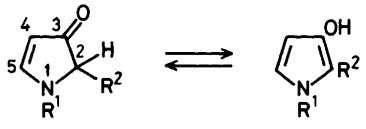
3-Hydroxypyrroles and 1*H*-Pyrrol-3(2*H*)-ones. Part 6.[1] ^{1}H and ^{13}C N.m.r. Spectra of 1-Substituted, 1,2-Disubstituted, and 1,2,2-Trisubstituted 1*H*-Pyrrol-3(2*H*)-ones

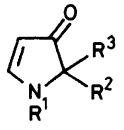
Hamish McNab* and Lilian C. Monahan
Department of Chemistry, University of Edinburgh, West Mains Road, Edinburgh EH9 3JJ

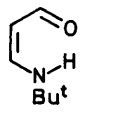
^{1}H and ^{13}C n.m.r. parameters of the 1*H*-pyrrol-3(2*H*)-one system are discussed. Typical values for the 1-t-butyl derivative (**2**) are as follows: 2-position, δ_H 3.70, $^4J_{2,5}$ 0.9 Hz; δ_C 54.19, $^1J_{CH}$ 141.2, and $^3J_{4-H}$ [= $^3J_{5-H}$] 5.2 Hz; 3-position, δ_C 199.76, $^3J_{5-H}$ 10.2, $^2J_{4-H}$ *ca.* 3, and $^2J_{2-H}$ *ca.* 4.5 Hz; 4-position, δ_H 5.09, $^3J_{4,5}$ 3.4 Hz; δ_C 99.13, $^1J_{CH}$ 176.5 and $^2J_{5-H}$ 6.8 Hz; 5-position, δ_H 7.93, $^3J_{4,5}$ 3.4 and $^4J_{2,5}$ 0.9 Hz; δ_C 162.58, $^1J_{CH}$ 173.0, $^2J_{4-H}$ 8.5, and $^3J_{2-H}$ 4.0 Hz. The effects of substituents on these parameters are also considered.

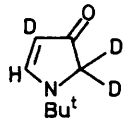
Although considerable n.m.r. data on the 1*H*-pyrrol-3(2*H*)-one (pyrrolone) (**1K**) tautomer of the 3-hydroxypyrrole system (**1E**) have been published in the literature, previous reports have been primarily an adjunct to synthetic work.[2] With the recent availability of a series of 4,5-unsubstituted pyrrolones containing a range of non-polar substituents[3] we are now able to present a systematic study of their ^{1}H and ^{13}C n.m.r. chemical shifts and coupling constants and to correlate the effect of ring substitution on these parameters. Derivatives with one or more hydrogen atoms at the 2-position may exist in solvent-dependent tautomeric equilibrium with 3-hydroxypyrroles (**1E**) but in this paper we deal exclusively with the keto forms (**1K**) which are normally dominant in chloroform solution.[1] The spectra of the enol forms are best considered alongside those of 3-alkoxypyrroles and will form the basis of a later Part of this series.



(**1K**) (**1E**)

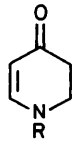






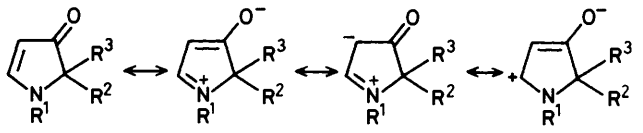
(**2**) R^1 = Bu^t, R^2 = R^3 = H
(**3**) R^1 = Ph, R^2 = R^3 = H
(**4**) R^1 = Et, R^2 = Me, R^3 = H
(**5**) R^1 = Ph, R^2 = Me, R^3 = H
(**6**) R^1 = Me, R^2 = Ph, R^3 = H
(**7**) R^1 = R^2 = Ph, R^3 = H
(**8**) R^1 = CH_2Ph, R^2 = Ph, R^3 = H
(**9**) R^1 = Pr^i, R^2 = R^3 = Me
(**10**) R^1 = Ph, R^2 = R^3 = Me
(**11**) R^1 = Pr^i, R^2 = Me, R^3 = Ph

(**12**) (**15**)



(**13**) R = Me
(**14**) R = Ph

Assignment of the ^{1}H and ^{13}C n.m.r. resonances of the pyrrolone system is a trivial matter, since it is well known[4] that alkene signals corresponding to sites α and β to the nitrogen atom of enaminones[5] occur in respectively deshielded and shielded positions in accord with their electron-deficient and electron-rich nature (Scheme).



Scheme.

