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CARBONYL CARBON CHEMICAL SHIFTS IN THE ^{13}C SPECTRA OF CYCLIC KETONES[a]

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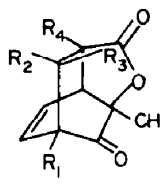
Abstract—The ketonic ^{13}C NMR signals of the keto lactones **1** and haplophytine (**4**) occur at exceptionally high field. These upfield shifts are interpreted in the context of a general consideration of the structural factors affecting the carbonyl carbon chemical shifts of cyclic ketones. It is concluded that dipole-dipole interactions are the major sources of the upfield shifts in the cases of both **1** and **4**.

INTRODUCTION

Recent work in these Laboratories has uncovered examples of two types of cyclic ketone whose ^{13}C NMR CO carbon chemical shifts are at exceptionally high field. One class comprises keto lactones of type **1**[2] and the other 3-azacycloalkanones of type **2**.[3] The potential magnitude of the upfield shift is indicated by the extreme cases of compound **3** (δ 197.3 ppm) and the natural product haplophytine (**4**; Ar = aryl system) (δ 197.2 ppm), which may be contrasted with cyclohexanone (δ 212.0[4]). In spite of the fact that α-substitution of ketones by alkyl groups normally leads to a *downfield* shift of the CO carbon signal (*vide infra*), compounds **3** and **4** have their ketonic carbon signals shifted *upfield* by 15 ppm relative to cyclohexanone, and these signals appear in the region normally associated with α,β-unsaturated ketones.[5a]



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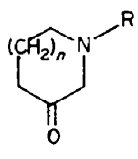
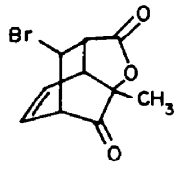
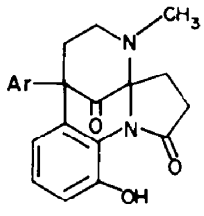


2(n = 0 or 1)



3(= **1e**)



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The origins of these upfield shifts are of intrinsic interest and also have relevance to the application of ^{13}C NMR spectroscopy to structure determination. We have sought to determine their structural source by comparison of the CO carbon chemical shifts of compounds of types **1** and **2** with each other and with related compounds and by consideration of the structural factors that have previously been observed to affect the CO carbon chemical shifts of cyclic ketones. We first discuss these observations and then consider the present results in relation to them.

Factors influencing the carbonyl carbon chemical shifts of cyclic ketones[b]

There is a marked variation of CO carbon shielding in cycloalkanones with ring size.[4] In cyclohexanone and the large ring ketones ($>C_{11}$) the shieldings are comparable to those of acyclic ketones. However, for cyclopentanone and medium-sized rings (C_7 to C_{11}) the CO carbon signal is at significantly lower field, with the deshielding effect being most pronounced for the 5-, 8- and 9-membered ring ketones. In cyclobutanone the CO carbon is shielded relative to cyclohexanone.

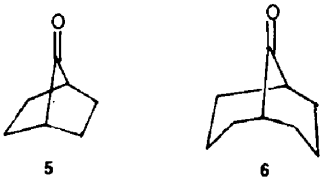
It has been reported[6] that there is a good linear correlation between the shifts in some cyclic and bicyclic ketones and the $n\rightarrow\pi^*$ transition energies and thus concluded that the excitation energy plays a dominant role. However, Stothers[7] has questioned whether a good linear correlation exists in general. He has related ring size effects to the preferred conformation of the respective rings and proposed that the CO groups that have minimal α-bond eclipsing interactions with adjacent C–H and C–C bonds are the most deshielded.[4c] It is clear that one or more additional factors must be involved, since cyclobutanone and cyclopentanone have CO chemical shifts (δ 209.1 and 220.5 ppm, respectively) that are widely different, although neither experiences any appreciable α-bond eclipsing. It may be suggested that angle strain is such a factor. The departure from sp^2 hybridization at the CO carbon associated with increased p character of the carbon orbitals utilized in C–C bond formation leads to increased s character in the hybrid carbon orbitals utilized in C–O bond formation. With this change the C–O bond becomes less polar, as evidenced by the dipole moments for the 4-, 5- and 6-membered rings (2.76, 2.86 and 3.08 D, respectively).[9] This reduc-

[a] For a preliminary account of part of this work, see Ref. 1.

[b] Chemical shifts are given in ppm relative to internal TMS, differential shifts are given for solutions in the same solvent, usually $CDCl_3$, with positive values denoting deshielding effects.

[c] Chemical reactivities of cyclic ketones are also affected by the presence or absence of α-bond eclipsing interactions and their relief in the transition state.[8] The striking similarity between the variation of the rate of borohydride reduction of cyclic ketones with ring size[8b] and that of carbonyl chemical shift lends support to Stothers' interpretation.

tion in polarization of the CO bond would be expected to cause increased CO carbon shielding in cyclobutanone vs cyclopentanone.



