3-Hydroxypyrroles and 1*H*-Pyrrol-3(2*H*)-ones. Part 11.[1] ^{1}H and ^{13}C NMR Spectra of 1-Substituted and 1,2-Disubstituted 3-Hydroxy- and 3-Alkoxypyrroles

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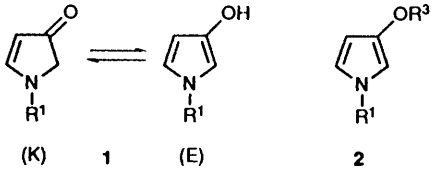
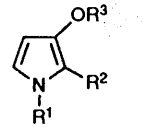
The ^{1}H and ^{13}C NMR parameters of a range of 1-substituted and 1,2-disubstituted 3-hydroxy- and 3-alkoxy-pyrroles are reported. Typical values for 1-*tert*-butyl-3-hydroxypyrrole (*J* values in Hz) are: δ_H 5.50 ($^3J_{4,5}$ 2.9, $^4J_{2,4}$ 2.0, 4-H), 6.26 ($^4J_{2,4}$ 2.0 and $^4J_{2,5}$ 2.6, 2-H) and 6.49 ($^3J_{4,5}$ 2.9 and $^4J_{2,5}$ 2.6, 5-H); δ_C 97.60 ($^1J_{4-H}$ 167.9, $^2J_{5-H}$ and $^3J_{2-H}$ 6.8, C-4), 101.16 ($^1J_{2-H}$ 182.7, $^3J_{4-H}$ and $^3J_{5-H}$ 4.3, C-2), 114.18 ($^1J_{5-H}$ 182.5, $^2J_{4-H}$ and $^3J_{2-H}$ 6.9, C-5) and 143.37 ($^2J_{2-H}$ 4.3, $^3J_{5-H}$ 9.0, C-3).

In earlier parts of this series, we have shown that polar, hydrogen-bond acceptor solvents such as dimethyl sulfoxide (DMSO) substantially favour the enol form **1**E of the 1*H*-pyrrol-3(2*H*)-one–3-hydroxypyrrole equilibrium,[2] and that the



system can be regiospecifically *O*-alkylated to give a good synthesis of 3-alkoxypyrroles, **2**.[1] In this paper, we report a detailed study of the ^{1}H and ^{13}C NMR spectra of simple 1-substituted and 1,2-disubstituted 3-hydroxy- and 3-alkoxy-pyrroles, all of which clearly share common structural features. This work complements our earlier report of the NMR spectra of the 1*H*-pyrrol-3(2*H*)-one system, **1**K.[3]

The 3-hydroxypyrroles **3**, **6**, **10**, **12**, **14** and **16** were prepared as their 1*H*-pyrrol-3(2*H*)-one tautomers by flash vacuum pyrolysis of appropriate aminomethylene Meldrum's acid derivatives,[4] and the enol forms were generated by solution in [$^2H_6$]DMSO. The corresponding 3-alkoxypyrroles **4**, **5**, **7**–**9**, **11**, **13**, **15** and **17** were made as described in part 10,[1] and their spectra were normally recorded using [^{2}H]chloroform as the solvent. The range of compounds studied was selected to include 1-alkyl-3-hydroxy- and alkoxy-pyrroles (**3**–**5**), and 1-aryl derivatives (**6**–**9**), together with 1,2-dialkyl (**10**–**11**), 1-alkyl-2-aryl (**12**–**13**), 1-aryl-2-alkyl (**14**–**15**), and 1,2-diaryl (**16**–**17**) compounds.