^{1}H *N.m.r. Spectra.*—The n.m.r. parameters of the ring protons of the pyrrolones (**2**)—(**11**) are given in Table 1. The chemical shifts of the *N*-t-butyl compound (**2**) are in line with those of the *Z-s-Z* form of an enaminone model compound (**12**)[4] which shows δ 4.95 and 6.91 for the sites electronically equivalent to 4-H and 5-H, respectively of the pyrrolone. The corresponding values for the dihydropyridinone (**13**) are δ 4.90 and 7.00.[6] The pronounced deshielding of the 5-H resonance in particular of the pyrrolone system may reflect better delocalisation due to the enforced planarity of the five-membered ring.

Substitution by *N*-aryl groups causes deshielding of the protons of the conjugated system. Thus the *N*-alkyl derivatives [(**2**), (**4**), (**6**), (**8**), (**9**), (**11**)] have 4-H resonances in the range δ 4.9—5.15, and 5-H signals in the range δ 7.7—8.2 while the corresponding signals of the *N*-aryl derivatives [(**3**), (**5**), (**7**), (**10**)] are shifted to δ 5.35—5.5 and δ 8.1—8.6, respectively. Effects of similar magnitude are found in the spectra of the dihydropyridinones (**13**) and (**14**).[6] Competitive delocalisation of the nitrogen atom's lone pair into the phenyl ring contributes to reduced electron density in the pyrrolone unit (see below) and this is probably the major influence on the relative chemical shifts of the 4-positions of *N*-aryl and *N*-alkyl derivatives. In addition, the 5- (and 2-) positions may be influenced by through-space effects; the anisotropic effect of an approximately coplanar[1] *N*-phenyl group may well contribute to deshielding in these cases, and also account for the relatively wider spread of chemical shift which is observed (Table 1).

The chemical shifts of the 4- and 5-position are little affected by 2-aryl substituents [Table 1, *cf.* (**2**) and (**6**)] though a 2-methyl group causes a slight low frequency shift at these sites [Table 2, *cf.* (**2**) and (**4**), and hence the pairs (**9**), (**11**) and (**4**), (**6**)].

The positions of the resonances of the substituents are unexceptional (see reference 3), though it should be noted that the methylene protons of the *N*-benzyl derivative (**8**) are diastereotopic and appear as two doublets centred at δ 5.15 and 5.55.

Table 1. ^{1}H N.m.r. parameters for the ring protons of the pyrrolones (**2**)—(**11**)[a]

Derivative	R^1	R^2	R^3	2-H	4-H	5-H	$^3J_{4,5}$/Hz
(**2**)	Bu^t	H	H	3.70	5.09	7.93	3.4
(**3**)	Ph	H	H	4.10	5.46	8.40	3.6
(**4**)	Et	Me	H	3.44	4.92	7.71	3.3
(**5**)	Ph	Me	H	4.15	5.42	8.30	3.6
(**6**)	Me	Ph	H	4.34	5.08	7.86	3.2
(**7**)	Ph	Ph	H	5.04	5.45	8.62	3.7
(**8**)	CH_2Ph	Ph	H	4.38	5.15	8.18	3.4
(**9**)	Pr^i	Me	Me		5.06	7.88	3.4
(**10**)	Ph	Me	Me		5.37	8.10	3.6
(**11**)	Pr^i	Me	Ph		5.11	8.08	3.3

[a] Recorded in [^{2}H]chloroform; chemical shifts are in p.p.m. relative to Me_4Si.

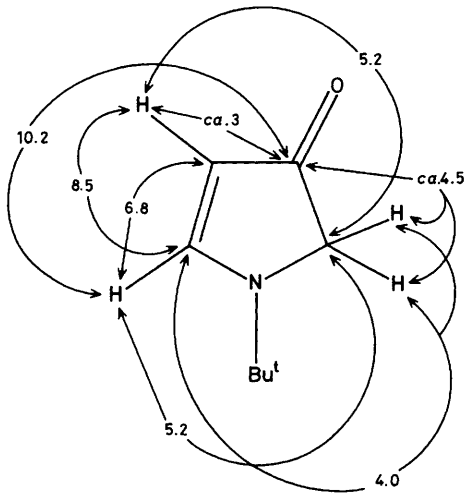


Figure. Long-range $^nJ_{CH}$ (Hz) for the pyrrolone (**2**)

The magnitude of the vicinal coupling $^3J_{4,5}$ (*ca.* 3.5 Hz) is affected both by ring size and by delocalisation.[7] It is much smaller than in the model enaminones (**12**;[4] 7.0 Hz) and (**13**;[6] 8.0 Hz) where the geometry either is, or approximates to, that of a six-membered ring: electron delocalisation promotes a further reduction outwith the 'normal' range for five-membered rings.[7] In addition, a small cross-ring coupling ($^4J_{2,5}$) leads to a noticeable broadening of the 5-H resonance, particularly when the 2-position is completely unsubstituted. In the case of the *N*-t-butyl compound (**2**) resolution enhancement gave a sharp first-order spectrum and values of $^3J_{4,5}$ and $^4J_{2,5}$ of 3.4 and 0.9 Hz, respectively.

