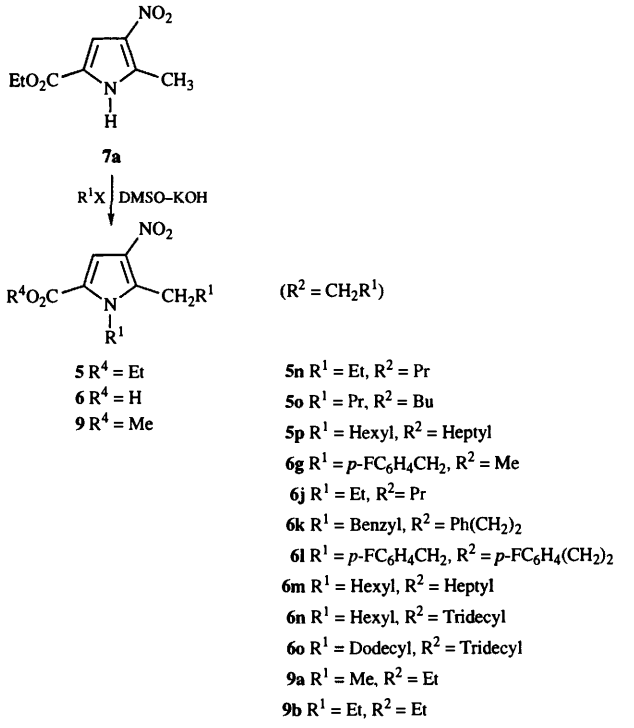
An alkoxycarbonyl group in the 2-position can easily be cleaved by the two-step procedure described in ref. 2, in which compounds **5** are treated with NaOH–H_2O at reflux temperature to give in good yield the corresponding carboxylic acids **6** (Tables 6 and 7) followed by treatment of these with metallic copper in quinoline at 180 °C (Tables 8 and 9). In some cases, cleavage can be achieved simply by acid hydrolysis and subsequent decarboxylation.

Finally, the nucleophilicity of the 2-methyl group in compounds **1a,g** and **11** (R^1 = H) was also studied in order to evaluate the absence of a carboxylic ester group. As expected, a base stronger than KOH (*e.g.* Bu^{t}OK) was needed to promote the reaction. In this way, compound **11** could be selectively *N*-alkylated upon treatment with an alkyl halide in the KOH–DMSO system and doubly alkylated if the reaction was carried out in KBu^{t}O–DMSO (see Table 10; entries 1 and 3). Reaction of compounds **1** with other electrophiles (such as aldehydes or Michael acceptors) was also studied (entries 4 and 5). Reaction of **1g** (R^1 = *p*-$FC_6H_4CH_2$, R^2 = Me) with ethyl acrylate gave compound **14** [R^1 = *p*-$FC_6H_4CH_2$, R^2 = $(CH_2)_3CO_2Et$] in good yield. In the same way, reaction of **1a** (R^1 = R^2 = Me) with benzaldehyde gave a mixture of the alkene **15** (R^2 = CH=CHPh) and the alcohol **16** [R^2 = $CH_2CH(OH)Ph$]. Compound **15** was assigned *E*-stereochemistry on the basis of the coupling constant (*J* 16 Hz) in the ^1H NMR spectrum for the ethylenic hydrogens; there was no evidence for the

Table 4 H NMR spectral data for 1,5-dialkyl-4-nitropyrrole-2-carboxylic ethyl esters **5**, methyl esters **9** and for 5-alkyl-4-nitropyrrole-2-carboxylic ethyl esters **7**; δ_H(80 MHz; $CDCl_3$; Me_4Si)

Compd.	R^1	R^2	CH_3CH_2O[a]	CH_3CH_2O[b]	H-4[c]	CH_xN	$CH_xC(5)$	Other
5a	Me	Me	1.40	4.32	7.50	3.92 (3 H, s)	2.64 (3 H, s)	—
5b	Et	Me	1.38	4.27	7.47	4.39 (2 H, q, *J* 7)	2.62 (3 H, s)	1.38 (3 H, t, *J* 7, CH_3CH_2N)
5c	Pr	Me	1.30	4.30	7.50	4.30 (2 H, t, *J* 7)	2.60 (3 H, s)	0.90 (3 H, t, *J* 7, $CH_3CH_2CH_2N$), 1.70 (2 H, m, $CH_3CH_2CH_2N$)
5d	Hexyl	Me	1.30[d]	4.30[d]	7.50	4.30[d]	2.60 (3 H, s)	0.90 [3 H, t, *J* 7, $CH_3(CH_2)_4CH_2N$], 1.25–1.35 [6 H, m, $CH_3(CH_2)_3CH_2CH_2N$], 1.70 (2 H, m, CH_2CH_2N)
5e	Dodecyl	Me	1.30[d]	4.30[d]	7.50	4.30[d]	2.60 (3 H, s)	0.80 [3 H, t, *J* 7, $CH_3(CH_2)_{11}N$], 1.25–1.35 [18 H, m, $CH_3(CH_2)_3CH_2CH_2N$], 1.70 (2 H, m, CH_2CH_2N)
5f	Benzyl	Me	1.32	4.26	7.59	5.71 (2 H, s)	2.59 (3 H, s)	6.90–7.30 (5 H, m, Ph)
5g	*p*-$FC_6H_4CH_2$	Me	1.33	4.27	7.59	5.66 (2 H, s)	2.60 (3 H, s)	6.94–7.04 (4 H, m, Ar)
5h	Pr	Et	1.3[f]	4.3[d]	7.50	4.3[d]	3.09 (2 H, q, *J* 7)	0.85 [3 H, t, *J* 7, $CH_3(CH_2)_2N$], 1.3 [3 H, m, $CH_3CH_2C(5)$],[f] 1.6–1.9 (2 H, m, $CH_3CH_2CH_2N$)
5i	Pr^i	Me	1.25	4.30	7.50	5.50 (1 H, m)	2.70 (3 H, s)	1.60 [6 H, d, *J* 7, $(CH_3)_2CHN$]
5j	Me	Et	1.25	4.30	7.49	3.94 (3 H, s)	3.11 (2 H, q, *J* 7)	1.35 [3 H, t, *J* 7, $CH_3CH_2C(5)$]
5k	Et	Et	1.25	4.30	7.49	4.39 (2 H, q, *J* 7)	3.11 (2 H, q, *J* 7)	1.35 [3 H, t, *J* 7, $CH_3CH_2C(5)$], 1.38 (3 H, t, *J* 7, CH_3CH_2N)
5l	Benzyl	Et	1.27	4.18	7.53	5.59 (2 H, s)	2.94 (2 H, q, *J* 7)	1.05 [3 H, t, *J* 7, $CH_3CH_2C(5)$], 6.85–6.95 (5 H, m, Ph)
5m	*p*-$FC_6H_4CH_2$	Et	1.25	4.17	7.53	5.63 (2 H, s)	2.94 (2 H, q, *J* 7)	1.05 [3 H, t, *J* 7, $CH_3CH_2C(5)$], 7.18–7.28 (4 H, m, Ar)
5n	Et	Pr	1.29	4.31	7.49	4.41 (2 H, q, *J* 7)	3.00 (2 H, t, *J* 7)	1.00 [3 H, t, *J* 7, $CH_3(CH_2)_2C(5)$], 1.31 (3 H, t, *J* 7, CH_3CH_2N), 1.59 [2 H, m, $CH_3CH_2CH_2C(5)$]
5o	Pr	Bu	1.30	4.3[d]	7.48	4.3[d]	3.00 (2 H, t, *J* 7)	0.90 [6 H, t, *J* 7, $CH_3(CH_2)_3C(5)$ and $CH_3(CH_2)_{11}N$]; 1.4–1.7 [6 H, m, $CH_3(CH_2)_2CH_2C(5)$ and $CH_3CH_2CH_2N$]
5p	Hexyl	Heptyl	1.3[e]	4.3[d]	7.51	4.3[d]	2.99 (2 H, t, *J* 7)	0.90 [6 H, t, *J* 7, $CH_3(CH_2)_6C(5)$ and $CH_3(CH_2)_5N$], 1.3–1.7 [18 H, m, $CH_3(CH_2)_5CH_2C(5)$ and $CH_3(CH_2)_4CH_2N$][e]
5q	Hexyl	Et	1.3[e]	4.3[d]	7.50	4.3[d]	3.10 (2 H, q, *J* 7)	0.80 [3 H, m, $CH_3(CH_2)_5N$], 1.1–1.5 [9 H, m, $CH_3(CH_2)_3CH_2CH_2N$ and $CH_3CH_2C(5)$],[e] 1.6–1.9 (2 H, m, RCH_2CH_2N)
5r	Dodecyl	Et	1.3[e]	4.2–4.3[d]	7.65	4.2–4.3[d]	3.10 (2 H, q, *J* 7)	0.80 [3 H, m, $CH_3(CH_2)_5N$], 1.1–1.5 [21 H, m, $CH_3(CH_2)_9CH_2CH_2N$ and $CH_3CH_2C(5)$],[e] 1.6–1.9 (2 H, m, RCH_2CH_2N)
7a	H	Me	1.39	4.36	7.39	—	2.69 (3 H, s)	9.5 (1 H, br, NH)
7b	H	Et	1.37	4.34	7.38	—	3.06 (2 H, q, *J* 7)	1.31 [3 H, q, *J* 7, $CH_3CH_2C(5)$], 9.8 (1 H, br, NH)
9a	Me	Et	—[f]	3.80 (3 H, s)[f]	7.41	3.90 (3 H, s)	3.12 (2 H, q, *J* 7)	1.23 (3 H, t, *J* 7, CH_3CH_2N)
9b	Et	Et	—[f]	3.80 (3 H, s)[f]	7.41	4.52 (2 H, q, *J* 7)	3.10 (2 H, q, *J* 7)	1.21 (3 H, t, *J* 7, CH_3CH_2N)

