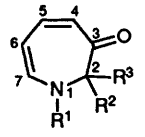
Azepinones. Part 2.[1] ^{1}H and ^{13}C NMR Spectra of 1-Substituted, 1,2-Disubstituted, and 1,2,2-Trisubstituted 1*H*-Azepin-3(2*H*)-ones

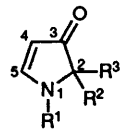
Hamish McNab* and Lilian C. Monahan
Department of Chemistry, University of Edinburgh, West Mains Road, Edinburgh EH9 3JJ

The ^{1}H and ^{13}C NMR parameters of the 1*H*-azepin-3(2*H*)-one system are assigned and discussed. Typical values, for the 1-methyl derivative (**1**) are as follows: 2-position, δ_H 3.57, δ_C 62.25, $^1J_{CH}$ 141.4, $^3J_{4\text{-}H}$ and $^3J_{7\text{-}H}$ *ca.* 4 Hz (with unresolved coupling to the *N*-methyl group); 3-position, δ_C 180.21, $^2J_{2\text{-}H}$ 3.7 and $^4J_{7\text{-}H}$ 11.6 Hz; 4-position, δ_H 6.17, $^3J_{4,5}$ 11.0 Hz, δ_C 123.33, $^1J_{CH}$ 159.6 and $^3J_{6\text{-}H}$ 8.3 Hz; 5-position, δ_H 6.84, $^3J_{4,5}$ 11.0, and $^3J_{5,6}$ 9.1 Hz, δ_C 142.01, $^1J_{CH}$ 151.7, and $^3J_{7\text{-}H}$ 8.2 Hz; 6-position, δ_H 5.17, $^3J_{5,6}$ 9.1 and $^3J_{6,7}$ 7.2 Hz, δ_C 99.41, $^1J_{CH}$ 161.7, $^2J_{7\text{-}H}$ 4.4 and $^3J_{4\text{-}H}$ 10.5 Hz; 7-position, δ_H 6.72, $^3J_{6,7}$ 7.2 Hz, δ_C 147.19, $^1J_{CH}$ 169.8, $^3J_{2\text{-}H}$ *ca.* 5 $^3J_{5\text{-}H}$ *ca.* 9 and $^2J_{6\text{-}H}$ *ca.* 4 Hz (with unresolved coupling to the *N*-methyl group).

In Part 1 of this series we described the first viable preparative route to *N*-substituted 1*H*-azepin-3(2*H*)-ones (**1**), and reported the X-ray crystal structure of a typical derivative.[1] Prior to an investigation of the chemistry of these new systems,[2–4] it is necessary to have a clear understanding of the factors which influence their NMR spectroscopic parameters, and we report here a detailed analysis of the ^{1}H and ^{13}C NMR spectra of

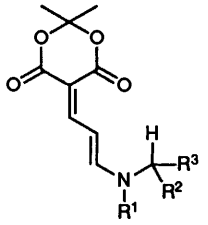


(1)

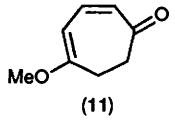


(7)

	R^1	R^2	R^3
(2)	Me	H	H
(3)	Ph	H	H
(4)	Et	Me	H
(5)	Pr^i	Me	Me
(6)	Ph	Me	Me



(8)

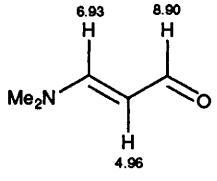


(11)

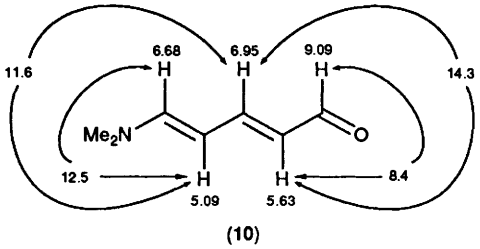
typical *N*-alkyl and *N*-aryl 2-unsubstituted, 2-monosubstituted and 2,2-disubstituted azepinones (**2**)–(**6**). These azepinones are vinylogues of the 1*H*-pyrrol-3(2*H*)-one system (**7**) whose spectroscopic properties we have previously reported.[5] All the azepinones were prepared by flash vacuum pyrolysis of the appropriate *N*,*N*-disubstituted aminopropenylidene derivative of Meldrum's acid (**8**).[1,6]