^{13}C *N.m.r. Spectra.*—The ^{13}C n.m.r. chemical shifts of the 1*H*-pyrrol-3(2*H*)-ones (**2**)—(**11**) (Table 2) also follow the established pattern for enaminones,[4] in which the pronounced shielding of the C-4 signal (δ_C *ca.* 100) and deshielding of the C-5 signal (δ_C *ca.* 160) are the most characteristic features. Both the C-4 and C-5 resonances of the *N*-t-butylpyrrolone (**2**) are deshielded relative to the *Z-s-Z* form of the open-chain model compound[4] (**12**; δ_C 94.00 and 149.00 for β- and α-carbon atoms, respectively) as observed in the ^{1}H n.m.r. spectra. Similar factors are presumably responsible. The influence of the dipolar canonical form (see Scheme) is reflected in the chemical shifts of the carbonyl carbon atoms (δ_C *ca.* 200), which are at lower frequency than either cyclopentanone or cyclopent-1-en-2-one (δ_C 214 and 208, respectively[8]). There is also a trend towards greater deshielding of the 3-position with increased substitution at the 2-position: 2-unsubstituted compounds give δ_C <200, 2-monosubstituted give δ_C 200—203, and 2,2-disubstituted give δ_C >203.5. The C-2 atoms of pyrrolones (**2**)—(**11**) give rise to a range of chemical shifts which follow the expected trends for the substituent pattern (methylene, methine, quaternary, *etc.*).

As in the ^{1}H n.m.r. spectra, the influence of substitution by *N*-alkyl and *N*-aryl groups is apparent. As expected, *N*-aryl substitution causes substantial deshielding at C-4, which can be explained by competitive lone pair delocalisation into the phenyl group [*e.g.* (**2**) and (**3**) δ_C 99.13 and 103.81 p.p.m.; (**4**) and (**5**) δ_C 96.46 and 101.36 p.p.m.]. The corresponding shielding at C-5 is consistent with a less strongly polarised π-system [*e.g.* (**2**) and (**3**) δ_C 162.58 and 158.31 p.p.m.; (**4**) and (**5**) δ_C 163.93 and 158.73 p.p.m.], and confirms that the *opposite* trend observed in the ^{1}H n.m.r. spectra is principally due to a through-space effect.

The chemical shift of the *para*-carbon atom of the *N*-phenyl substituent offers a sensitive probe of the ability of the lone pair of the nitrogen atom to interact with the phenyl ring (Table 3). Thus a shift to low frequency of 5.5 p.p.m. relative to benzene is observed for the *N*-phenyl compound (**3**), where the two rings are known to be almost coplanar[1] and therefore significant delocalisation is possible. In this case, the electron-donating ability of the *N*-pyrrolone group as a whole is approximately equivalent to that of an acetamido substituent[9] [$\Delta\delta_C$(NHAc) −5.6 p.p.m.]. Though one substituent in the 2-position of the pyrrolone has little effect (Table 3) two substituents reduce the shielding effect at the *para*-carbon atom of the *N*-phenyl group to only 3.0 p.p.m., which is equivalent to the influence of only a methyl substituent[9] [$\Delta\delta_C$(Me) −2.9 p.p.m.]. These results are clearly due to reduced delocalisation caused by the five- and six-membered rings being forced out of coplanarity by the adjacent substituents.[1] This also gives rise to anomalies in the chemical shifts of the five-membered-ring carbon atoms. For example, signals due to C-3 and C-5 of (**10**) are both deshielded relative to the *N*-alkyl analogue (**9**), while the reverse is usually observed; surprisingly the 'normal' deshielding at C-4 associated with the *N*-aryl substituent is maintained in (**10**) (Table 2).

One-bond coupling constants ($^1J_{CH}$) for both C-4 and C-5 lie in the range 170—180 Hz (Table 2), with the former always slightly greater in magnitude than the latter. The values of both parameters are increased by phenyl substitution at either the 1- or 2-position and are in any case larger than for open-chain enaminones[4] ($^1J_{CH}$ *ca.* 160—170 Hz).