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A similar interpretation has been advanced[10] to account for the well known increase in the IR CO-stretching frequencies of small ring cyclic ketones with reduction of ring size.[d] A further example of this effect can be discerned for the bicyclic ketones **5** and **6**; they would be expected to have similar α-eclipsing interactions, but their CO carbon chemical shifts are 221.7 and 216.8 ppm, respectively,[12] and the frequencies of their CO-stretching vibrations are 1713 and 1725 cm^{-1}, respectively.[13]

The effects of both alkyl and heteroatomic substituents on the ^{13}C chemical shifts of cycloalkanes has been investigated extensively, but their effects on the CO carbon chemical shifts of cyclic ketones have received less attention. Roberts and Stothers *et al.*[14,15] have found that substitution of a Me group on an α-carbon of cyclohexanones, cyclopentanones, bicyclo[2.2.1]heptan-2-ones and bicyclo[2.2.2]-octanones results in a β-deshielding effect at the CO carbon. The deshielding effects are dependent on the orientation of the Me group with respect to the CO group and lie in the range 1.0–3.4 ppm. The deshielding is usually considerably less than the analogous β-effect[5b,14–19] of Me substitution in the corresponding hydrocarbons (Table 1). This reduction in the magnitude of the effect and the dependence on orientation is attributable in part to steric interaction of the Me groups with the CO oxygen atoms.[15a] Geminal α-substitution of two Me groups in cyclic ketones is associated with attenuation of their β effect at the CO carbon. In the case of several bridged cyclic ketones this attenuation falls in the range −0.4 to −1.6 ppm;[4] similar attenuation is observed for cyclic hydrocarbons.[14] A related factor may contribute to the smaller β effect of C.1 relative to C.3 Me substitution in bicyclo[2.2.1]heptan-2-one, although differential steric interaction with the CO oxygen also plays a role.

Substitution of a Me group on a β-carbon of cyclohexanones, cyclopentanones, bicyclo[2.2.1]heptan-2-ones, and bicyclo[2.2.2]octanones gives rise to γ effects at the CO carbon that are usually slightly shielding (Table 1). These γ effects are small ($|\Delta\delta| \leq 1.0$ ppm) even when a large γ-*gauche* effect ($\Delta\delta$ −5.3, −7.5 ppm) is observed in the case of the corresponding hydrocarbon, presumably because the H–H steric interaction that is usually considered to give rise to this effect in the hydrocarbons is necessarily absent in the ketones.

Schneider[20] has recently discussed in detail the effects of heteroatomic substituents on the ^{13}C chemical shifts of cyclohexanes. The β effects are uniformly deshielding and their magnitude is dependent on the nature of the substituent and its equatorial or axial orientation, a smaller β effect normally being associated with the latter. Thus, for example, equatorial and axial OH groups have β-effects of 8.5 and 6 ppm, respectively. Related, but larger, deshielding effects have been observed at C.3 in bicyclo[2.2.1]heptane and bicyclo[2.2.2]octane and their Δ^5 analogues, where substitution of a OH group at C.2 leads to deshielding by 10–13 ppm.[14,21] The deshielding effect of such substitution on the tertiary C.1 position is in the range 6–8 ppm. Substitution of a OH group at C.1 in bicyclo[2.2.2]octane also leads to a downfield shift at C.2 that falls in the latter range.[22]

The β-effect of heteroatomic substituents on the CO carbon of cyclic ketones has been studied less extensively,

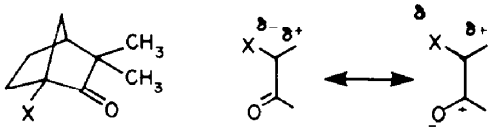
[d] It should be noted, however, that the difference in CO-stretching frequencies involves other factors.[11]

Table 1. β and γ Effects of methyl substituents on ^{13}C NMR chemical shifts of carbonyl carbons in cyclic ketones[a,b]

	Methyl	β-Effects[c]	Methyl	γ Effects[c]
Cyclohexanone	2-eq	1.4 (8.7)	3-eq	-0.5 (-0.25)
	2-ax	3.3 (5.3)	3-ax	0.0 (-5.3)
Cyclopentanone	2	1.5 (9.3[d])	3	-0.7 (-0.1[d])
Bicyclo[2.2.2]heptan-2-one	1	1.0 (7.0[d])	4	-0.7[e] (1.5[d])
	3-exo	2.6 (10.2)	6-exo	-1.0 (-0.9)
	3-endo	2.4 (10.6)	6-endo	-0.7 (-7.5)
			7-syn	0.0[d] (-2.9[d])
			7-anti	-0.2[d] (0.9[d])
Bicyclo[2.2.2]octan-2-one	3-Me	3.4 (9.7)	4-Me	-0.1 (0.7)

[a] In ppm for solutions in $CDCl_3$, unless otherwise specified; positive values denote deshielding effects. [b] Refs. 14-18. [c] Figures in parentheses are the β and γ effects for the corresponding hydrocarbons. [d] In dioxane. [e] In C_6H_6-d.

but it is clear that it has the *opposite sign* to that in the case of cyclic hydrocarbons. Thus in a series of 1-heterosubstituted camphenilones (**7**), upfield shifts of −0.3 to −14.1 ppm in the CO carbon chemical shift relative to camphenilone itself (**7**, X = H) are observed.[23] This β-shielding of ketones is readily explicable as a dipole



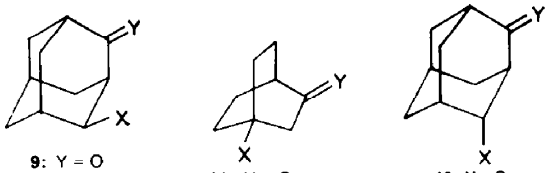
7

effect resulting in destabilization of the polar resonance contributor of the CO group (*cf* **8**). Such an interpretation is in accord with the fact that the *β-gauche* effects of bromine in *exo*- and *endo*-3-bromonorcamphor (−6.0 and −5.5 ppm, respectively[24]) are appreciably less than the β eclipsed effect of bromine in 1-bromocamphenilone (**7**, X = Br) (−9.2 ppm[23]). An analogous effect on CO stretching frequencies is well known in IR spectroscopy.[25] The effects of OH and amino substitution in **7** are relatively small (−1.3 and −0.3 ppm, respectively), but this is attributable to the countervailing effect of H-bonding.