^{1}H NMR Spectra.—The principal NMR parameters of the ring protons of the azepinones (**2**)–(**6**) are given in Table 1. The protons at the extremities of the conjugated system are readily distinguished from the 'inner' protons by their coupling patterns [doublet, and double doublet (or apparent triplet) respectively]. As expected for an extended enaminone system, protons at the electron rich sites (4-H and 6-H) are shielded relative to 5-H and 7-H, though the differences are not as marked as in the 5-membered ring series.[5] Similar trends are noted in the spectra of the open-chain model compounds (**9**)[7] and (**10**),[8] whose ^{1}H NMR parameters are given for comparison in Fig. 1. The 4-H of the azepinone—and the equivalent position in (**10**)—is always shifted to higher frequency than the 6-H. Since this is also found in the ^{13}C NMR spectra (see below), the effect is probably due to the relative electron density at the two sites, rather than the proximity of the deshielding zone of the carbonyl group. The relative positions of the 5-H and 7-H signals are variable and dependent on the nitrogen substituent.

In the 1*H*-pyrrol-3(2*H*)-one series (**7**), substitution by *N*-aryl groups causes deshielding of all the ring protons due to competitive delocalisation of the lone pair of the nitrogen atom away from the enaminone system, and also due to the ring current which affects the 2- and 5-positions.[5] Although the two rings of the azepinone (**3**) are twisted by nearly 50° relative to each other,[1] similar deshielding effects in the spectrum of (**3**) are



(9)



(10)

Fig. 1. ^{1}H NMR parameters of the enaminone (**9**) and dienaminone (**10**).

Table 1. ^{1}H NMR parameters for the ring protons of the azepinones (**2**)–(**6**).[a]

Derivative	R^1	R^2	R^3	2-H	4-H	5-H	6-H	7-H	$^3J_{4,5}$[b]	$^3J_{5,6}$[b]	$^3J_{6,7}$[b]
(**2**)	Me	H	H	3.57	6.17	6.84	5.17	6.72	11.0	9.1	7.2
(**3**)	Ph	H	H	4.14	6.34	6.89	5.49	6.99	11.3	8.6	8.0
(**4**)	Et	Me	H	3.81	6.10	6.75	5.16	6.60	11.3	9.0	7.7
(**5**)	Pr^i	Me	Me	—	6.08	6.61	5.31	6.63	11.4	8.3	8.3
(**6**)	Ph	Me	Me	—	6.30	6.75	5.28	6.68	11.5	8.5	8.5

[a] Recorded in [^{2}H]chloroform; chemical shifts are in ppm relative to Me_4Si. [b] Coupling constants are in Hz; minor couplings are discussed in the text.

observed at all positions relative to the *N*-alkyl derivative (**2**) (Table 1). However, the effect is negligible for the 2,2-dimethyl-1-phenyl compound (**6**) [*cf.* (**5**)] for which a further increase in dihedral angle would be expected [1] (see below).

Substitution at the 2-position by one or by two alkyl groups has little consistent effect on the chemical shifts of the remaining protons in the molecule. [Table 1; *cf.* (**2**), (**4**), and (**5**)].

The size of the vicinal coupling constant $^3J_{4,5}$ (11.0–11.5 Hz) is much as expected for a *Z*-olefinic coupling in a seven-membered ring system,[9] though the other alkene unit shows a much smaller value ($^3J_{6,7}$ 7.2–8.5 Hz). It is known that such couplings should decrease with an increase in H–C=C bond angle,[9] and indeed the X-ray crystal structure of the 1-phenyl compound (**3**) [1] shows that both the angles C(5)–C(6)–C(7) and C(6)–C(7)–N(1) (126.7° and 125.8°) are smaller than expected for a regular 7-membered ring (129°), which will tend to increase the angle between the appropriate hydrogen atom and the double bond giving rise to the reduced coupling. The remaining vicinal coupling constant $^3J_{5,6}$ (8.3–9.1 Hz) is similar in size to, or slightly larger than $^3J_{6,7}$, even though it is across a formal single bond: a very similar value (8 Hz) has been reported [10] for the corresponding coupling in the cycloheptadienone (**11**).