	R^1	R^2	R^3
3	Bu^t	H	H
4	Bu^t	H	Me
5	Bu^t	H	Et
6	Ph	H	H
7	Ph	H	Me
8	Ph	H	Et
9	Ph	H	Pr^i
10	Et	Me	H
11	Et	Me	Me
12	Me	Ph	H
13	Me	Ph	Me
14	Ph	Me	H
15	Ph	Me	Me
16	Ph	Ph	H
17	Ph	Ph	Me

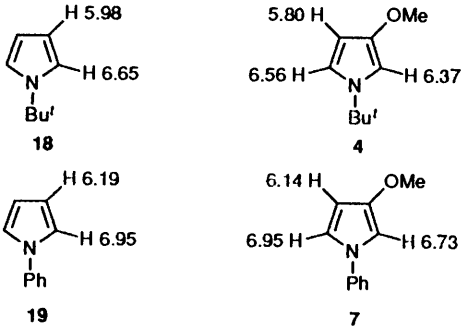


Fig. 1 A comparison of ^{1}H NMR chemical shifts δ_H of the pyrroles **18** and **19**[7] and the methoxypyrroles **4** and **7**

Results and Discussion

^{1}H NMR Spectra.—The ^{1}H NMR parameters of the ring protons of the pyrroles **3**–**17** are given in Table 1. The assignment of chemical shifts as $\delta_{5-H} > \delta_{2-H} > \delta_{4-H}$ follows intuitively, since the α-protons of pyrroles are usually deshielded relative to the β-protons,[5] and the conjugative electron-donating effect of the hydroxy- or alkoxy-substituent would be expected to affect only the 2-position. A number of experiments have confirmed these assignments. Thus the spectrum of the [2-^{13}C]-labelled 3-hydroxy-2-phenylpyrrole (**6**)[6] provides unambiguous confirmation of δ_{2-H}, and a nuclear Overhauser effect (NOE) experiment on the corresponding 3-methoxy compound **7** has established the relationship between 4-H and 5-H, since irradiation at δ_H = 6.14 gives a significant enhancement at δ_H = 6.95. In addition, a spectrum of [2,4-$^2H_2$]-1-*tert*-butyl-3-hydroxypyrrole (**3**)[3] showed the remaining ring proton signal at δ_H = 6.48, which is fully consistent with the above findings. The relative positions of the 2-, 4- and 5-proton resonances of the 3-hydroxy-and 3-alkoxy-pyrroles are independent of the nature of the 1-, 3- (and, where appropriate 2-) substituent (Table 1), as confirmed by the close similarity in the sizes of the 3- and 4-bond coupling constants (see below) for the various derivatives.

As expected, the incorporation of a 3-methoxy substituent into the pyrrole ring has little effect on δ_{4-H} and δ_{5-H}, but the chemical shift of 2-H is shifted to low frequency (Fig. 1). *N*-Aryl groups have a general deshielding effect on the pyrrole

Table 1 ^{1}H NMR chemical shifts[a] and coupling constants[b] of 3-hydroxypyrroles and 3-alkoxypyrroles

Compound	R^1	R^2	R^3	2-H	4-H	5-H	$^3J_{4,5}$	$^4J_{2,4}$	$^4J_{2,5}$
3[c]	Bu^t	H	H	6.26	5.50	6.49	2.9	2.0	2.6
4[d]	Bu^t	H	Me	6.37	5.80	6.56	3.0	2.0	2.7
5[d]	Bu^t	H	Et	6.36	5.78	6.54	3.0	2.0	2.6
6[c]	Ph	H	H	6.74	5.85	7.06	3.1	1.9	2.6
7[d]	Ph	H	Me	6.73	6.14	6.95	3.1	2.0	2.5
7[c]	Ph	H	Me	7.19	6.00	7.00	—	—	—
8[d]	Ph	H	Et	6.68	6.08	6.90	3.1	1.9	2.5
9[d]	Ph	H	Pr^i	6.67	6.05	6.88	3.1	2.0	2.5
10[c]	Et	Me	H	—	5.52	6.30	3.0	—	—
11[d]	Et	Me	Me	—	5.86	6.37	3.2	—	—
12[c]	Me	Ph	H	—	5.72	6.51	2.8	—	—
13[d]	Me	Ph	Me	—	6.07	6.55	3.0	—	—
14[c]	Ph	Me	H	—	5.78	6.56	3.0	—	—
15[d]	Ph	Me	Me	—	6.18	6.68	3.2	—	—
16[c]	Ph	Ph	H	—	5.97	6.78	3.1	—	—
17[d]	Ph	Ph	Me	—	6.19	6.73	3.2	—	—

[a] ppm. [b] Hz. [c] [$^2H_6$]DMSO solution. [d] [^{2}H]chloroform solution.