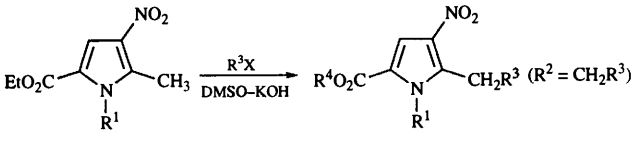
[a] Unless otherwise specified integral and multiplicity for signals are 3 H, t, *J* 7. [b] Unless otherwise specified: 2 H, q, *J* 7. [c] Integral and multiplicity for signals are 1 H, s. [d] In these compounds signals corresponding to CH_2N and CH_2O are overlapped, resulting in a multiplet with an integral of 4 H. [e] This signal overlapped with the multiplet signal corresponding to methylene hydrogens of alkyl residues. [f] Methyl ester.



7a

5 R^4 = Et
6 R^4 = H
9 R^4 = Me

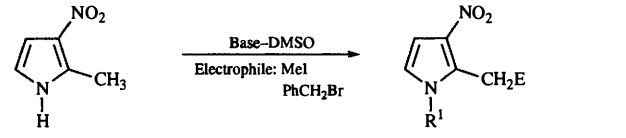
5n R^1 = Et, R^2 = Pr
5o R^1 = Pr, R^2 = Bu
5p R^1 = Hexyl, R^2 = Heptyl
6g R^1 = *p*-$FC_6H_4CH_2$, R^2 = Me
6j R^1 = Et, R^2 = Pr
6k R^1 = Benzyl, R^2 = $Ph(CH_2)_2$
6l R^1 = *p*-$FC_6H_4CH_2$, R^2 = *p*-$FC_6H_4(CH_2)_2$
6m R^1 = Hexyl, R^2 = Heptyl
6n R^1 = Hexyl, R^2 = Tridecyl
6o R^1 = Dodecyl, R^2 = Tridecyl
9a R^1 = Me, R^2 = Et
9b R^1 = Et, R^2 = Et



5a R^1 = Me
5b R^1 = Et
5c R^1 = Pr
5d R^1 = Hexyl
5e R^1 = Dodecyl

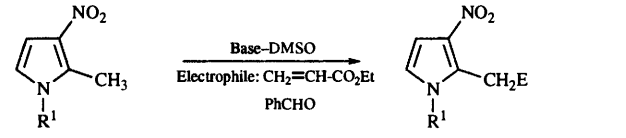
5 R^4 = Et
6 R^4 = H
9 R^4 = Me

Scheme 4



11

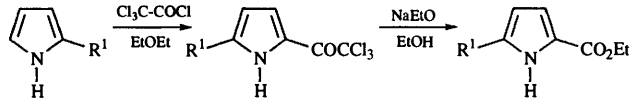
1a R^1 = Me, E = H
1f R^1 = Benzyl, E = H
1h R^1 = Me, E = Me



1a R = Me
1g R^1 = *p*-$FC_6H_4CH_3$

14 R^1 = *p*-$FC_6H_4CH_2$, E = $(CH_2)_2CO_2Et$
15 R^1 = Me, E = =CH-Ph
16 R^1 = Me, E = CH(OH)Ph

Scheme 5



17a R^1 = Me
b R^1 = Et

18a R^1 = Me
b R^1 = Et

3a R^1 = Me
b R^1 = Et

Scheme 6

corresponding *Z*-isomer. Further studies dealing with functionalization of the side chain in compounds **1** and **5** are currently in progress and will be the subject of a future report.

Experimental

IR spectra were recorded on a Nicolet 5PC FT-IR spectrophotometer. ^{1}H NMR spectra were recorded at 80 and 200 MHz on Bruker WP 80 SY and Varian Gemini 200 spectrometers respectively; *J* values are given in Hz. Chemical analyses were carried out by Centre d'Investigació i Desenvolupament-C.S.I.C. and by Centro de Investigación Ferrer S.A., Barcelona. Melting points were determined in a Büchi 510 apparatus and are uncorrected. All commercially available reagents and solvents were synthetic grade and used without further purification. Ether refers to diethyl ether. Compounds **3** were synthesized following the method described in ref. 10 (Scheme 6). Starting materials 2-methylpyrrole **17a** and 2-ethylpyrrole **17b** were obtained following previously described procedures.[4,5]

5-Methyl-2-trichloroacetylpyrrole 18a

To a stirred solution of **29** (16 g, 18 ml, 0.160 mol) of trichloroacetyl chloride in anhydrous ether (100 ml), freshly distilled 2-methylpyrrole (10 g, 0.123 mol) **17a** in diethyl ether (30 ml) was added dropwise over 1 h. The mixture was shaken for a further 1 h, after which K_2CO_3 (10 g) in water (30 ml) was slowly added through a dropping funnel. The layers were separated and the organic phase was dried ($MgSO_4$) and treated with Norite (2 g) for 15 min at room temperature. The solvent was removed by distillation under reduced pressure and recrystallization (hexane) of the residue yielded pure **18a** (23.7 g, 85%), mp 104–106 °C (Found: C, 37.09; H, 2.61; N, 6.09. $C_7H_6Cl_3NO$ requires C, 37.12; H, 2.67; N, 6.18%); ν_{max}(K-Br)/cm^{-1} 3320 (NH) and 1645 (CO); δ_H(80 MHz; $CDCl_3$) 2.7 (3 H, s, Me), 6.25 (1 H, dd, $J_{3,4}$ 3.5, $J_{1,3}$ 2.5, 4-H), 7.55 (1 H, dd, $J_{3,4}$ 3.5, $J_{1,4}$ 2.5, 3-H) and 9.0 (1 H, br, NH).

5-Ethyl-2-trichloroacetylpyrrole 18b

Compound **18b** was synthesized following the same procedure used for obtaining **18a**. 2-Ethylpyrrole (12 g, 0.13 mol) **17b** yielded **18b** (25.5 g, 81%), mp 74–76 °C (Found: C, 40.0; H, 3.3; N, 5.8; $C_8H_8Cl_3NO$ requires C, 39.95; H, 3.35; N, 5.82%); ν_{max}(KBr)/cm^{-1} 3305 (NH) and 1635 (CO); δ_H(80 MHz; $CDCl_3$) 1.4 (3 H, t, *J* 7, Me), 2.75 (2 H, q, *J* 7, CH_2), 6.3 (1 H, dd, $J_{3,4}$ 3.5, $J_{1,3}$ 2.5, 4-H), 7.6 (1 H, dd, $J_{3,4}$ 3.5, $J_{1,4}$ 2.5, 3-H) and 8.9 (1 H, br, NH).