Endocyclic heteroatom effects in 6-membered rings have been extensively studied by Lambert, Hirsch, Havinga and their coworkers.[26] In N-alkyl- and N-acylpiperidines the nitrogen exerts a small β shielding effect (−1.1 to −1.4 ppm) at C.3 relative to cyclohexane (δ 27.2 ppm[16]).[e] A shielding effect of a similar magnitude (−1.0 to −1.1 ppm) is observed at C.3 in the corresponding 4-piperidinones relative to C.2 in cyclohexanone (δ 42.0 ppm).[4] However, the β shielding effect is significantly greater (−3.0 to −4.6 ppm) at C.5 in N-alkyl and N-acyl-3-piperidinones and larger yet (−6.1 to −7.9 ppm) at the CO carbon (C.3) relative to C.3 (δ 27.1 ppm) and C.1 (δ 212.0 ppm) in cyclohexanone,[4] respectively. Both inductive and electrostatic effects are probably operative in these cases, with predominant importance of the latter at CO carbon.

The γ-effects of heteroatom substituents in cyclohexanes are again dependent on the nature and orientation of the substituent.[20,27] Axial heteroatom substituents give rise to a *γ-gauche* shielding effect in the range −5.5 to −7.5 ppm (e.g., OH −6.9 ppm), comparable to that of a Me group (−6.5 ppm). Equatorial oxygen and other first row substituents can engender an upfield shift of −1 to −3.5 ppm (e.g., OH −2.3 ppm); this significant *γ anti* effect is not observed in the case of an equatorial Me substituent (Δδ −0.2 ppm). However, there is a striking reversal of this effect if C_α is tertiary, when a *γ-anti deshielding* effect of 2.5–4 ppm is observed. Related effects have been observed in bicyclo[2.2.1]heptane and bicyclo[2.2.2]octane and their Δ^5 analogues,[21,28] where substitution of OH at C.2 leads to *γ-gauche* and *γ-anti* shielding effects at the corresponding secondary sp^3 carbons of −7.5 to −9.5 ppm and −2.3 to −5.2 ppm, respectively.[f] The effects of OH substitution at C.2 on the tertiary carbon C.4 are small and of variable sign ($|\Delta\delta| \leq 1.1$ ppm). In the bicyclo[2.2.1]heptane series an *exo*-2-OH group leads to significant shielding (−3.9, −2.9 ppm) of C.7 but an *endo*-2-OH group has little effect at this carbon (−0.7, −0.3 ppm). In these latter cases the bond relationship is neither *gauche* nor *anti*. In the case of bicyclo[2.2.2]octane, substitution of an OH group at tertiary C.2 leads to a *γ-anti deshielding* effect (*vide supra*).[28] Substitution of an OH group at C.1 of bicyclo[2.2.2]octane gives rise to a negligible *γ-anti* effect (−0.2).[22]

In the few cases where the γ effects of heteroatomic substituents at the CO carbon of cyclic ketones have been examined they have been found to be shielding.[22,30] Thus the *γ-gauche* effects of C.4 oxygen substituents at the CO carbon (C.2) of the adamantanones **9** fall in the range of −0.7 to −3.2 ppm; however, the effects are smaller than those at the corresponding carbon in the adamantanes **10** (−5.9 to −6.6 ppm), although halogen substituents give rise to more similar effects in the two series. For the case of 4-hydroxy-2-adamantanone (**9**, X = OH) the effect is smallest (−0.7 ppm); this is probably due in part to a compensatory deshielding effect resulting from H-bonding. The *γ-anti* effects of C.4 oxygen substituents at



9: Y = O
10: Y = H_2
11: Y = O
12: Y = H_2
13: Y = O
14: Y = H_2

the CO carbon (C.2) in the bicyclo[2.2.2]octanones **11** (−3.5 to −4.9 ppm) are more shielding than in the bicyclo[2.2.2]octanes **12** (−0.2 to −0.5 ppm). The enhanced effect here is probably due to hyperconjugative donation of lone-pair electrons to the CO carbon, an interpretation that also accounts for the enhancement of the CO carbon shielding in the adamantanones **13** (−2.6 to −4.3 ppm) relative to the adamantanes **14** (−1.1 to −1.3 ppm).[22] Related *γ-gauche* and *γ-anti* effects have been observed for bicyclo[3.2.1]octan-8-ones and bicyclo[3.3.1]nonan-9-ones.[12b,30]

Endocyclic heteroatoms in 6-membered rings exert a γ-shielding effect at C.4 relative to cyclohexane.[26] In tetrahydropyran and N-alkyl and N-acyl piperidines this falls in the range −2.6 to −3.4 ppm. Similar γ-effects are observed at C.4 of the corresponding 1-hetera-3-cyclohexanones relative to C.2 of cyclohexanone. In the case of the corresponding 1-hetera-4-cyclohexanones the γ-shielding effects at the CO carbon (C.4) relative to C.1 of cyclohexanone are enhanced (−4.3 to −6.0 ppm). Since in both the piperidine and the 4-piperidinone cases quaternization of the nitrogen leads to yet greater shielding, it is unlikely that hyperconjugation or homoconjugation is important here, and the shielding effects most probably have their major origin in electrostatic interaction.[26]

The δ-effects on the chemical shifts of CO carbon resulting from γ-alkyl or γ-heteroatom substitution in cyclic ketones appear to be small and we do not discuss them here.