Table 2 ^{13}C NMR parameters[a] for the ring carbon atoms of 3-hydroxypyrroles[b] and 3-alkoxypyrroles[c]

				C-2			C-3			C-4			C-5		
Compound	R^1	R^2	R^3	δ_C	$^1J_{2-H}$	$^3J_{4-H} = {}^3J_{5-H}$	δ_C	$^2J_{2-H}$	$^3J_{5-H}$	δ_C	$^1J_{4-H}$	$^2J_{5-H} = {}^3J_{2-H}$	δ_C	$^1J_{5-H}$	$^2J_{4-H} = {}^3J_{2-H}$
3	Bu^t	H	H	101.16	182.7	4.3	143.37	4.3	9.0	97.60	167.9	6.8	114.18	182.5	6.9
4	Bu^t	H	Me	99.76	182.3	4.6	148.36	*d*	*d*	95.80	170.9	6.9	115.04	183.3	6.7
5	Bu^t	H	Et	100.53	182.8	4.3	147.29	*d*	*d*	96.45	170.3	7.0	114.79	183.0	6.8
6	Ph	H	H	101.54	185.8	4.1	146.07	3.8	9.8	102.18	170.9	7.0	115.96	186.5	6.6
7	Ph	H	Me	100.86	185.7	3.9	150.83	*d*	*d*	100.32	172.5	7.0	116.99	186.0	6.6
8	Ph	H	Et	101.49	185.8	4.2	149.61	*d*	*d*	100.78	172.0	7.0	116.84	186.2	6.4
9	Ph	H	Pr^i	102.98	185.7	4.2	147.79	*d*	*d*	101.57	172.5	7.1	116.62	185.7	6.3
10	Et	Me	H	109.94	—	*d*	139.40	—	9.3[e]	97.69	168.1	7.5	114.19	182.7	7.7[f]
11	Et	Me	Me	112.10	—	—	144.05	—	—	95.18	—	—	114.37	—	—
12	Me	Ph	H	116.50	—	*d*	141.62	—	7.8	98.11	170.0	7.8	120.29	184.3	6.9[g]
13	Me	Ph	Me	118.44	—	*d*	145.48	—	*d*	95.52	170.4	7.9	119.53	186.8	*d*
14	Ph	Me	H	110.47	—	*d*	141.40	—	*d*	100.45	170.8	6.5	116.41	186.2	7.3
15	Ph	Me	Me	112.93	—	*d*	145.42	—	*d*	97.21	170.8	7.7	116.75	185.7	6.8
16	Ph	Ph	H	115.04	—	*d*	143.96	—	9.4	101.08	171.5	7.5	121.46	188.0	7.5
17	Ph	Ph	Me	116.91	—	*d*	146.93	—	*d*	97.29	171.9	7.6	120.43	187.4	6.7

[a] Coupling constants are quoted in Hz. [b] [$^2H_6$]DMSO solution. [c] [^{2}H]Chloroform solution. [d] Complicated by further coupling. [e] $^3J_{2\text{-Me}} = 4.0$ Hz. [f] $^3J_{N\text{-}CH_2} = 4.1$ Hz. [g] $^3J_{N\text{-Me}} = 3.5$ Hz.

ring proton resonances, due to competitive delocalisation of the nitrogen atom's lone pair (4-H) and/or ring current effects (2- and 5-H) (Table 1 and Fig. 1).