Ethyl 5-methylpyrrole-2-carboxylate 3a

To a stirred solution of sodium ethoxide (0.83 g, 0.012 mol) in absolute ethanol (75 ml), 2-trichloroacetyl-5-methylpyrrole **18a** (22.5 g, 0.099 mol) was added portionwise. After the addition, the mixture was shaken at room temperature for 30 min. It was then concentrated to dryness under reduced pressure. 3 M Aq. HCl (30 ml) and ether (100 ml) were added to the residue and the layers were separated. The organic phase was washed with aq. $NaHCO_3$ and then with water, dried ($MgSO_4$) and then concentrated by removal of solvent under reduced pressure. Recrystallization (isopropyl alcohol) of the residue yielded **3a** (14 g, 76%). Analytical and spectral data for compounds **3** are shown in Tables 1 and 2.

Ethyl 5-ethylpyrrole-2-carboxylate 3b

Compound **3b** was synthesized following the same procedure used to obtain **3a**, starting from 2-trichloroacetyl-5-ethylpyrrole **18b**.

Table 5 Reaction of compounds **7a** (R^1 = H) and **5** (R^1 = alkyl) with alkyl halides (Scheme 4)

Entry	Starting compd.	R^1 [a]	Alkyl halide R^3X	Base	Molar ratio **5(7a)**:R^3X:base	Compound obtained: Compd.	R^2(=R^3CH_2)	R^4	Yield (%)[b]
1	**7a**	H	MeI	KOH	1:10:10	**9a**	Et	Me[c,d]	46
2	**7a**	H	EtI	KOH	1:10:10	**5n** + **6j**	Pr	Et + H	76 + 22
3	**7a**	H	EtI	KOH	1:1.1:10	**6j**	Pr	H	50[e]
4	**7a**	H	EtI	KOH	1:10:3	**5n** + **5b**	Pr + Me	Et[d]	40 + 20
5	**7a**	H	$PhCH_2Br$	KOH	1:1.1:10	**6k**	$Ph(CH_2)_2$	H	46[e]
6	**7a**	H	p-$FCH_2C_6H_4$	KOH	1:1.1:10	**6l** + **6g**	p-$FC_6H_4(CH_2)_2$ + Me	H	23 + 20[e,f]
7	**5a**	Me	MeI	KOH	1:14:7	**9a**	Et	Me[c]	83[e]
8	**5b**	Et	MeI	KOH	1:14:7	**9b**	Et	Me[c]	88[c]
9	**5c**	Pr	PrI	KBu^{t}O	1:3.5:2	**5o**	Bu	Et[h]	30[h]
10	**5d**	Hexyl	$C_6H_{13}Br$	KOH	1:3:10	**6m**	Heptyl	H[g]	32
11	**5d**	Hexyl	$C_6H_{13}Br$	KBu^{t}O	1:3.5:2	**5p**	Heptyl	Et[h]	30[h]
12	**5d**	Hexyl	$C_{12}H_{25}Br$	KOH	1:3:10	**6n**	Tridecyl	H[g]	34
13	**5e**	Dodecyl	$C_{12}H_{25}Br$	KOH	1:3:10	**6o**	Tridecyl	H[g]	25
14	**5c**	Pr	PrI + O_2	KOH	1:3:10	**12**	$CH(OH)(CH_2)_2CH_3$	H[g]	27
15	**5j**	Me	O_2	KOH	1:0:10[i]	**13**	$CH(OH)CH_3$	H[g]	70

[a] With the exception of entry 15, R^2 = Me in all starting compounds. When compound **7a** (R^1 = H) was used as starting material, *N*-alkylation was always present (*i.e.* in the reaction products of entries 1–6, $R^1 = R^3$). [b] Yields are calculated considering the amount of isolated product obtained after purification. [c] Methyl ester was obtained (see text). [d] The reaction was carried out in anhydrous DMSO and under an argon atmosphere. [e] A significant amount (approx. 50%) of unreacted **7a** was recovered. [f] Mixture of compounds. Yield calculated after isolation by column chromatography. [g] Carboxylic acids (hydrolysis of ester groups) were the compounds mainly obtained but the corresponding esters were also detected by TLC. [h] Hydrolysis of ester group due to small amounts of moisture present in DMSO was always observed. Variable amounts of the non-alkylated and alkylated carboxylic acids were detected. Yield is an average of different experiments. [i] No alkylating agent was present in the medium. In the starting compound R^2 = Et.

Alkylation of ethyl 5-methylpyrrole-2-carboxylate

Sample procedure: synthesis of ethyl 1,5-dimethylpyrrole-2-carboxylate 4a (R^1 = Me). To a stirred mixture of finely crushed potassium hydroxide (5 g, 0.075 mol) in DMSO (20 ml), under a dry, inert atmosphere, was added compound **3a** (3 g, 0.02 mol). The dark brown reaction mixture was stirred for 1 h after which methyl iodide (3.6 g, 0.025 mol) was then slowly added with rapid stirring while the reaction temperature was kept < 30 °C. After being stirred for 1 h the brown slurry was quenched in ice–water and extracted with ether. The ethereal phase was washed with 2 M aqueous sodium hydroxide, water and brine, dried ($MgSO_4$) and evaporated *in vacuo* to give an oily residue. This was distilled at reduced pressure (108–110 °C, 10 mmHg) to yield pure **4a** (3.05 g, 92%). Analytical and spectral data for compounds **4** are shown in Tables 1 and 2.

The following compounds were obtained in a similar way by treating **3a** with the corresponding alkyl halide: ethyl 1-ethyl-5-methylpyrrole-2-carboxylate **4b** (R^1 = Et); ethyl 1-benzyl-5-methylpyrrole-2-carboxylate **4c** (R^1 = benzyl); ethyl 1-(*p*-fluorobenzyl)-5-methylpyrrole-2-carboxylate **4d** (R^1 = *p*-$FC_6H_4CH_2$).

Synthesis of 1,5-dialkyl-4-nitropyrrole-2-carboxylates 5

Method A: nitration of the corresponding ethyl 1,5-dialkylpyrrole-2-carboxylate 4 in a sample procedure. *Synthesis of ethyl 1,5-dimethyl-4-nitropyrrole-2-carboxylate* **5a** (R^1 = Me; R^2 = Me).—Compound **4a** (3.34 g, 0.02 mol) was added dropwise to 70% nitric acid (*d* 1.41) (30 ml, 0.47 mol) with rapid stirring. During the whole operation (*ca.* 1 h) the internal reaction temperature was kept strictly at 30 ± 1 °C (ice-cooling if necessary). The brown reaction mixture was then stirred at room temperature for a further 30 min, after which it was poured into ice–water. The precipitated solid was collected, washed exhaustively with water, dried and recrystallized (isopropyl alcohol) to yield **5a** (2.8 g, 65%). Analytical and spectral data for compounds **5** are shown in Tables 3 and 4.

The following compounds were obtained in a similar way by treating the corresponding compound **4** with 70% HNO_3: ethyl 1-ethyl-5-methyl-4-nitropyrrole-2-carboxylate **5b** (R^1 = Et, R^2 = Me); ethyl 1-(*p*-fluorophenylmethyl)-5-methyl-4-nitropyrrole-2-carboxylate **5g** (R^1 = *p*-$FC_6H_4CH_2$; R^2 = Me).

Synthesis of ethyl 1-benzyl-5-methyl-4-nitropyrrole-2-carboxylate **5f** (R^1 = $PhCH_2$, R^2 = Me).—By treating compound **4a** with 70% nitric acid, a complex crude mixture was obtained. Purification of this by chromatography on silica gel yielded **5f** (1.28 g, 22%), a product which is better synthesized following method B.

Method B: alkylation of the potassium salt of ethyl 5-alkyl-4-nitropyrrole-2-carboxylate 8 in a PTC system. *Synthesis of ethyl 5-methyl-4-nitropyrrole-2-carboxylate* **7a** (R^1 = H; R^2 = Me).—Compound **3a** (5g, 0.033 mol) was added portionwise to 70% nitric acid (*d* 1.41) (40 ml, 0.63 mol) with rapid stirring. During the whole operation (*ca.* 2 h) the internal reaction temperature was kept strictly at 30 ± 1 °C (ice-cooling if necessary). The brown reaction mixture was then stirred at room temperature for a further 1 h after which it was poured into ice–water. The light-brown precipitate was collected, washed exhaustively with water, dried and recrystallized (isopropyl alcohol) to yield **7a** (4.0 g, 61%). Analytical and spectral data for compounds **7** are displayed in Tables 3 and 4.