A four bond coupling ($^4J_{4,6}$, *ca.* 1.0 Hz) is usually observed, but a number of other minor couplings become apparent when the spectra are subjected to resolution enhancement. At 200 MHz, these are often not fully resolved but can be inferred from the broad linewidths. However, the 2-substituted compound (**4**) showed particularly good resolution, and a full analysis of the coupling pattern (Fig. 2) was possible with the aid of decoupling

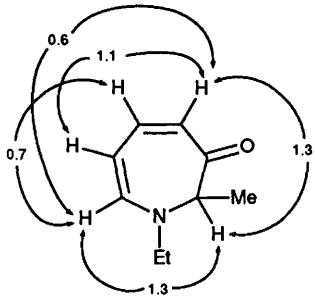
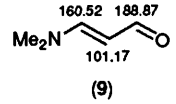


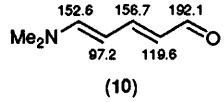
Fig. 2. Long range coupling constants of the azepinone (**4**) ($J_{H,H}$/Hz).

experiments. The following signals were observed: 2-H, quartet of triplets; 4-H, doublet of apparent quartets; 5-H doublet of doublets of doublets; 6-H doublet of doublets of doublets; 7-H, doublet of apparent quintets. Decoupling at 2-H affected minor couplings at 4-H and 7-H (both ^4J 1.3 Hz), whereas irradiation at 4-H affected fine structure at 6-H, 2-H (as expected), and 7-H ($^5J_{4,7}$ *ca.* 0.6 Hz). The remaining minor coupling [at H-5 (0.7 Hz)] was identified by decoupling H-7. The observed lineshape at 4-H and 7-H is a result of adventitious combination of linewidth and coupling constants.

^{13}C *NMR Spectra.*—The ^{13}C NMR chemical shifts of the azepinones (**2**)–(**6**) are listed in Table 2. For the *N*-phenyl compound (**3**), unambiguous assignment was made by selective irradiation of the individual proton resonances, which served to distinguish the C-4/C-6 and C-5/C-7 pairs. Although the chemical shifts of 5-H and 7-H were too close together for a clear result to be obtained directly by this method, *low power* irradiation of 7-H (δ_H 6.99) removed *minor* coupling at δ_C 140.17 which must therefore be due to C-5 (see below). Other assignments given in Table 2 were made by analogy; although the relative positions of C-5 and C-7 are somewhat variable, they can be clearly distinguished by their characteristic patterns (doublet of doublets and doublet of multiplets respectively) in their ^{1}H-coupled ^{13}C spectra. In similar fashion, the *p*-carbon resonance of the *N*-aryl compounds (**3**) and (**6**) (doublet of triplets) and that of the C-4 atom (doublet of doublets) can be assigned, even though both occur in the range δ_C 123–128. The chemical shifts of the open-chain model compounds (**9**) [7] and (**10**) [11,12] are quoted in Fig. 3.



(**9**)



(**10**)

Fig. 3. ^{13}C NMR chemical shifts of the enaminone (**9**) and dienaminone (**10**).

As found in the ^{1}H NMR spectra, the electron deficient sites of the azepinones (C-5 and C-7) occur at higher frequency (δ_C 137–147) than C-4 or C-6, but these signals are considerably shielded relative to the corresponding resonances of the pyrrolones [5] (C-5; δ_C 158–166), and even those of the open-chain dienaminone (**10**) [11,12] (Fig. 3). The signals due to the electron-rich 4- and 6-positions are well separated (usually >20 ppm) with the C-6 resonance at particularly low frequency (δ_C *ca.* 100). This effect appears to be general for the dienaminone system (Fig. 3), and has been correlated with the π-electron density of the system.[11,12] Despite these ground state considerations, it appears that the 4-position of the azepinones is more reactive to electrophilic substitution than the 6-position [3] owing to increased stabilisation of the cationic intermediate.

The carbonyl carbon atom (C-3) resonates at δ_C 180–185 (Table 2), which is shielded by some 20 ppm relative to the corresponding pyrrolone resonance:[5] this may be primarily a ring size effect.[13] Although there is a trend to higher frequency with increased substitution at the 2-position, the effect is not as marked as for the pyrrolones.[5] The signals corresponding to the 2-position are consistently deshielded (*ca.* 4 ppm) with respect to the smaller ring system with similar substitution.