A comparison of the data in Table 1 shows that variation of the alkoxy substituent produces little significant difference in the ^{1}H NMR parameters of the ring protons (*cf.* **4**, **5** and **7**–**9**). The apparent influence of the hydroxy or alkoxy substituent on δ_{2-H} and δ_{4-H} may be due in part to the change in solvent {*cf.* spectrum of **7** in [^{2}H]chloroform and [$^2H_6$]-DMSO, (Table 1)}: hydrogen bonding between [$^2H_6$]DMSO and the 3-hydroxy group is known to be important.[2]

In the *N*-aryl series, a 2-alkyl or 2-aryl substituent causes shielding at the 5-position, but leaves δ_{4-H} almost unaffected (Table 1, *cf.* **6**, **14**, **16** and **7**, **15** and **17**). The effect is much less regular in the *N*-alkyl series (Table 1), but this may be due to the variation in *N*-alkyl substituent.

For the 2-unsubstituted compounds, 3- and 4-bond coupling constants ($^3J_{4,5}$, $^4J_{2,4}$ and $^4J_{2,5}$) were observed in all cases (Table 1) and are expressed in Hz. The relative magnitudes [$^3J_{4,5}$ (3.0 ± 0.2) > $^4J_{2,5}$ (2.6 ± 0.1) > $^4J_{2,4}$ (2.0 ± 0.1)] provided independent confirmation of the consistency of the chemical shift assignments (see above), and are in reasonable agreement with data for other 1,3-disubstituted pyrroles (*e.g.* 1-benzyl-3-nitropyrrole,[8] $^3J_{4,5}$ 3.2, $^4J_{2,5}$ 2.5, $^4J_{2,4}$ 1.9). 2-Substituted 3-alkoxy- and 3-hydroxypyrroles show a value of $^3J_{4,5}$ in line with the above (Table 1).

^{13}C *NMR Spectra.*—The ^{13}C NMR parameters for the ring carbon atoms of the pyrroles **3**–**17** are given in Table 2. The assignment of C-2, C-4 and C-5 followed from a proton–carbon correlation experiment on the 1-*tert*-butyl-3-methoxypyrrole (**4**), which showed that $\delta_{C-5} > \delta_{C-2} > \delta_{C-4}$, *i.e.* the same relative order as in the ^{1}H NMR spectra. In some cases, the chemical shifts of C-2 and C-4 are very close, but they can be clearly distinguished by their one-bond coupling constants ($^1J_{CH}$), which are much larger for pyrrole α-carbons than for β-carbon atoms[9] (see below). This assignment was confirmed for [^{13}C-2]-3-hydroxy-1-phenylpyrrole (**6**)[6] in which the signal due to the enriched carbon atom was found at δ_C 101.45 (*cf.* Table 2).

The effect of the 3-hydroxy or alkoxy substituent on the chemical shift of the pyrrole ring carbon atoms is given in Table 3, where the values are compared with those of the analogous benzene derivatives **20** and **21**.[10] In all cases, a large high frequency shift is observed at the *ipso*-position, with the effect greatest in magnitude for the alkoxy compounds. In both pyrrole series, a shielding effect at C-2 and C-4 is observed, with the magnitude greater at C-2 where direct conjugation is

Table 3 Effect of hydroxy and methoxy groups on the ^{13}C NMR chemical shifts of pyrrole and benzene derivatives

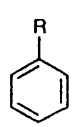
Compound	R^1	R^3	C-2	C-3	C-4	C-5
3[a]	Bu^t	H	−15.5	+35.5	−9.5	−2.5
4[a]	Bu^t	Me	−16.9	+40.5	−11.3	−1.7
6[b]	Ph	H	−17.5	+36.0	−7.9	−3.0
7[b]	Ph	Me	−18.1	+40.7	−9.8	−2.0
		R	*ortho*	α	*meta*	
20[10]		OH	−12.7	+26.9	+1.4	
21[10]		OMe	−14.4	+31.4	+1.0	

[a] *N-tert*-butylpyrrole; δ_C 116.7 (C-2, C-5), 107.9 (C-3, C-4). [b] *N*-phenylpyrrole;[12] δ_C 119.0 (C-2, C-5) 110.1 (C-3, C-4).