The above-mentioned procedure was used to obtain ethyl 5-ethyl-4-nitropyrrole-2-carboxylate **7b** (R^1 = H, R^2 = Et).

Synthesis of the potassium salt of ethyl 5-methyl-4-nitropyrrole-2-carboxylate **8a** (R^2 = Me).—To a vigorously stirred solution of compound **7a** (5 g, 0.025 mol) in absolute ethanol (50 ml) was added dropwise, 0.5 M ethanolic KOH (100 ml, 0.05 mol). When the addition was completed (*ca.* 15 min.) the flask was gently heated until a yellow precipitate appeared. The stirred mixture was then allowed to cool to room temperature after which it was stored at 0 °C for 18 h. Precipitated compound **8a** (5.2 g, 88%) was filtered off, rinsed with ethanol and ether and dried; mp 277–279 °C; ν_{max}(KBr)/cm^{-1} 1665 (CO), 1505 and 1305 (NO_2).

Synthesis of the potassium salt of ethyl 5-ethyl-4-nitropyrrole-2-carboxylate **8b** (R^2 = Et).—The above-mentioned procedure carried out on **7b** yielded **8b** (4.85 g, 77%), mp 244–246 °C; ν_{max}(KBr)/cm^{-1} 1655 (CO), 1505 and 1300 (NO_2).

Alkylation of the potassium salt of ethyl 5-alkyl-4-nitropyrrole-2-carboxylate. Sample Procedure: synthesis of ethyl 1,5-dimethyl-4-nitropyrrole-2-carboxylate **5a** (R^1 = R^2 = Me).—A stirred mixture of the potassium salt **8a** (2.4 g, 0.01

Table 6 Analytical data for *N*-alkyl-4-nitropyrrolecarboxylic acids **6**

Compound (formula)	R^1	R^2	Yield (%)[a]	ν_{max}/cm^{-1}(KBr)			Mp (°C)	Found (%) (required)		
				OH	CO	NO_2		C	H	N
6a ($C_7H_8N_2O_4$)	Me	Me	90	3500–2100	1670	1510, 1320	212–213[b]	45.7 (45.66)	4.4 (4.38)	15.1 (15.21)
6b ($C_8H_{10}N_2O_4$)	Et	Me	91	3500–2100	1670	1520, 1325	170–171	48.55 (48.49)	5.1 (5.09)	14.15 (14.14)
6c ($C_9H_{12}N_2O_4$)	Pr	Me	80	3500–2000	1675	1510, 1320	136–138[b]	50.65 (50.94)	5.6 (5.70)	12.9 (13.20)
6d ($C_{12}H_{18}N_2O_4$)	Hexyl	Me	73	3500–2100	1690	1520, 1320	167–169[b]	56.6 (56.68)	7.2 (7.14)	10.95 (11.02)
6e ($C_{18}H_{30}N_2O_4$)	Dodecyl	Me	73	2500–2100	1680	1510, 1320	83–86[b]	63.8 (63.87)	8.8 (8.93)	8.3 (8.27)
6f ($C_{13}H_{12}N_2O_4$)	Benzyl	Me	82	3500–2100	1680	1510, 1315	202–204	60.0 (59.99)	4.7 (4.65)	10.6 (10.76)
6g ($C_{13}H_{11}FN_2O_4$)	*p*-$FC_6H_4CH_2$	Me	84	3500–2000	1690	1510, 1320	232–233	55.9 (56.12)	4.0 (3.98)	9.5 (10.07)
6h ($C_8H_{10}N_2O_4$)	Me	Et	85	3200–2200	1680	1510, 1315	179–180	48.3 (48.49)	5.1 (5.09)	14.05 (14.14)
6i ($C_9H_{12}N_2O_4$)	Et	Et	80	3200–2200	1670	1515, 1330	184–187	50.9 (50.94)	5.7 (5.70)	13.1 (13.20)
6j ($C_{10}H_{16}N_2O_4$)	Et	Pr	50	3500–2100	1675	1515, 1325	169–171[b]	53.2 (53.09)	6.4 (6.24)	12.0 (12.38)
6k ($C_{20}H_{18}N_2O_4$)	Benzyl	$Ph(CH_2)_2$	45	3200–2500	1685	1510, 1320	202–204	68.45 (68.56)	5.1 (5.18)	8.0 (7.99)
6l ($C_{20}H_{16}F_2N_2O_4H_2O$)	*p*-$FC_6H_4CH_2$	*p*-$FC_6H_4(CH_2)_2$	20	3200–2500	1685	1510, 1320	215–220	59.1 (59.41)	4.4 (4.49)	6.6 (6.93)
6m ($C_{18}H_{30}N_2O_4$)	Hexyl	Heptyl	30	3200–2400	1680	1510, 1320	70–71	64.0 (63.88)	8.95 (8.93)	8.0 (8.28)
6n ($C_{24}H_{42}N_2O_4$)	Hexyl	Tridecyl	34	3200–2400	1695	1515, 1315	38–43	68.2 (68.21)	9.9 (10.02)	6.55 (6.63)
6o ($C_{30}H_{54}N_2O_4$)	Dodecyl	Tridecyl	25	3200–2400	1685	1510, 1320	74–75	71.6 (71.10)	11.0 (10.74)	5.1 (5.33)
10 ($C_6H_6N_2O_4$)	H	Me	90	3200–2200[c]	1680	1530, 1320	265(d)	42.4 (42.36)	3.6 (3.56)	16.3 (16.47)
12 ($C_{12}H_{20}N_2O_5$)	Pr	$CH_3(CH_2)_2CH(OH)$	27	3300–2200[d]	1685	1515, 1320	132–134	53.1 (53.33)	6.6 (6.66)	10.55 (10.37)
13 ($C_8H_{10}N_2O_5$)	Me	$CH_3CH(OH)$	70	3400–2100[d]	1715	1510, 1315	151–153	44.8 (44.86)	4.6 (4.71)	13.0 (13.08)

[a] For compounds **6a–i** and **10** yields refer to the hydrolysis of the corresponding ester (treatment with 2 M NaOH). For other compounds yields refer to treatment of the corresponding ester **5** with an alkyl halide in the KOH–moist DMSO system (see Experimental section). [b] Compounds **6a**, **6c**, **6d**, **6e** and **6j** are described in the literature. The reported mp are **6a**: 208–213 °C (ref. 2), **6c**: 136–138, **6d**: 167–169, **6e**: 83–86, **6j**: 169–171 (ref. 1). [c] 3320 cm^{-1} (br NH st). [d] 3520 cm^{-1} (br OH st alcohol).

Table 7 ^{1}H NMR spectral data for the carboxylic acids **6** and related compounds; δ_H(200 MHz; $CDCl_3$; Me_4Si)[a]