Amongst the *N*-alkyl examples (**2**), (**4**) and (**5**) the chemical shifts of C(4)–C(6) are relatively constant and show little effect of increased substitution at the 2-position (Table 2). However, the position of the C-7 resonance is shielded by some 10 ppm in the 2,2-dimethyl-1-isopropyl derivative (**5**) with respect to the *N*-methyl compound (**2**). Since a similar effect is *not* shown in the *N*-aryl series (Table 2) it is possible that the change in *N*-alkyl substituent may be contributing.

Table 2. ^{13}C NMR chemical shifts of 1*H*-azepin-3(2*H*)-ones (**2**)–(**6**).[a]

Derivative	R^1	R^2	R^3	C-2	C-3	C-4	C-5	C-6	C-7
(**2**)	Me	H	H	62.25	180.21	123.33	142.01	99.41	147.19
(**3**)	Ph	H	H	59.38	182.87	126.71	140.17	103.86	141.54
(**4**)	Et	Me	H	65.35	184.37	120.74	140.11	99.23	142.77
(**5**)	Pr^i	Me	Me	63.76	184.11	121.67	138.11	102.68	137.50
(**6**)	Ph	Me	Me	64.50	185.79	123.34	138.14	100.84	142.53

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

Table 3. Effect of 2-methyl groups on the chemical shift of the *para*-carbon atom of the *N*-phenyl compounds (**3**), (**6**) and (**7**; R^1 = Ph).

				Pyrrolone		Azepinone	
Derivative	R^1	R^2	R^3	δ_C(*para*-C)	$\Delta\delta_C$[a]	δ_C(*para*-C)	$\Delta\delta_C$[a]
(**3**)/(**7**)	Ph	H	H	122.97	−5.5	124.73	−3.8
(**6**)/(**7**)	Ph	Me	Me	125.47	−3.0	127.65	−0.8

[a] Assumes δ_C(benzene) = 128.5.

Table 4. Carbon–proton coupling constants (H_2) for 1*H*-azepin-3-(2*H*)-ones.

(*a*) *One-bond couplings*

Azepinone	R^1	R^2	R^3	C-2	C-4	C-5	C-6	C-7
(**2**)	Me	H	H	141.4	159.6	151.7	161.7	169.8
(**3**)	Ph	H	H	141.4	160.1	152.6	161.5	173.1
(**5**)	Pr^i	Me	Me	—	158.4	152.5	161.4	166.5

(*b*) *Long-range couplings*

				C-2		C-3		C-4	C-5	C-6		C-7[a]		
Azepinone	R^1	R^2	R^3	$^3J_{4\text{-H}}$	$^3J_{7\text{-H}}$	$^2J_{2\text{-H}}$	$^4J_{7\text{-H}}$	$^3J_{6\text{-H}}$	$^3J_{7\text{-H}}$	$^2J_{7\text{-H}}$	$^3J_{4\text{-H}}$	$^3J_{2\text{-H}}$	$^3J_{5\text{-H}}$	$^2J_{6\text{-H}}$
(**2**)	Me	H	H	*b*	*b*	3.7	11.6	8.3	8.2	4.4	10.5	*b*	*b*	*b*
(**3**)	Ph	H	H	4.3	4.3	3.8	11.2	8.9	8.2	4.6	10.6	*ca.* 5.0	9.4	3.7
(**5**)	Pr^i	Me	Me	*c*	*c*	—	*c*	8.7	8.7	2.8	10.8	—	9.2	4.6[d]

[a] Values deduced from low-power decoupled spectra. [b] Not resolved due to additional coupling to *N*-methyl groups. [c] Not resolved due to additional coupling to 2-methyl groups. [d] Also $^3J_{N.CH}$ 4.6 Hz.