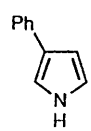
Table 4 Effect of pyrrole rings on the ^{13}C NMR chemical shift of the *para*-carbon atom of phenylpyrroles

Compound	R^1	R^2	R^3	(*C-para*)	$\Delta\delta_C$[a]
6	Ph	H	H	124.07	−4.4
7	Ph	H	Me	124.82	−3.7
19	*N*-phenylpyrrole[12]			125.3	−3.2
6	Ph (keto form)[3]			122.97	−5.5
15	Ph	Me	Me	126.17	−2.3
12	Me	Ph	H	125.08	−3.4
13	Me	Ph	Me	126.02	−2.4
22	3-phenylpyrrole[13]			124.5	−4.0

[a] Assumes δ_C(benzene) 128.5.[10]



20 R = OH
21 R = OMe



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possible. The average of these is similar in size to the *ortho*-effect in the benzene derivatives. Surprisingly, a small shielding effect is found at C-5 of the pyrroles, whereas the shift is in the opposite direction in the benzene series. Very similar results to these have been reported for certain highly substituted alkoxypyrroles.[11]

As expected, *N*-aryl substitution causes deshielding of the pyrrole resonances due to competitive delocalisation of the lone pair of the nitrogen atom: the effect is most pronounced at the 3- and 4-positions (Table 2). 2-Aryl substituents can fully interact with the pyrrole ring only by conjugative electron withdrawal and the net effect is to cause substantial deshielding at C-5 (Table 2). These interactions are also manifest in the chemical shift of the *para*-carbon atom of the aryl ring (Table 4): in all cases, the aryl ring acts as an electron acceptor, with the resonance shifted to low frequency with respect to benzene. In the *N*-aryl series, the alkoxy- and hydroxy-pyrroles are slightly better electron donors than pyrrole itself (Table 4),[12] but the effect is reduced on substitution at the 2-position where the two rings are unable to achieve coplanarity. It is of interest that the 1*H*-pyrrol-3(2*H*)-one system[3] (**1**K: R^1 = Ph) is a much better electron donor into an *N*-phenyl substituent than the hydroxy- or alkoxy-pyrroles: the delocalisation of the lone pair through the enaminone system may therefore be less efficient than that required to obtain a 6π system in the 'aromatic' pyrroles. In the *N*-methyl-2-phenyl series **12** and **13** (where coplanarity may again be a problem), it is clear that the pyrrole ring nevertheless acts as an electron donor, with the effect of similar magnitude to that of a methyl group.[10] However, a larger shift has been recorded with other *C*-arylpyrroles[13] (Table 4).

Alkyl substitution at the 2-position causes substantial deshielding at C-2 of the pyrrole ring (*ca.* 10 ppm) and shielding at C-3 (*ca.* 4 ppm) with very much smaller effects at the other positions. Similar effects have been noted in the spectra of other alkylpyrroles.[11]

One bond carbon–proton couplings for the β(C-4) and α(C-2 and -5) positions of the 3-hydroxy- and 3-alkoxy-pyrroles are fairly constant at 170 ± 2 and 185 ± 3 Hz, respectively. There is even less spread if the *N*-phenyl and *N*-alkyl examples are considered separately (Table 2). These values compare well with the corresponding couplings for pyrrole itself[9] [$^1J_{CH(\beta)}$ = 168.8; $^1J_{CH(\alpha)}$ = 183.3]. These well defined one bond coupling constants further confirmed the assignment of the resonances corresponding to the C-2 and C-4 atoms of 3-hydroxy-1-phenylpyrrole (**6**); the coupling constant of the signal at δ_C = 101.54 (185.8 Hz) compared with that of the signal at δ_C = 102.18 (170.9 Hz) indicates that in this example the C-2 atom is the more shielded in contrast to the *N*-alkyl examples. The one bond coupling constants in the phenyl substituted cases are all around 3 Hz larger than those for the other derivatives.

Long-range couplings were assigned by substitution of the 1- and/or 2-positions with phenyl or *tert*-butyl groups which are incapable of exhibiting long-range couplings to the ring resonances, and by deuteriation of the 2- and 4-positions.