Compd.	R^1	R^2	H-4	CH_xN	$CH_xC(5)$	Other
6a	Me	Me	7.70	3.96 (3 H, s)	2.73	—
6b	Et	Me	7.65	4.43 (2 H, q, *J* 7)	2.70	1.38 (3 H, t, *J* 7, CH_3CH_2N)
6c	Pr	Me	7.60	4.32 (2 H, t, *J* 7)	2.70	0.91 (3 H, t, *J* 7, $CH_3CH_2CH_2N$), 1.70 (2 H, m, $CH_3CH_2CH_2N$)
6d	Hexyl	Me	7.60	4.31 (2 H, t, *J* 7)	2.70	0.89 [3 H, t, *J* 7, $CH_3(CH_2)_5N$], 1.00–1.40 [6 H, m, $CH_3(CH_2)_3CH_2CH_2N$], 1.70 (2 H, m, CH_2CH_2N)
6e	Dodecyl	Me	7.60	4.29 (2 H, t, *J* 7)	2.70	0.83 [3 H, t, *J* 7, $CH_3(CH_2)_{11}N$], 1.00–1.40 [18 H, m, $CH_3(CH_2)_9CH_2CH_2N$], 1.70 [2 H, m, CH_2CH_2N]
6f	Benzyl	Me	7.71	5.69 (2 H, s)	2.61	7.40 (5 H, m, Ph)
6g	*p*-$FC_6H_4CH_2$	Me	7.70	5.65 (2 H, s)	2.62	6.95–7.05 (4 H, m, Ar)
6h	Me	Et	7.69	3.88 (3 H, s)	3.03 (2 H, q, *J* 7)	1.14 [3 H, t, *J* 7, $CH_3CH_2C(5)$]
6i	Et	Et	7.68	4.46 (2 H, q, *J* 7)	3.14 (2 H, q, *J* 7)	1.45 [3 H, t, *J* 7, $CH_3CH_2C(5)$], 1.34 (3 H, t, *J* 7, CH_3CH_2N)
6j	Et	Pr	7.59	4.40 (2 H, q, *J* 7)	3.00 (2 H, t, *J* 7)	1.00 [3 H, t, *J* 7, $CH_3(CH_2)_2C(5)$], 1.39 (3 H, t, *J* 7, CH_3CH_2N), 1.72 [2 H, m, $CH_3CH_2CH_2$-C(5)]
6k	Benzyl	$PhCH_2CH_2$	7.68	5.41 (2 H, s)	3.60 (2 H, dd, J_1 8, J_2 7)	2.80 (2 H, dd, J_1 8, J_2 7, CH_2CH_2Ph), 6.80–7.30 (10 H, m, Ph)
6l	*p*-$FC_6H_4CH_2$	*p*-$FC_6H_4(CH_2)_2$	7.53	5.68 (2 H, s)	3.09 (2 H, m)	2.70 (2 H, m, CH_2CH_2Ar), 6.94–7.07 (8 H, m, Ar)
6m	Hexyl	Heptyl	7.79	4.30 (2 H, t, *J* 7)	3.10 (2 H, t, *J* 7)	0.90 [3 H, t, *J* 7, $CH_3(CH_2)_6C(5)$], 1.00 [3 H, t, *J* 7, $CH_3(CH_2)_5N$], 1.1–1.9 [18 H, m, $CH_3(CH_2)_5CH_2C(5)$ and $R(CH_2)_4CH_2N$]
6n	Hexyl	Tridecyl	7.80	4.22 (2 H, t, *J* 7)	3.10 (2 H, t, *J* 7)	0.90 [3 H, t, *J* 7, $CH_3(CH_2)_{12}C(5)$], 1.0–1.9 [33 H, m, $CH_3(CH_2)_{11}CH_2C(5)$ and $CH_3(CH_{24}CH_2N$]
6o	Dodecyl	Tridecyl	7.70	4.29 (2 H, t, *J* 7)	3.09 (2 H, t, *J* 7)	0.90 [3 H, t, *J* 7, $CH_3(CH_2)_{12}C(5)$], 1.0–1.9 [45 H, m, $CH_3(CH_2)_{11}CH_2C(5)$ and $CH_3(CH_2)_{10}CH_2N$]
10	H	Me	7.23	—	2.63	> 10 (2 H, br, NH and CO_2H)
12	Pr	$CH(OH)(CH_2)_2CH_3$	7.60	4.2–4.7 (2 H, m)	5.1–5.2 (1 H, m)	1.00 [6 H, t, *J* 7, $CH_3(CH_2)_2CH(OH)C(5)$ and $CH_3(CH_2)_2N$], 1.5–1.9 [4 H, m, $CH_3CH_2CH_2CH(OH)C(5)$ and CH_2CH_2N], 2.2 [2 H, m, $CH_3CH_2CH_2CH(OH)C(5)$], > 10 2 H, br, OH and CO_2H)
13	Me	$CH(OH)CH_3$	7.61	4.08(3 H, s)	5.51 (1 H, q, *J* 7)	1.65[3 H, d, *J* 7, $CH_3CH(OH)C(5)$]

[a] Spectra for both **6a** and **10** recorded in [$^2H_6$]DMSO. Unless otherwise specified, integral and multiplicity for signals are: H-4: (1 H, s), $CH_xC(5)$: (3 H, s). A broad signal over 10 ppm was observed in the spectra of all compounds.

Table 8 Analytical data for 1,2-dialkyl-3-nitropyrroles **1** and related compounds

Compd. (formula)	R^1	R^2	Yield[a] (%)	Mp (°C)	ν_{max}/cm^{-1} [b] (NO_2)	Found (%) (required) C	H	N
1a ($C_6H_8N_2O_2$)	Me	Me	86	103–104[c]	1510, 1320	51.35 (51.42)	5.81 (5.75)	20.1 (19.99)
1b ($C_7H_{10}N_2O_2$)	Et	Me	88	60–63	1520, 1325	54.6 (54.54)	6.42 (6.54)	18.15 (18.17)
1c ($C_8H_{12}N_2O_2$)	Pr	Me	89	—[c,d]	1510, 1320	57.3 (57.13)	7.3 (7.19)	16.4 (16.66)
1d ($C_{11}H_{18}N_2O_2$)	Hexyl	Me	88	—[c,d]	1520, 1320	62.7 (62.83)	8.45 (8.63)	13.45 (13.32)
1e ($C_{17}H_{30}N_2O_2$)	Dodecyl	Me	92	—[c,d]	1510, 1320	69.5 (69.35)	10.4 (10.27)	9.2 (9.51)
1f ($C_{12}H_{12}N_2O_2$)	Benzyl	Me	86	86–87	1510, 1315	66.65 (66.65)	5.6 (5.59)	12.9 (12.95)
1g ($C_{12}H_{11}FN_2O_2$)	*p*-$FC_6H_4CH_2$	Me	82	98–100	1510, 1320	61.3 (61.53)	4.75 (4.73)	11.9 (11.96)
1h ($C_7H_{10}N_2O_2$)	Me	Et	78	53–54	1510, 1315	54.5 (54.54)	6.55 (6.54)	18.15 (18.17)
1i ($C_8H_{12}N_2O_2$)	Et	Et	78	53–55	1515, 1330	57.2 (57.13)	7.25 (7.19)	16.7 (16.66)
1j ($C_9H_{14}N_{22}O_2$)	Et	Pr	72	—[c,d]	1515, 1300	59.5 (59.32)	7.8 (7.74)	15.2 (15.37)
1k ($C_{19}H_{16}F_2N_2O_2$)	*p*-$FC_6H_4CH_2$	*p*-$FC_6H_4(CH_2)_2$	80	109–111	1510–1300	66.6 (66.66)	4.5 (4.71)	8.2 (8.18)
1l ($C_{29}H_{54}N_2O_2$)	Dodecyl	Tridecyl	70	—[d]	1500–1300	75.7 (75.27)	11.9 (11.76)	5.9 (6.05)
11 ($C_5H_6N_2O_2$)	H	Me	73	166–169	1580, 1325[d]	47.7 (47.61)	4.8 (4.80)	22.2 (22.21)
14 ($C_{17}H_{19}FN_2O_4$)	*p*-$FC_6H_4CH_2$	$(CH_2)_3CO_2Et$	83	—[d]	1510, 1300[f]	61.3 (61.07)	5.9 (5.73)	8.1 (8.38)
15 ($C_{13}H_{12}N_2O_2$)	Me	CH=CHPh[g]	45	—[d]	1495, 1300	68.6 (68.41)	5.5 (5.30)	12.1 (12.27)
16 ($C_{13}H_{14}N_2O_3$)	Me	$CH_2CH(OH)Ph$	40	—[d]	1500, 1300[h]	63.7 (63.40)	5.9 (5.73)	11.05 (11.38)

[a] For compounds **1** and **11**, yields refer to the decarboxylation of the corresponding carboxylic acid (treatment with metallic copper in quinoline). For compounds **14**, **15** and **16** yields refer to treatment of the corresponding compound **1** with an electrophile (see Table 10). [b] IR spectra: **1a**, **1b**, **1f**, **1g**, **1h**, **1i**, **11**; KBr. Other compounds: liq. film on NaCl. [c] Compounds **1a**, **1c**, **1d**, **1e** and **1j** are described in the literature. The reported mp are **1a**: 103–104 °C (ref. 2), **1c**, **1d**, **1e** and **1j**: oils (ref. 1). [d] These compounds were obtained as yellowish oils. [e] 3260 cm^{-1} (NH st.) [f] 1730 cm^{-1} (vs; C=O st.). [g] Mainly *E*-isomer. [h] 3440 cm^{-1} (br OH st.)

mol), hexadecyl(tributyl)phosphonium bromide (0.1 g, 0.002 mol) and acetonitrile (50 ml) was heated to 45 °C. Methyl iodide (1.8 g, 0.013 mol) was added dropwise to the mixture after which it was stirred for a further 1.5 h and then allowed to cool to room temperature. The solid was filtered off and ether was added to the filtrate to give recovered catalyst as a white solid precipitate; this too was filtered off. The filtrate was then passed through a small silica gel column and evaporated to provide compound **8a** (1.83 g, 86%), pure enough to be used in the following synthetic steps without further purification; mp 79–80 °C.