N-Aryl substitution in the pyrrolone series[5] causes deshielding of the resonance due to the electron-rich position (C-4), and shielding of that due to the electron-deficient centre (C-5). A similar trend is apparent in the spectra of the *N*-phenyl compound (**3**) relative to its *N*-alkyl analogue (**2**), despite the substantial differences in geometry between the 5- and 7-membered ring series noted above. The effects on electron delocalisation caused by the large dihedral angle between the phenyl and azepinone rings are illustrated by the chemical shifts of the *p*-carbon of the aryl ring. It can be seen from Table 3 that the shielding, relative to benzene, is much smaller in the azepinone series than in the corresponding pyrrolone,[5] and is hardly present at all for the 2,2-dimethyl compound (**6**). The corresponding effect on UV spectra has been reported.[1]

The one-bond and long-range carbon–proton coupling constants of the representative azepinones (**2**), (**3**) and (**5**) are given in Table 4. The one-bond constants of the conjugated system [C(4)–C(7)] are generally smaller in magnitude than for the corresponding pyrrolones,[5] and only $^1J_{C\text{-}7,7\text{-}H}$ is significantly dependent on the substitution pattern; a slight increase for *N*-aryl substituents, and decrease for 2,2-dialkyl substituents was also observed for the 5-membered ring series.[5] The pattern of one-bond coupling constants is similar to that of the open-chain model compound[11] (**10**) (Fig. 4). The largest value is found at the position adjacent to the nitrogen atom (*cf.* ref. 14) whereas the other electron deficient site gives rise to a notably small constant. The two electron rich sites give intermediate values.

The analysis of the long-range couplings shown in Table 4 was achieved by sequences of low-power decoupling experiments on the *N*-methyl and *N*-phenyl compounds (**2**) and (**3**). Thus, for example, the ^{1}H-coupled spectrum of (**3**) has the following appearance: C-2, triplet of apparent triplets; C-3, doublet of triplets; C-4, doublet of doublets; C-5, doublet of doublets; C-6, doublet of doublets of doublets; C-7, doublet of complex multiplets. This latter signal collapses to a doublet of doublets of doublets on irradiation at the 2-H (methylene) signal, and in addition the C-3 multiplet is thereby reduced to a simple doublet ($^2J_{C\text{-}3,2\text{-}H}$ 3.8 Hz). Decoupling of 4-H affects one of the minor couplings (4.3 Hz) to C-2, and also the principal (10.6 Hz) minor coupling to C-6, whereas decoupling of 5-H only has an effect on the C-7 multiplet. Only the C-4 signal is clearly collapsed by irradiation at 6-H ($^3J_{C\text{-}4,6\text{-}H}$ 8.9 Hz), though again the C-7 multiplet may be affected. Finally, irradiation at 7-H affects C-2 ($^3J_{C\text{-}2,7\text{-}H}$ 4.3 Hz), C-3 ($^4J_{C\text{-}3,7\text{-}H}$ 11.2 Hz), C-5 ($^3J_{C\text{-}5,7\text{-}H}$ 8.2 Hz), and the minor coupling (4.6 Hz) at C-6. Hence, all the minor couplings (Table 4) were clearly identified except for those at C-7, which can now be analysed as a doublet of doublets of doublets of triplets (due to 2-H long range coupling). Unambiguous assignment of the major and minor doublet splittings was made by low-power

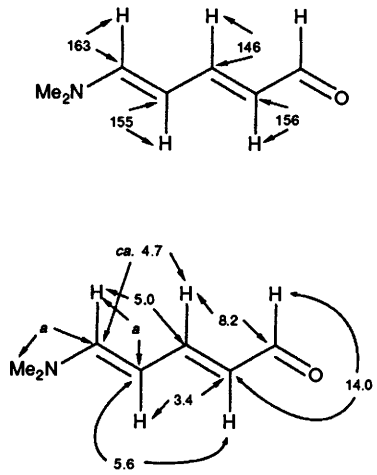


Fig. 4. One-bond and long-range carbon–proton coupling constants of the dienaminone (**10**) ($J_{C,H}$/Hz). [a] Not resolved.