The final structural factor that we consider is the influence of an ethylenic double bond. It has long been recognized that introduction of an α,β-ethylenic double bond into a ketone results in an upfield shift of the CO carbon signal by *ca.* 10 ppm—an effect that is most simply interpreted in terms of increased electron density at the CO carbon resulting from conjugation.[5a] Introduction of a β,γ-ethylenic double bond can also lead to increased

[e] Because of an anomaly in the spectrum reported[29] for N-methylpiperidine in $CDCl_3$, we have recorded this spectrum again and find δ 56.6 (C.2), 26.1 (C.3), 23.9 (C.4) and 46.9 ppm (N-CH_3); these values have been used in the present discussion.

[f] Analogous, but smaller, effects are observed at sp^2 carbon.

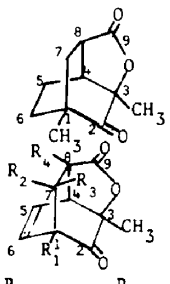
shielding. Thus Stothers[12a] has found that introduction of such a bond into bicyclo[2.2.1]heptanones, bicyclo[2.2.2]-octanone, and bicyclo[3.2.1]octanones results in an upfield shift of the CO carbon signal by −2.7 to −11.5 ppm. In the cases of bicyclo[2.2.1]heptan-2-one and several of its Me derivatives, the shielding effect falls in the range −1.1 to −4.0 ppm,[15b] while for an analogous series of bicyclo-[2.2.2]octanones the range is −4.3 to −6.0 ppm.[15c] Related shielding effects have also been observed in some γ,δ-unsaturated cyclic ketones. An important factor, although not the only one, in the effect of a β,γ-ethylenic double bond is undoubtedly its homoconjugation with the CO double bond; as expected on this basis the β olefinic carbons are shielded and the γ-olefinic carbons deshielded in the unsaturated ketones relative to the corresponding olefins.[12a,15c] It has been proposed that an additional factor affecting the observed shieldings in these bicyclic systems is variation in bonding parameters resulting from variation in strain energy.[12a]

Bicyclo[2.2.2]*octane keto lactones* (**1**)

The ketonic carbon chemical shifts for the unsaturated keto lactones **1a–1i** are given in Table 2 together with that of **15**, the saturated analogue of **1a**. Corresponding data for other bicyclo[2.2.2]octan-2-ones and bicyclo[2.2.2]oct-5-en-2-ones[a] recorded in the present work or reported by other workers are given in Tables 3 and 4, respectively. The

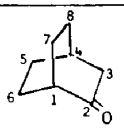
[a]Some of these compounds are not relevant to the present discussion but are included for reference purposes.

Table 2. ^{13}C NMR chemical shifts of sp^2 carbons in keto lactones **1** and **15**

					δ^{CDCl_3}			
					C.2	C.9	C.5	C.6
15					208.1	177.8	-	-
	R_1	R_2	R_3	R_4				
1a	CH_3	H	H	H	202.5 (-5.6)[a]	177.6	128.6	138.9
1b	CH_3	CH_3	H	CH_3	202.7 (-5.4)	180.1	128.7	136.4
1c	CH_3	C_6H_5[b]	H	H	201.9 (-6.2)	176.4	129.9[b]	135.5[b]
1d	CH_3	Br	H	H	198.3 (-9.3)	173.8	128.6	136.4
1e	H	Br	H	H	197.3 (-10.8)	173.5	128.8	131.6
1f	CH_3	H	Br	H	199.3 (-8.8)	172.1	129.7	136.9
1g	CH_3	CO_2Me[c]	H	H	200.0 (-8.1)	175.7	129.5	135.0
1h	CH_3	H	CO_2Me[c]	H	199.9 (-8.2)	175.0	129.0	138.5
1i	H	H	CO_2Me[c]	H	198.2 (-9.9)	174.7	129.6	133.3

[a]Figures in parentheses are differential shifts of ketonic carbon in **1a-i** relative to **15**; negative values denote shielding effects. [b] The aromatic and ethylenic carbon signals for **1c** are at δ 138.6(s), 135.5(d), 129.9(d), 129.4(d), 128.1(d), and 127.7(d) ppm; assignments of the ethylenic carbon signals are based on their positions, multiplicities, and intensities. [c]Ester carbonyl carbon signal at δ 169.8 (**1g**), 170.5 (**1h**), and 171.7 ppm (**1i**).