The following compounds were obtained in a similar way by treating the corresponding compound **8** with the corresponding alkyl halide (specified solvent, temperature and reaction time in [ ]); yields, analytical and spectral data are shown in Tables 3 and 4. Ethyl 1-ethyl-5-methyl-4-nitropyrrole-2-carboxylate **5b** (R^1 = Et, R^2 = Me) [acetonitrile, 45 °C, 3 h]; ethyl 5-methyl-1-propyl-4-nitropyrrole-2-carboxylate **5c** (R^1 = Pr, R^2 = Me) [acetonitrile, reflux, 1.5 h]; ethyl 1-hexyl-5-methyl-4-nitropyrrole-2-carboxylate **5d** (R^1 = hexyl, R^2 = Me) [toluene, 100 °C, 24 h]; ethyl 1-dodecyl-5-methyl-4-nitropyrrole-2-carboxylate **5e** (R^1 = dodecyl, R^2 = Me) [toluene, 100 °C, 24 h]; ethyl 1-benzyl-5-methyl-4-nitropyrrole-2-carboxylate **5f** (R^1 = CH_2Ph, R^2 = Me) [acetonitrile, reflux, 1.5 h]; ethyl 1-(*p*-fluorophenylmethyl)-5-methyl-4-nitropyrrole-2-carboxylate **5g** (R^1 = *p*-$FC_6H_4CH_2$, R^2 = Me) [acetonitrile, reflux, 1.5 h]; ethyl 5-ethyl-4-nitro-1-propylpyrrole-2-carboxylate **5h** (R^1 = Pr, R^2 = Et) [acetonitrile, reflux, 1.5 h]; ethyl 1-isopropyl-5-methyl-4-nitropyrrole-2-carboxylate **5i** (R^1 = Pr^i, R^2 = Me) [toluene, 70 °C, 6 h]; ethyl 1-methyl-5-ethyl-4-nitropyrrole-2-carboxylate **5j** (R^1 = Me, R^2 = Et) [acetonitrile, RT, 24 h]; ethyl 1,5-diethyl-4-nitropyrrole-2-carboxylate **5k** (R^1 = R^2 = Et) [acetonitrile, RT, 24 h]; ethyl 1-benzyl-5-ethyl-4-nitropyrrole-2-carboxylate **5l** (R^1 = $CH_2C_6H_5$, R^2 = Et) [acetonitrile, reflux, 1.5 h]; ethyl 5-ethyl-1-(*p*-fluorobenzyl)-4-nitropyrrole-2-carboxylate **5m** (R^1 = *p*-$FC_6H_4CH_2$, R^2 = Et) [acetonitrile, reflux, 1.5 h]; ethyl 5-ethyl-1-hexyl-4-nitropyrrole-2-carboxylate **5q**; (R^1 = hexyl, R^2 = Et) [toluene, 100 °C, 24 h]; ethyl 5-ethyl-1-dodecyl-4-nitropyrrole-2-carboxylate **5r** (R^1 = dodecyl, R^2 = Et) [toluene, 100 °C, 24 h].

Method C: reaction of compounds 7a and 5 with electrophiles. *Alkylation of* **7a** *in the DMSO–KOH system* (*Table 5, entries* 1-6). *Sample procedure: Treatment of* **7a** *in the molar ratio* **7a**.—R^3X:KOH = 1:10:10 (entry 2; R^3X = EtI) *to give* **5n** (R^1 = Et, R^2 = Pr, R^4 = Et) *and* **6j** (R^1 = Et, R^2 = Pr, R^4 = H).—To a rapidly stirred mixture, under an anhydrous inert atmosphere, of finely crushed potassium hydroxide (3.3 g, 0.05 mol) in DMSO (20 ml) was added compound **7a** (1 g, 0.005 mol) and ethyl iodide (7.8 g, 0.05 mol). After the mixture had been quenched in ice–water it was basified by the addition of a little solid KOH and then extracted with ether. This ethereal solution (A) contained non-acidic compounds while the basic aqueous solution contained hydrolysis products alkylated at the 1-position and unchanged **7a**. This aqueous phase was acidified by addition of 6 M HCl. The solid precipitate was filtered off, treated with saturated aqueous $NaHCO_3$ and filtered again (unreacted **7a**). The aqueous solution was acidified with 2 M HCl and stored at 0 °C for 18 h. The resulting white solid was filtered off and crystallized to yield pure 5-propyl-1-ethyl-4-nitropyrrole-2-carboxylic acid **6j** (0.25 g, 22%). Solution (A) was evaporated to yield ethyl 5-propyl-1-ethyl-4-nitropyrrole-2-carboxylate **5n** (0.97 g, 76%).

The following compounds were obtained in a similar way by treating **7a** with the corresponding alkyl halide. Methyl 2-ethyl-1-methyl-4-nitropyrrole-2-carboxylate **9a** (R^1 = R^4 = Me, R^2 = Et, R^3X = MeI); methyl 1,2-diethyl-4-nitropyrrole-2-carboxylate **9b** (R^1 = R^2 = Et, R^4 = Me, R^3X = MeI); 1-benzyl-5-phenethyl-4-nitropyrrole-2-carboxylic acid **6k** (R^1 = benzyl, R^2 = Ph[CH_2]$_2$, R^4 = H; R^3X = $PhCH_2Br$); 1-(*p*-fluorobenzyl)-5-[2-(*p*-fluorophenyl)ethyl]-4-nitropyrrole-2-carboxylic acid **6l** [R^1 = *p*-$FC_6H_4CH_2$, R^2 = *p*-$FC_6H_4(CH_2)_2$, R^4 = H; R^3X = *p*-$FC_6H_4CH_2Br$].

Treatment of compounds **5** *with alkyl halides in the DMSO–KOH system* (*Table 5, entries* 7–13). *Sample procedure: synthesis of 5-heptyl-4-nitro-1-hexylpyrrole-2-carboxylic acid* **6m** (R^1 = hexyl, R^2 = heptyl, R^4 = H) (*Table 5, entry* 10; R^3X = $C_6H_{13}Br$).—To a stirred mixture of finely crushed potassium hydroxide (2.2 g, 0.033 mol) in DMSO (15 ml), under an inert atmosphere at room temperature, were added compound **5d** (R^1 = hexyl, R^2 = Me, R^4 = H) (0.9 g, 0.0033 mol) and hexyl bromide (1.4 ml, 1.65 g, 0.01 mol). After being stirred for 1 h,

Table 9 ^{1}H NMR spectral data for 1,2-dialkyl-3-nitropyrroles **1** and related compounds; δ_H(200 MHz; $CDCl_3$; Me_4Si)[a]