The 2-unsubstituted hydroxy and alkoxy compounds give triplets of doublets corresponding to the C-2, C-4 and C-5 atoms. Thus, each of these carbon atoms couples to the hydrogen atoms attached to the other two with approximately the same coupling constant. Both the ^2J and ^3J couplings to the C-4 and C-5 positions are between 6.5 and 7.0 Hz which are reasonably close to the corresponding ^3J couplings in pyrrole itself[9] ($^3J_{C-4.2-H}$ 7.43, $^3J_{C-5.2-H}$ 6.63) but rather less than the related ^2J couplings[9] ($^2J_{C-5.4-H}$ 8.69, $^2J_{C-4.5-H}$ 8.34). The ^3J couplings observed to the 2-position are 4.2 ± 0.4 Hz, which is considerably less than those observed in the parent compound ($^3J_{C-2.4-H}$ 7.45, $^3J_{C-2.5-H}$ 6.63). 2-Substituted 3-hydroxy- and 3-alkoxy-pyrroles give unresolved multiplets for the signals corresponding to the C-2 atom, due to coupling to the substituent, but show well resolved ^2J coupling for the C-4 and C-5 atoms (Table 2). The C-5 resonances are sometimes further split by coupling to the *N*-substituent: for example this is found to be 3.5 Hz in 3-hydroxy-1-methyl-2-phenylpyrrole (**12**).

The long-range couplings to the C-3 atom attached to the oxygen function is more complex and often not resolved, particularly in the case of the alkoxy derivatives. However, these interactions have been analysed for 2-unsubstituted-3-hydroxypyrroles with the aid of deuteriated examples. A doublet of doublets pattern is normally observed for these cases, with couplings of *ca.* 4 and 9 Hz. The [2,4-$^2H_2$]-1-*tert*-butyl-3-hydroxypyrrole (**3**) gives rise to a doublet of 9.6 Hz and the larger value is therefore assigned to the three-bond coupling to 5-H. As the 2-substituted compounds which give well defined C-3 signals (*e.g.* **12** or **16**) do not show the smaller (4 Hz) coupling it is clear this must be the two bond coupling to 2-H. The complete long-range coupling pattern of 1-*tert*-butyl-3-hydroxypyrrole is depicted in Fig. 2.

In one example, 3-hydroxy-1-methyl-2-phenylpyrrole (**12**), a coupling of less than 2 Hz is also observed which may be a ^2J coupling to 4-H which is not resolved in more complex cases ($^2J_{C-3.4-H}$ in pyrrole itself[9] is 4.61 Hz). 2-Methyl groups can further split the C-3 signal into quartets with a coupling of around 4 Hz (*e.g.* **10**).

Experimental

^1H and ^{13}C NMR spectra were generally recorded at 200 and

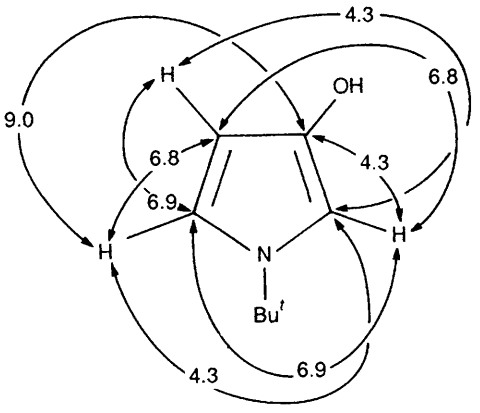

Fig. 2 Long-range couplings $^nJ_{CH}$/Hz for the 3-hydroxypyrrole **3**

50 MHz respectively using a Bruker WP200SY instrument. The digtal resolution in the ^1H and ^{13}C spectra was 0.27 and 1.4 Hz respectively.

3-Hydroxypyrrole Derivatives **3**, **6**, **10**, **12**, **14** *and* **16**.—These compounds were prepared as their 1*H*-pyrrol-3(2*H*)-one tautomers as previously described,[4] and the hydroxy form was generated in [$^2H_6$]DMSO solution.[2]

3-Alkoxypyrrole Derivatives **4**, **5**, **7**–**9**, **11**, **13**, **15** *and* **17**.—These derivatives were obtained as reported in part 10 of this series.[1]

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