Table 3. ^{13}C NMR chemical shifts of ketonic carbon in bicyclo[2.2.2]octan-2-ones

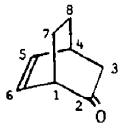
	δ^{CDCl_3}	$\Delta\delta$[a]	Ref.
	217.7[b], 216.7[c], 216.9[d] 217.3[e], 216.8[f]	-	
1-Me	217.9	0.2	b
3-Me	220.1	3.4	c
4-Me	216.6	-0.1	c
1,4-Me_2	216.9		g
3,3-Me_2	221.9	5.2	c
3,4-Me_2	219.9	3.2	c
endo, cis-5,6-Me_2	216.8	0.1	h
1,5,5-Me_3	217.8	0.1	b
3,3,4-Me_3	222.2	5.5	c
endo-3, endo, cis-5,6-Me_3	220.3	3.6	h
exo-3, endo, cis-5,6-Me_3	219.6	2.9	h
4,6,6-Me_3	216.3	-0.4	c
3,3, endo, cis-5,6-Me_4	221.3	4.5	h
1,5,5, anti-8-Me_4	217.2	0.5	c
1,5,5, syn-8-Me_4	217.7	1.0	c
3-OAc	212.4	-5.3	b
3-OAc-1,3-Me_2	212.6	-5.1	b
3-OH	219.6	1.9	b
3-OH — 3-Me	220.7	3.0	b
4-OH	213.3	-3.5	f
endo-6-Cl	211.4	-5.9	e
exo-6-Cl	212.9	-4.4	e
endo-5-CO_2H	216.4	-0.5	d
endo-5-CO_2H-exo-5-Me	214.3	-2.6	d
endo-6-CO_2H-endo-3-OH-1,3-Me_2	216.3	-1.4	b
5-oxo	211.4	-5.5	d

[a]Differential shifts of ketonic carbon relative to bicyclo[2.2.2]octan-2-one; positive values denote deshielding effects; comparisons are made between data from the same Laboratory. [b]Present work. [c]Ref. 15c. [d]Ref. 28. [e]Ref. 31. [f]Ref. 22. [g]Ref. 32. [h]Ref. 21.

values observed for bicyclo[2.2.2]octanone itself from several different Laboratories vary from 217.7 to 216.7 ppm, presumably reflecting differences in solution concentration and temperature. Wherever possible the differential shifts used for the analysis of structural effects have been calculated by comparison of data from the same Laboratory, but clearly little significance can be attached to differential shifts that are < 1 ppm.

Comparison of the saturated keto lactone **15** with bicyclo[2.2.2]octanone shows that the introduction of the 1- and 3-Me groups together with the lactone ring leads to an upfield shift of -9.6 ppm. As discussed in the Introduction α-Me substitution in cyclic ketones leads to β deshielding effects that are of smaller magnitude than in the cases of the corresponding hydrocarbons. For bicyclo-[2.2.2]octanone substitution of 1- and 3-Me groups results in downfield shifts of 0.2 and 3.4 ppm, respectively. Comparison of **1d** and **1h** with **1e** and **1i**, respectively, shows that the deshielding effect of 1-Me substitution in these unsaturated keto lactones is 1.0 and 1.7 ppm, respectively. The effect of the 3-Me substituent in **15** is expected to be less than that in bicyclo[2.2.2]octanone itself because of geminal substitution. Indeed, comparison of 3-acetoxy-1,3-dimethylbicyclo[2.2.2]octanone with 3-acetoxybicyclo[2.2.2]octanone reveals that in this case the combined effect of 1- and 3-Me substitution is very small

Table 4. ^{13}C NMR chemical shifts of sp^2 carbons in bicyclo[2.2.2]oct-5-en-2-ones

	δ_{CDCl_3}			Ref.
	C.2	C.5	C.6	
	212.9	137.0	128.5	[a]
	212.4	136.8	128.3	[b]
1-Me	213.5	136.7	133.9	[a]
	(0.6)[c]			
endo-3-Me	214.1	136.0	127.2	[b]
	(1.7)			
exo-3-Me	215.1	136.0	128.1	[b]
	(2.7)			
4-Me	212.1	141.5	127.7	[b]
	(-0.3)			
$3,3\text{-Me}_2$	216.7	138.6	126.1	[b]
	(4.3)			
$1,8,8\text{-Me}_3$	213.5	138.3	132.3	[a]
	(0.6)			
$4,7,7\text{-Me}_3$	211.6	140.6	127.8	[b]
	(-0.8)			
$1,5,8,8\text{-Me}_4$	213.1	147.1	124.1	[b]
	(0.7)			
endo-3-OAc-1,exo-3-Me_2[d]	207.8	134.9[e]	133.3[e]	[a]
	(-5.1)			

[a]Present work. [b]Ref. 15c. [c]Figures in parentheses are differential shifts of ketonic carbon relative to bicyclo[2.2.2]oct-5-en-2-one; positive values denote deshielding effects; comparisons are made between data from the same Laboratory. [d]Acetoxyl carbonyl signal at δ 169.9 ppm. [e]Individual assignments provisional.

(0.2 ppm). However, this may be partly due to a change in the preferred orientation of the acetoxyl group a circumstance not duplicated in **15**. Thus the deshielding effect of the two Me groups in **15** may be estimated to lie in the range 0.2–3.5 ppm, leading to a range of −10 to −13 ppm for ths shielding effect of the lactone ring. The sign of this β effect is in accord with previous observations on the effects of α heteroatom substituents on ketonic carbon chemical shifts, but its magnitude is exceptionally large. It may be compared with the effect of −5.3 ppm engendered by substitution of a 3-acetoxy group in bicyclo[2.2.2]octanone. Factors that may contribute to this increase in magnitude are (i) increased electrostatic interaction due to the rigidly held orientation of the lactone CO group with respect to the ketonic CO group and (ii) distortion of the geometry of the bicyclo[2.2.2]octanone system due to the presence of the lactone ring (the existence of such distortion has been indicated by ^1H NMR studies[2]).