Compd.	R^1	R^2	H-4[a]	H-5[a]	CH_xN	$CH_xC(5)$	Other
1a	Me	Me	6.10	6.70	3.66 (3 H, s)	2.61 (3 H, s)	—
1b	Et	Me	6.47	6.71	3.90 (2 H, q, *J* 7)	2.60 (3 H, s)	1.39 (3 H, t, *J* 7, CH_3CH_2N)
1c	Pr	Me	6.41	6.69	3.80 (2 H, t, *J* 7)	2.60 (3 H, s)	0.91 (3 H, t, *J* 7, $CH_3CH_2CH_2N$), 1.70 (2 H, m, $CH_3CH_2CH_2N$)
1d	Hexyl	Me	6.41	6.71	3.80 (2 H, t, *J* 7)	2.60 (3 H, s)	0.81 [3 H, t, *J* 7, $CH_3(CH_2)_4CH_2N$], 1.25–1.35 [6 H, m, $CH_3(CH_2)_3CH_2CH_2N$], 1.60 [2 H, m, $CH_3(CH_2)_3CH_2CH_2N$]
1e	Dodecyl	Me	6.41	6.71	3.80 (2 H, t, *J* 7)	2.60 (3 H, s)	0.80 [3 H, t, *J* 7, $CH_3(CH_2)_{11}N$], 1.20–1.30 [18 H, m, $CH_3(CH_2)_3CH_2CH_2N$], 1.60–1.70 [2 H, m, $CH_3(CH_2)_9CH_2CH_2N$]
1f	Benzyl	Me	6.51	6.79	5.06 (2 H, s)	2.51 (3 H, s)	6.90–7.40 (5 H, m, Ph)
1g	*p*-$FC_6H_4CH_2$	Me	6.51	6.79	5.05 (2 H, s)	2.54 (3 H, s)	7.00–7.07 (4 H, m, Ar)
1h	Me	Et	6.38	6.67	3.58 (3 H, s)	3.02 (2 H, q, *J* 7)	1.18 [3 H, t, *J* 7, $CH_3CH_2C(2)$]
1i	Et	Et	6.50	6.70	3.94 (2 H, q, *J* 7)	3.05 (2 H, q, *J* 7)	1.25 [3 H, t, *J* 7, $CH_3CH_2C(2)$], 1.46 (3 H, t, *J* 7, CH_3CH_2N)
1j	Et	Pr	6.40	6.70	3.94 (2 H, q, *J* 7)	3.02 (2 H, t, *J* 7)	1.01 [3 H, t, *J* 7, $CH_3(CH_2)_2C(2)$], 1.38 (3 H, t, *J* 7, CH_3CH_2N), 1.60 [3 H, t, *J* 7, $CH_3CH_2CH_2C(2)$]
1k	*p*-$FC_6H_4CH_2$	*p*-$FC_6H_4(CH_2)_2$	6.47	6.83	4.6 (2 H, s)	3.15 (2 H, t, *J* 7)	2.77 [2 H, t, *J* 7, $ArCH_2CH_2C(2)$], 6.90–7.90 (8 H, m, Ar)
1l	Dodecyl	Tridecyl	6.45	6.73	3.72 (2 H, t, *J* 7)	2.96 (2 H, t, *J* 7)	0.90 [6 H, *J* 7, $CH_3(CH_2)_{12}C(2)$ + $CH_3(CH_2)_{11}N$], 1.0–1.5 [42 H, m, $CH_3(CH_2)_{11}CH_2C(2)$ + $CH_3(CH_2)_{10}CH_2N$], 1.6 [2 H, m, $RCH_2CH_2C(2)$], 1.75 (2 H, m, RCH_2CHN)
1l	H	Me	6.35		—	2.46 (3 H, s)	
14	*p*-$FC_6H_4CH_2$	$(CH_2)_3CO_2Et$	6.48	6.79	5.13 (2 H, s)	2.97–3.02 (2 H, m)	1.25 (3 H, t, *J* 7, CH_3CH_2O), 1.82–1.90 [2 H, m, $C(2)CH_2CH_2R$], 2.40 [2 H, t, *J* 7, $C(2)(CH_2)_2CH_2CO_2Et$]
15	Me	CH=CHPh[b]	6.55	6.80	3.78 (3 H, s)	7.56 (1 H, d, *J* 16)	7.00 (1 H, d, *J* 16, CH=*CH*Ph), 7.55 (2 H, dd, $J_1$8, $J_2$2) + 7.3–7.4 (3 H, m, Ph)
16	Me	$CH_2CH(OH)Ph$	6.41	6.76	3.38 (3 H, s)	2.35 (1 H, dd, $J_1$14, $J_2$8) + 3.48 (1 H, dd, $J_1$14, $J_2$5)	5.14 [1 H, dd, $J_1$8, $J_2$5, $CH_2CH(OH)Ph$], 7.3–7.4 (5 H, m, Ph), 2.5 (1 H, br, OH)

[a] Integral and multiplicity for signals are: (1 H, d, *J* 3.5). [b] (*E*)-Isomer.

Table 10 Reaction of compounds **11** (R^1 = H) and **1** (R^1 = alkyl) with electrophiles

Entry	Starting compd.	R^1	Electrophile	Base	Molar ratio **1** (**11**):E:base	Product	R^1	R^2	Yield (%)[a]
1	**11**	H	MeI	KOH	1:3:10	**1a**	Me	Me[b]	83[b]
2	**11**	H	$PhCH_2Br$	KOH	1:1.1:3	**1f**	Benzyl	Me[b]	90[b]
3	**11**	H	MeI	KBu^{t}O	1:3:10	**1a** + **1h**	Me	Me + Et	40 + 56[c]
4	**1g**	*p*-$FC_6H_4CH_2$	CH_2=$CHCO_2Et$	KOH	1:1.3:2	**14**	*p*-$FC_6H_4CH_2$	$(CH_2)_3CO_2Et$	83
5	**1a**	Me	PhCHO	KOH	1:1.8:2.3	**15** + **16**	Me	CH=CHPh + $CH_2CH(OH)Ph$	45 + 40[c]

[a] Yields are calculated considering the amount of isolated product obtained after purification. [b] The compound corresponding to *N*-alkylation (R^1 alkyl) was the only product obtained. [c] Mixture of compounds. Yield calculated after isolation by column chromatography.

the slurry was quenched in ice–water, acidified with concentrated hydrochloric acid and extracted with ether. The ethereal phase was washed twice with water and once with brine, dried ($MgSO_4$) and evaporated *in vacuo* to afford an oily residue. This was purified by column chromatography on silica gel using hexane–ethyl acetate as the eluent to give pure **6m** (0.36 g, 32%). The following compounds were obtained in a similar way by treating the corresponding compound **5** with the corresponding alkyl halide; yields are shown in Table 5. Analytical and spectral data of compounds **6** are shown in Tables 6 and 7.

1-Hexyl-4-nitro-5-tridecylpyrrole-2-carboxylic acid **6n** (R^1 = hexyl, R^2 = tridecyl, $R^3X = C_{12}H_{25}Br$) 1-dodecyl-4-nitro-5-tridecylpyrrole-2-carboxylic acid **6o** (R^1 = dodecyl, R^2 = tridecyl, R^3-X = $C_{12}H_{25}Br$).

Hydroxylated compounds. 5-(1-*Hydroxybutyl*)-4-*nitro*-1-*propylpyrrole*-2-*carboxylic acid* **12** [R^1 = Pr, R^2 = CH(OH)-$(CH_2)_2CH_3$, R^4 = H] (*Table* 5, *entry* 14; R^3X = PrI).—The above-mentioned procedure was followed but the system was open to air. The solid residue obtained after eliminating the solvent was purified by column chromatography on silica gel using hexane–ethyl acetate as the eluent to give pure **12** (0.24 g 27%); analytical and spectral data are shown in Tables 6 and 7.

5-(1-*Hydroxyethyl*)-1-*methyl*-4-*nitropyrrole*-2-*carboxylic acid* **13** [R^1 = Me, R^2 = $CH(OH)CH_3$, R^4 = H] (*Table* 5, *entry* 15).—The above-mentioned procedure was followed starting from **5j** (0.3 g, 0.0011 mol) but no electrophile was added and the reaction took place in an air stream (reaction time: 96 h). The oily residue was purified by column chromatography on silica gel using chloroform–methanol (9:1) as the eluent to yield pure **6h** (0.02 g, 12%) and **13** (0.17 g, 70%); analytical and spectral data are shown in Tables 6 and 7.

Treatment with alkyl halides in the potassium tert-*butoxide–DMSO system. Sample Procedure: synthesis of ethyl* 5-*butyl*-4-*nitro*-1-*propylpyrrole*-2-*carboxylate* **5o** (R^1 = Pr, R^2 = Bu, R^4 = Et) (*Table* 5, *entry* 9).—To a stirred mixture of potassium *tert*-butoxide (0.74 g, 6.6 mmol) in DMSO (15 ml), under inert atmosphere at room temperature were added compound **5c** (R^1 = Pr, R^2 = Me) (0.8 g, 3.3 mmol) and propyl iodide (1.2 ml, 2.0 g, 12 mmol). After being stirred for 24 h, the slurry was quenched in ice–water and a similar work-up procedure to that described above gave an oily residue. This was purified by column chromatography on silica gel using hexane–ethyl acetate (75:25) as the eluent to yield pure **5o** (0.28 g, 30%). Analytical and spectral data for compounds **5** are shown in Tables 3 and 4.

Compound **5p** (R^1 = hexyl, R^2 = heptyl, R^4 = Et) was obtained in a similar way by treating **5d** with hexyl bromide.