The minor couplings ($^nJ_{CH}$) were established by a detailed study of the *N*-t-butyl derivative (**2**) (Figure), and the remainder of those given in Table 2 were assigned by analogy. In detail, the C-2 resonance of (**2**) appears as a triplet of triplets (due to approximately equal long-range coupling to two protons), which collapses to a triplet of doublets on low power irradiation at either 4-H or 5-H. Hence $^3J_{C\text{-}2,4\text{-}H}$ and $^3J_{C\text{-}2,5\text{-}H}$ were established as *ca.* 5 Hz. When the 2-position is substituted, further coupling to the substituent results in complicated patterns for the C-2 resonances, which were not analysed. The C-4 signal of (**2**) is a simple doublet of doublets; irradiation of

Table 2. ^{13}C N.m.r. parameters for the ring carbon atoms of the pyrrolones (**2**)—(**11**)[a,b]

Derivative	R^1	R^2	R^3	C-2 δ_C	C-2 $^1J_{2\text{-H}}$	C-2 $^3J_{4\text{-},5\text{-H}}$	C-3[c] δ_C	C-4 δ_C	C-4 $^1J_{4\text{-H}}$	C-4 $^2J_{5\text{-H}}$	C-5 δ_C	C-5 $^1J_{5\text{-}H}$	C-5 $^2J_{4\text{-H}}$	^3J[d,e]
(**2**)	Bu^t	H	H	54.19	141.2	5.2	199.76	99.13	176.5	6.8	162.58	173.0	8.5	4.0[d]
(**3**)	Ph	H	H	55.65	143.2	4.4	198.71	103.81	179.2	6.2	158.31	176.7	9.4	3.6[d]
(**4**)	Et	Me	H	61.85	140.0	*g*	203.07	96.46	176.5	6.8	163.93	173.2	8.4	4.2[e]
(**5**)	Ph	Me	H	61.13	146.3	*g*	202.92	101.36	178.9	6.4	158.73	175.8	8.9	3.1[d]
(**6**)[f]	Me	Ph	H											
(**7**)	Ph	Ph	H	69.39			199.81	101.26			159.60			
(**8**)	CH_2Ph	Ph	H	69.89			201.31	97.30			166.13			
(**9**)	Pr^i	Me	Me	67.56		*g*	204.68	94.28	176.1	6.6	158.78	170.0	8.6	5.9[e]
(**10**)	Ph	Me	Me	68.65		*g*	205.73	99.11	178.2	7.0	160.19	175.6	8.7	
(**11**)	Pr^i	Me	Ph	72.69			203.50	94.34	177.5	6.6	160.73	171.2	8.9	5.2[e]

[a] Recorded for [^{2}H]chloroform solutions. [b] Coupling constants are quoted in Hz. [c] Minor couplings are complex (see text). [d] Coupling to 2-H. [e] Coupling to α-CH on *N*-substituents. [f] 70% Enol in [^{2}H]chloroform, spectrum not recorded. [g] Complex pattern not assigned.

Table 3. Effect of 2-methyl groups on the chemical shift of the *para*-carbon atom of the *N*-phenylpyrrolones (**3**), (**5**), and (**10**)

Derivative	R^1	R^2	R^3	δ_C(*para*-C)	$\Delta\delta_C$[a]
(**3**)	Ph	H	H	122.97	−5.5
(**5**)	Ph	Me	H	123.55	−5.0
(**10**)	Ph	Me	Me	125.47	−3.0

[a] Assumes δ_C (benzene) = 128.5.[8]

the only other unique proton (5-H) confirmed that the minor coupling (6.8 Hz) is indeed $^2J_{\text{C-4,5-H}}$. This pattern was also found for all the other derivatives (Table 2), and the magnitude of the two-bond coupling (6—7 Hz) is substantially larger than for other five-membered-ring enones[10] and for the enaminone model compound (**12**).[4] In contrast, the pattern for the C-5 signal was considerably more complex, approximating, in the case of (**2**), to a doublet of quintets, which collapsed to a doublet of doublets, and a doublet of closer triplets on irradiation at 2-H and 4-H, respectively. The values of $^2J_{\text{C-5,4-H}}$ (8—10 Hz) so obtained are again larger than might be expected.[4,10] In other examples (Table 2) coupling to the α-protons of *N*-alkyl substituents may be superimposed leading to considerable complexity. The signal for the carbonyl carbon C-3 of the *N*-t-butyl derivative (**2**) showed a poorly resolved pattern of at least seven lines (total line width $\Sigma^n J_{CH}$ 22.2 Hz). Observable effects were obtained by irradiation at 2-, 4-, and 5-H, but only the first gave a clear pattern (approx. doublet of doublets, *J ca.* 10 and 3 Hz). These were distinguished by recording the spectrum of the [$^2H_3$] analogue (**15**), obtained by exhaustive deuteriation of (**2**) in [$^2H_4$]methanol solution, which showed a clean doublet for C-3 in the fully coupled ^{13}C n.m.r. spectrum corresponding to $^3J_{\text{C-3,5-H}}$ (10.2 Hz). The 3 Hz coupling is therefore $^2J_{\text{C-3,4-H}}$, allowing an estimate of $^2J_{\text{C-3,2-H}}$, by difference, as *ca.* 4.5 Hz (Figure). The difficulties encountered in assigning these splittings were compounded by the low intensity of the carbonyl signal, and were not attempted for the other derivatives (**3**)—(**11**), where interaction with 2-substituents (for example) can result in even greater complexity.