Comparison of **15** with its unsaturated analogue **1a** shows that introduction of the ethylenic double bond leads to an upfield shift of −5.6 ppm; this falls within the range −4.3 to −6.0 ppm observed for a large number of bicyclo[2.2.2]octanones (see Tables 3 and 4). As discussed previously the β-olefinic carbons of simple β,γ-unsaturated cyclic ketones are usually shielded relative to the corresponding olefin and the γ-olefinic carbons are deshielded. Thus for bicyclo[2.2.2]oct-5-en-2-one the olefinic carbon signals are at 136.8 and 128.3 ppm, straddling the value (134.1 ppm) for bicyclo[2.2.2]octene, and Stothers[15c] has assigned these to C.5 and C.6, respectively, on the basis of comparison with the olefinic

carbon chemical shifts of 4-methylbicyclo[2.2.2]oct-5-en-2-one and the expectation that the C.4 Me group will deshield C.5 and shield C.6 as in other olefinic systems. The olefinic carbon signal assignments of the other bicyclo[2.2.2]octenones with a C.4 Me substituent in Table 4 followed on this basis. We have confirmed these conclusions by comparison with the olefinic carbon chemical shift for 1-methylbicyclo[2.2.2]oct-5-en-2-one, where in accord with expectation the C.1 Me group deshields C.6 and shields C.5. The effects of the bridgehead Me are satisfyingly analogous in the C.1 and C.4 cases: C.1 substitution leads to shifts of the C.5 and C.6 signals by −0.3 and 5.4 ppm, respectively, while C.4 substitution leads to shifts in these signals of 4.7 and −0.6 ppm, respectively. The olefinic carbon signals of the other bicyclo[2.2.2]octenones with a C.1 Me substituent in Table 4 are assigned on a similar basis. It is of considerable interest that comparison of the olefinic carbon chemical shifts of **1d** with **1e** and of **1h** with **1i** shows that introduction of a C.1 Me group into **1e** and **1i** leads in each case to an appreciable downfield shift (4.8, 5.2 ppm) of the *lower field* olefinic carbon signal and a small upfield shift (−0.2, −0.6 ppm) of the *higher field* olefinic carbon signal. It is therefore concluded that in the cases of **1d**, **1e**, **1h**, and **1i** the lower field olefinic signals must be assigned to C.6 and the higher field signals to C.5.[h]

These assignments were confirmed in the case of **1i** by examination of **1i**-1,5-d_2,[i] whose proton-noise decoupled spectrum showed a strong singlet at 133.0 ppm and a weak triplet at 129.5 ppm, demonstrating that the higher field olefinic carbon signal is that of C.5.[j] The other olefinic carbon assignments in Table 2 follow from this conclusion, as was confirmed in the case of **1d** by examination of its ^{13}C NMR spectrum with single proton decoupling at the resonance frequency of the higher field proton signal. This led to collapse of the lower field olefinic carbon signal from a doublet to a singlet, while the higher field olefinic carbon signal remained as a doublet, establsihing that the former carbon signal arises from C.6, since the proton-proton coupling pattern in the ^1H NMR spectrum of **1d** establishes that the higher field olefinic proton signal arises from the proton at C.6.[2]

The upfield shift of the C.5 and the downfield shift of the C.6 signals in **1e** and **1i** relative to the corresponding carbon signal in bicyclo[2.2.2]oct-5-en-2-one (and analogous effects in **1a–1d** and **1f–1h** relative to 1-(methylbicyclo-[2.2.2]oct-5-en-2-one) must arise in part from substituent effects, particularly of the lactone ring. It seems unlikely, however, that the lactone substituent effect would be large enough to account for the overall effects observed. It may therefore be suggested that the distortion of the geometry of the bicyclo[2.2.2]octenone system upon introduction of the lactone ring referred to above also plays a role by decreasing the homoconjugative interaction between the ethylenic double bond and the ketonic carbonyl group. If indeed this is the case, strength is lent to Stothers' view that the upfield shift of the CO carbon signal in bicyclo[2.2.2]-octenone relative to bicyclo[2.2.2]octanone is due in part only to homoconjugation.

Returning to the ketonic carbon chemical shifts of these lactones, we discuss next the effect of substituents at C.7 (Table 2). For both the *anti*- and *syn*-7-bromo compounds **1d** and **1f**, the ketonic carbon signal is shifted upfield relative to that in **1a** by −3 to −4 ppm. Similar γ upfield shifts are observed in the case of the 6-chlorobicyclo-[2.2.2]octanones (Table 3), although here the *syn* isomer has the greater effect, *syn* and *anti*-7-carbomethoxy substituents also give rise to similar upfield shifts (−2.4, −2.5 ppm). These similarities of γ-*syn* and γ-*anti* effects are reminiscent of the γ-effects of second row heteroatoms on the CO carbon shifts of other ketones (*vide supra*) and presumably result coincidentally from a combination of different factors. As expected the γ-effects of the *anti*-Me and phenyl substituents in **1b** and **1c** on the ketonic carbon signal are small (< 1 ppm).

In summary the exceptionally high field signals of the ketonic carbons of the keto lactones **1** can be accounted for in terms of a combination of shielding effects engendered by one or more of the following structural features: lactone (−10 to −13 ppm), ethylenic double bond (−4 to −6 ppm), and C.7 bromo or carbomethoxy substituent (−2.5 to −4 ppm). In general the combination of these is little offset by the combined deshielding effect of the C.1 and C.3 Me groups (0.2–3.5 ppm). In the extreme case of **1e** (≡ **3**) the combination of effects results in an upfield shift of 20 ppm relative to bicyclo[2.2.2]octanone.