Hydrolysis of ethyl 1,5-dialkyl-4-nitropyrrole-2-carboxylate

Typical procedure: synthesis of 1,5-dimethyl-4-nitropyrrole-2-carboxylic acid 6a (R^1 = R^2 = Me). A stirred mixture of compound **5a** (2.35 g, 0.011 mol), 2 M aqueous sodium hydroxide (15 ml, 0.03 mol) and ethanol (5 ml) was refluxed for 2 h. The resulting clear brownish solution was concentrated to approx. half of its volume, cooled, diluted with water (4-fold) and filtered. Ice was added to the filtrate which was then cautiously acidified with concentrated hydrochloric acid and set aside for 18 h in the cold. The resulting precipitate was collected, washed with water, dissolved in saturated aqueous $NaHCO_3$ and the solution filtered. The clear yellowish solution was cautiously acidified with 6 M hydrochloric acid to precipitate a white solid which was filtered off, rinsed with water and dried to yield almost pure **6a** (1.8 g, 90%). An analytical sample was obtained by recrystallization (1,2-dichloroethane). Analytical and spectral data for these compounds are shown in Tables 6 and 7.

The following compounds were obtained in a similar way: 5-methyl-4-nitropyrrole-2-carboxylic acid **10**; 1-ethyl-5-methyl-4-nitropyrrole-2-carboxylic acid **6b**; 5-methyl-1-propyl-4-nitropyrrole-2-carboxylic acid **6c**; 1-hexyl-5-methyl-4-nitropyrrole-2-carboxylic acid **6d**; 1-dodecyl-5-methyl-4-nitropyrrole-2-carboxylic acid **6e**; 1-benzyl-5-methyl-4-nitropyrrole-2-carboxylic acid **6f**; 1-(*p*-fluorobenzyl)-5-methyl-4-nitropyrrole-2-carboxylic acid **6g**; 5-ethyl-1-methyl-4-nitropyrrole-2-carboxylic acid **6h**; 1,5-diethyl-4-nitropyrrole-2-carboxylic acid **6i**.

Decarboxylation of 1,5-dialkyl-4-nitropyrrole-2-carboxylic acids

Typical procedure: synthesis of 1,2-dimethyl-3-nitropyrrole 1a (R^1 = R^2 = Me). A mixture of **6a** (1.9 g, 10 mmol), Cu powder (1 g, 16 mmol) and quinoline (10 ml) was heated to 195 °C for 1 h. The resulting dark slurry was allowed to cool and then diluted with ether, washed throughly with 2 M hydrochloric acid and brine, dried ($MgSO_4$) and evaporated. The oily residue was stored at room temperature for several hours to give a crystalline solid. Recrystallization (isobutyl alcohol) yielded **1a** (1.2 g, 86%). Analytical and spectral data for these compounds are shown in Tables 8 and 9.

The following compounds were obtained in a similar way: 1-ethyl-2-methyl-3-nitropyrrole **1b**; 2-methyl-1-propyl-3-nitropyrrole **1c**; 1-hexyl-2-methyl-3-nitropyrrole **1d**; 1-dodecyl-2-methyl-3-nitropyrrole **1e**; 1-benzyl-2-methyl-3-nitropyrrole **1f**; 1-(*p*-fluorobenzyl)-2-methyl-3-nitropyrrole **1g**; 2-ethyl-1-methyl-3-nitropyrrole **1h**; 1,2-diethyl-3-nitropyrrole **1i**; 1-ethyl-2-propyl-3-nitropyrrole **1j**; 1-(*p*-fluorobenzyl)-2-[2-(*p*-fluorophenyl)ethyl]-3-nitropyrrole **1k**; 2-tridecyl-1-dodecyl-3-nitropyrrole **1l**; 2-methyl-3-nitropyrrole **11**.

Cleavage of an ester group by acidic hydrolysis and subsequent decarboxylation (alternative method)

Typical procedure: synthesis of 1-ethyl-2-methyl-3-nitropyrrole 1b (R^1 = Et, R^2 = Me). A mixture of **5b** (2.1 g, 0.09 mol) and 2 M hydrochloric acid (25 ml) was heated to reflux temperature for 5 days. The resulting dark slurry was allowed to cool after which it was diluted with chloroform and the layers were separated. The organic phase was dried ($MgSO_4$) and evaporated to give an oily residue which when stored at room temperature for several hours gave a crystalline solid. Recrystallization (isobutyl alcohol) of this yielded pure **1b** (0.8 g, 62%).

The following compounds were obtained in a similar way: 1,2-dimethyl-3-nitropyrrole **1a**; 2-methyl-1-propyl-3-nitropyrrole **1c**; 1-ethyl-2-propyl-3-nitropyrrole **1j**; 2-methyl-3-nitropyrrole **11**.

Reaction of compounds 1 and 11 with alkyl halides in the DMSO–base system

Treatment with methyl iodide (Table 10; entry 1; E = MeI). To a stirred mixture of finely crushed potassium hydroxide (0.13 g, 2.2 mmol) in DMSO (2 ml), under an inert atmosphere, were added compound **11** (R^1 = H, R^2 = Me) (0.10 g, 0.8 mmol) and methyl iodide (0.1 ml, 0.22 g, 1.5 mol). After being stirred for 1 h, the slurry was quenched in ice–water, acidified with 6 M hydrochloric acid and extracted with ether. The extract was washed twice with water and once with brine, dried ($MgSO_4$) and evaporated *in vacuo* to yield almost pure **1a** (R^1 = R^2 = Me) (0.11 g, 82%).

Treatment with benzyl bromide (Table 10; entry 2; E = $PhCH_2Br$). The above-mentioned procedure was used to give a crude reaction product which was purified by filtration through silica gel, to yield pure **1f** (R^1 = CH_2Ph, R^2 = Me) (0.17 g, 90%).

Treatment with methyl iodide in the DMSO–potassium *tert*-butoxide system (Table 10; entry 3; E = MeI). To a stirred mixture of potassium *tert*-butoxide (0.27 g, 2.2 mmol) in

DMSO (2 ml), under an inert atmosphere, were added compound **11** (R^1 = H, R^2 = Me) (0.10 g, 0.8 mmol) and methyl iodide (0.4 ml, 0.90 g, 6.4 mmol). The mixture was stirred at room temperature for 2 h after which the isolation procedure described above yielded an oily residue. The ^{1}H NMR spectrum of this showed that it was a mixture of compounds **1h** (R^1 = Me, R^2 = Et) (56%) and **1a** (R^1 = R^2 = Me) (44%).

Treatment with ethyl acrylate: synthesis of ethyl 4-[1-(*p*-fluorobenzyl)-3-nitropyrrol-2-yl]butyrate 14 [R^1 = *p*-$FC_6H_4CH_2$, R^2 = $(CH_2)_3CO_2Et$] (Table 10; entry 4; E = CH_2=$CHCO_2Et$). The above-mentioned procedure was followed (reaction time: 1 h). Starting from **1g** (R^1 = *p*-$FC_6H_4CH_2$, R^2 = Me) (0.1 g, 0.5 mmol), KOH (0.048 g, 0.09 mmol) and ethyl acrylate (0.05 ml, 0.04 g, 0.4 mmol), an oily residue was obtained. Purification of this by column chromatography on silica gel using hexane–ether (5:1) as the eluent yielded **14** (0.12 g, 83%).

Treatment with benzaldehyde: synthesis of 2-(2-phenylvinyl)-1-methyl-3-nitropyrrole 15 (R^1 = Me, R^2 = CH=CHPh) and 2-(2-hydroxyphenethyl)-1-methyl-3-nitropyrrole 16 [R^1 = Me, R^2 = $CH_2CH(OH)Ph$] (Table 10; entry 5; E = C_6H_4CHO). The same above-mentioned procedure was followed, but the reaction time was 2 h. Starting from **1a** (R^1 = R^2 = Me) (0.74 g, 5.3 mmol), KOH (0.69 g, 12 mmol) and benzaldehyde (0.2 ml, 0.21 g, 9.4 mmol), a mixture of two compounds was obtained as an oily residue. Purification of this by column chromatography on silica gel using hexane–ether (5:1) as the eluent yielded **15** (0.74 g, 45%; (*E*)-isomer) and further elution with hexane–ethyl acetate (7:3) yielded pure **16** (0.52 g, 40%).

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