Experimental

^1H and ^{13}C n.m.r. spectra were generally recorded at 200 MHz and 50 MHz, respectively, using a Bruker WP 200 SY instrument. The digital resolution in the ^1H and ^{13}C n.m.r. spectra was 0.27 and 1.4 Hz, respectively. All spectra were recorded for solutions in [^{2}H]chloroform.

1H-*Pyrrol*-3(2H)-*one Derivatives.*—Compounds (**2**)—(**8**),[4] (**9**),[4,11] (**10**),[12] and (**11**)[13] have been previously described. These papers should be consulted for complete listings of the ^1H and ^{13}C n.m.r. spectra.

2,2,4-[$^2H_3$]-1-*t-Butyl*-1H-*pyrrol*-3(2H)-*one.*—The 2,2,4-[$^1H_3$] compound was dissolved in [$^2H_4$]methanol and the exchange was monitored by ^1H n.m.r. spectroscopy.[14] Reaction at the 2-position was rapid (*ca.* 2 h) and was followed by slow exchange at 4-H over a period of days. The solvent was then removed under reduced pressure, and the residue was dissolved immediately in [^{2}H]chloroform. Attempts to specifically label the 4-position were unsuccessful due to a rapid equilibration of the label between the 2- and 4-position when in solution.

Acknowledgements

We are grateful to the S.E.R.C. for a Research Studentship (to L. C. M.).

References

1 Part 5, A. J. Blake, H. McNab, and L. C. Monahan, *J. Chem. Soc., Perkin Trans. 2*, preceding paper.
2 For example, T. Momose, T. Tanaka, T. Yokota, N. Nagamoto, and K. Yamada, *Chem. Pharm. Bull.*, 1979, **27**, 1448; M. Beyer, R. Ghaffari-Tabrizi, M. Jung, and P. Margaretha, *Helv. Chim. Acta*, 1984, **67**, 1535; G. Pfeiffer and H. Bauer, *Liebigs Ann. Chem.*, 1980, 564, and references therein.
3 H. McNab and L. C. Monahan, *J. Chem. Soc., Perkin Trans. 1*, 1988, 863.
4 H. McNab, *J. Chem. Soc., Perkin Trans. 2*, 1981, 1283, and references therein.
5 J. V. Greenhill, *Chem. Soc. Rev.*, 1977, **6**, 277.
6 Y. Tamura, M. Kunitomo, T. Masui, and M. Terashima, *Chem. Ind. (London)*, 1972, 168.
7 L. M. Jackman and S. Sternhell, 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' 2nd edn., Pergamon, Oxford, 1969, p. 302—304.
8 G. C. Levy, R. L. Lichter, and G. L. Nelson, 'Carbon-13 Nuclear Magnetic Resonance Spectroscopy,' 2nd edn., Wiley, New York, 1980, ch. 5.
9 Ref. 8, p. 111—112.
10 For example, H. McNab, *J. Chem. Soc., Perkin Trans. 1*, 1987, 657, and references therein.
11 E. Anklam, R. Ghaffari-Tabrizi, H. Hombrecher, S. Lau, and P. Margaretha, *Helv. Chim. Acta*, 1984, **67**, 1402.
12 C. L. Hickson, E. M. Keith, J. C. Martin, H. McNab, L. C. Monahan, and M. D. Walkinshaw, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1485.
13 H. McNab and L. C. Monahan, *J. Chem. Soc., Perkin Trans. 1*, 1988, 869.
14 H. McNab, L. C. Monahan, and J. C. Walton, *J. Chem. Soc., Perkin Trans. 2*, 1988. 759.

Received 14*th December* 1987; *Paper* 7/2187