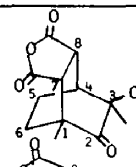
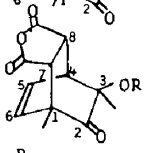
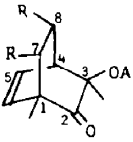
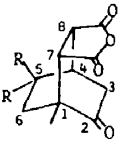
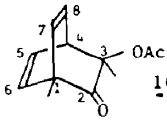
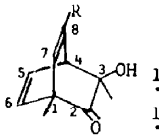
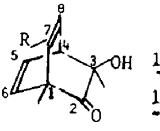
The ketonic and olefinic carbon chemical shifts of compounds **16a–l**,[34,35] related to the keto lactones **1**, are listed in Table 5. These will not be discussed in detail but the following features may be noted. Fusion of an *anti*-5-membered cyclic anhydride ring at a saturated two carbon bridge in bicyclo[2.2.2]octanones and bicyclo-[2.2.2]octenones shields the CO carbon by −6 to −7 ppm; the effect of a *syn*-anhydride ring is also strongly shielding (~ −8 ppm). The ethylenic carbons of the unsaturated anhydrides have similar chemical shifts and cannot be differentiated. Conversion of an *anti*-anhydride ring to the corresponding dimethyl ester results in a reduction in CO shielding (1.6 ppm) and an upfield shift (−2.5 ppm) of the signal of one of the ethylenic carbons, in the single case examined. Similar conversion of a *syn*-anhydride ring also results in reduction in CO carbon shielding (3.1 ppm). Introduction of a second ethylenic double bond into the bicyclo[2.2.2]octenone system to give a bicyclo[2.2.2]octa-dienone results in an upfield shift of the ketonic CO signal (~ −8 ppm) that is larger than that which results from introduction of an ethylenic double bond into the bicyclo[2.2.2]octane system (−4 to −6 ppm). This again indicates that homoconjugation is not the only factor leading to these upfield shifts, since attenuation of this effect would be expected on introduction of the second ethylenic double bond. The proposal[12a] that variation in bonding parameters can also be an important factor (*vide supra*) could account for the present observations, since the dienone system must be considerably more strained than the enone system. It is also noteworthy that the effect on the ketonic CO carbon chemical shift of a carbomethoxy substituent on one of the ethylenic double bonds of the dienone system is essentially independent of whether the carbomethoxy group is β- or γ- to the ketonic group, once more suggesting the intervention of factors in

[h]The possibility that there is a "cross-over" in the relative signal positions in each pair of compounds upon C.1 Me substitution and that the C.6 signals of **1e** and **1i** are at higher field than the C.5 signals is remote since this would require differential shifts on C.1 Me substitution (−3.0 and −4.3 ppm at C.5 and 7.6 and 8.9 ppm at C.6) that are much greater in absolute magnitude than in the cases cited above.

[i]Compound **1i**-1,5-d_2 was prepared by treatment of *o*-cresol-4,6-d_2[33] with methyl hydrogen maleate and red lead oxide in benzene.[2]

[j]The ^1H NMR spectrum of **1i**-1,5-d_2 revealed that the C.5 olefinic proton of **1i** also resonates at higher field than the C.6 olefinic proton.

Table 5. ^{13}C NMR chemical shifts of sp^2 carbons in bicyclo[2.2.2]octane derivatives **16**

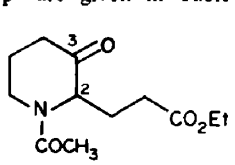
			δ[a]		
			C.2	C.5,6,7,8[b]	Other C=O
	16a	R = H	214.3	-	172.5,170.1
	16b	R = Ac	206.6	-	172.3,170.3,170.1
	16c	R = H	208.7	134.5,133.7	172.0,169.3
	16d	R = Ac	201.4	134.9,134.0	171.4,170.0,169.4
	16e	R = CO_2Me	203.0	134.9,131.5	171.7,171.2,169.8
	16f	R = H[c]	211.0	-	173.4,171.7
	16g	R = Me[d]	209.9	-	173.1,170.3
	16h		199.6	135.7,135.3 134.4,133.1	169.7
	16i	R = CO_2Me	204.5	142.7,138.8, 135.5,134.5	164.8
	16j	R = CO_2Et	204.4	142.3,139.3, 135.6,134.6	164.3
	16k	R = CO_2Me	204.8	146.3,136.6, 135.1,134.3	164.7
	16l	R = CO_2H[e]	205.7	147.5,137.4, 136.3,136.0	167.6

[a] In $CDCl_3$ unless otherwise specified. [b] Some individual assignments uncertain, see text. [c] In DMSO-d_6. [d] Signals at δ 210.7, 173.9, and 171.5 ppm in DMSO-d_6. [e] In CH_3OD.

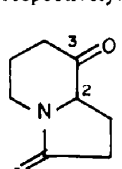
addition to homoconjugation: in this case it is likely that electrostatic interaction is such a factor.