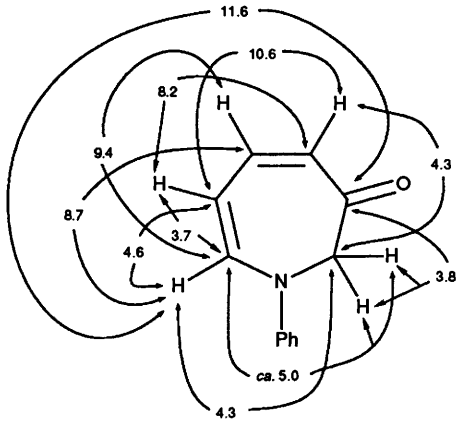


Fig. 5. Long-range carbon–proton coupling constants of the azepinone (**3**) ($J_{C,H}$/Hz).

irradiation experiments on the 2,2-dimethyl compound (**6**) which lacks the complicating triplet structure, and the value of $^3J_{C\text{-}7,2\text{-}H}$ was estimated by difference. The full coupling pattern is shown in Fig. 5.

The spectra of the *N*-alkylazepinones [*e.g.* (**2**)] are closely similar (Table 4), except that the C-2 and C-7 signals are complicated by further coupling to the *N*-alkyl substituent.

For comparison, the minor couplings of the open-chain model compound (**10**)[8] were determined and analysed, and the results are shown in Fig. 4. Because of the dependence of these couplings on geometric factors[14] it is not surprising that little similarity is observed. Coupling constants of the *E,E* compound (**10**) (Fig. 4) are dominated by 3–8 Hz three-bond interactions (except at the extremities of the conjugated system), whereas the *Z,Z* azepinones (Fig. 5 and Table 4) show a rich coupling pattern, of two-, three- and four-bond interactions of 3–12 Hz magnitude.

The effect on the NMR spectra of the 1*H*-azepin-3(2*H*)-one system, of *O*-protonation, *O*-alkylation, and substitution by halogen atoms will be considered in the following paper.[3]

Experimental

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

Azepinone Derivatives.—The synthesis of compounds (**2**), (**3**) and (**6**) has been previously described in full.[1] Details of the preparation of (**4**)[6] (with Mr. T. Gray) and (**5**) will follow in a later paper in this series.

Acknowledgements

We are most grateful to the SERC for a Research Studentship (to L. C. M.), and to Lonza Ltd., for a generous gift of the Meldrum's acid used to synthesise the azepinones.

References

1 Part 1, A. J. Blake, H. McNab and L. C. Monahan, *J. Chem. Soc., Perkin Trans. 1*, 1989, 425.
2 H. McNab and L. C. Monahan, *J. Chem. Soc., Chem. Commun.*, 1987, 141.
3 H. McNab, L. C. Monahan and A. J. Blake, *J. Chem. Soc., Perkin Trans. 1*, 1990, following paper.
4 H. McNab and L. C. Monahan, *J. Chem. Soc., Perkin Trans. 1*, 1990, 3169.
5 H. McNab and L. C. Monahan, *J. Chem. Soc., Perkin Trans. 2*, 1988, 1459.
6 H. McNab, L. C. Monahan and T. Gray, *J. Chem. Soc., Chem. Commun.*, 1987, 140.
7 For example, H. McNab, *J. Chem. Res.*, 1979, (*S*), 121; (*M*), 1451.
8 S. S. Malhotra and M. C. Whiting, *J. Chem. Soc.*, 1960, 3812.
9 For example, L. M. Jackman and S. Sternhell, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, Pergamon, Oxford, 2nd edn., 1969, p. 303.
10 O. L. Chapman, D. J. Pasto and A. A. Griswold, *J. Am. Chem. Soc.*, 1962, **84**, 1213, quoted in ref. 9, p. 285.
11 R. Radeglia, *J. Prakt. Chem.*, 1973, **315**, 1121.
12 R. Radeglia, E. Gey, T. Steiger, S. Kulpe, R. Lück, M. Ruthenberg, M. Stierl and S. Dähne, *J. Prakt. Chem.*, 1974, **316**, 766.
13 For example, G. C. Levy, R. L. Lichter and G. L. Nelson, *Carbon-13 Nuclear Magnetic Resonance Spectroscopy*, Wiley, New York, 2nd edn., 1980, p. 137.
14 P. E. Hansen, *Prog. Nucl. Magn. Reson. Spectrosc.*, 1981, **14**, 175.

Paper 0/02351E
Received 25*th May* 1990
Accepted 25*th June* 1990