3-Azacycloalkanones (2)

The ketonic carbon chemical shifts for the 3-piperidinones **2a–g**, **17a** and **17b**[3,26] and 3-pyrrolidinones **2h–p**[3] are given in Table 6 and 7, respectively. As



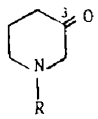
17a



17b

mentioned earlier, the nitrogen in N-alkyl- and N-acylpiperidines exerts a small β-shielding effect (−1.1 to −1.4 ppm) at C.3 relative to cyclohexane.[26] Lambert [26a] has suggested that this may reflect the Pople–Gordon alternation of sign for charge polarization with a large attenuation with increased distance.[37] The β-shielding effect of the nitrogen in the 3-piperidinones **2a–g** is considerably greater; for the N-alkyl and N-benzyl derivatives it falls in the range −5 to −6 ppm and increases to −7 to −8 ppm in the N-acyl derivatives. For the N-acyl derivatives **17a** and **17b** the shielding effect falls in the former range. This downfield shift relative to the N-acyl-3-piperidinones **2d–g** is readily attributed to a small deshielding effect of the substituent at C.2 in **17a** and **17b**. In the case of **17a** this must result from a combination of β deshielding and γ shielding effects of the side chain; in that of **17b** it would be expected that the C.2 substituent would exert only a β deshielding effect and the fact that its ketonic CO carbon signal is upfield from that of **17a** presumably reflects changes in the geometry of the 3-piperidinone system on closure of the lactam ring. The β

Table 6. ^{13}C NMR chemical shifts of carbonyl carbons in 3-piperidinones **2a–g**, **17a** and **17b**

			δ^{CDCl_3}		Ref.
			C.3	N-C=O	
		R			
	2a	CH_3	205.9 (-6.1)[b]		a
	2b	CH_2CH_3	206.7 (-5.3)		c
	2c	$CH_2C_6H_5$	206.8 (-5.2)		c
			205.8 (-6.2)		a
	2d	$COCH_3$	205.1, 204.6[d] (-6.9, -7.4)	169.6, 169.4[d]	c
			205.0[e] (-7.0)	169.4[e]	a
	2e	COC_6H_5	204.1[e] (-7.9)	170.0[e]	a
	2f	CO_2Me	205.1 (-6.9)	155.7	a
	2g	CO_2Et	205.4 (-6.6)	155.4	c
			204.9 (-7.1)	155.2	a
17a			207.2, 206.9[d] (-4.8, -5.1)	169.9, 169.7[d]	c
17b			205.8 (-6.2)	173.5	c

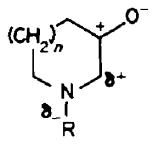
[a]Ref. 26c. [b]Figures in parentheses are differential shifts of ketonic carbon in 2a-i relative to cyclohexanone (δ 212.0 ppm[4]); negative values denote shielding effects. [c]Present work. [d]Two signals arise from conformational isomerism about the N-CO bond; cf. ref. 36. [e]Above coalescence temperature for conformational isomers. [f]Ester carbonyl signals at δ 172.7 and 172.2 ppm.

shielding effect of the nitrogen in the 3-pyrrolidinones[k] **2h–p** is again large and greater in the case of the N-acyl derivatives (−8 to −9 ppm) than in that of the N-alkyl and N-benzyl derivatives (−4 to −6 ppm).

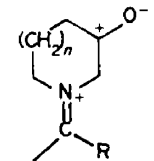
The large β shielding effect of nitrogen in compounds **2a–p**, **17a** and **17b** at the ketonic CO carbon relative to that at C.3 in the N-alkyl- and N-acyl-piperidines indicates that one or more additional shielding mechanisms are involved. We suggest that the most important factor is a dipole-dipole interaction analogous to that discussed earlier in relation to the β-shielding effect of α-heteroatom substituents on the CO carbon of cyclic ketones. In the present case this is symbolized by the resonance contributor **18**. Here the dihedral angle between the C.3–O and C.2–N bonds is ~120°, while in the case of **7** the corresponding angle is ~0°; however, calculation shows that the dipole interaction remains significant (~60% of that for a nitrogen substituent with a dihedral angle of 0°). The larger effect in the N-acyl derivatives relative to the N-alkyl and N-benzyl compounds can be ascribed to a further electrostatic effect symbolized by resonance contributors of type **19**.[l]

[k]The differential shifts are calculated relative to the cyclopentanone with the same alkyl substitution pattern; a value of δ 222.7 ppm was taken for 2,2-dimethylcyclopentanone based on the values reported[15a] for cyclopentanone (δ 219.4 ppm), 3-methylcyclopentanone (δ 218.7 ppm), and 2,2,4-trimethylcyclopentanone (δ 222.0 ppm).

[l]In these terms, the similarity of the ketonic CO carbon chemical shifts for the members of the rotamer pairs **2d**, **2j** and **17a** reflects the remoteness of the negative (oxygen) end of the amide dipole from the ketonic CO group.

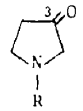
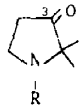
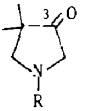


18



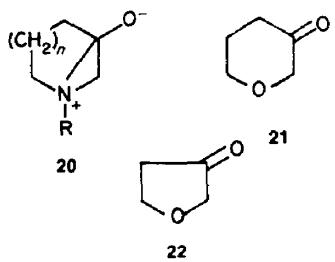
19

Table 7. ^{13}C NMR chemical shifts of carbonyl carbons in 3-pyrrolidinones **2h–p**

		R	δ^{CDCL_3} C.3	N-C=O
	2h	$CH_2C_6H_5$	213.5 (-6.1)[a]	
	2i	CO_2CH_3	210.5 (-8.9)	155.6
	2j	$COCH_3$	210.0, 210.2[b] (-9.4, -9.2)	169.6, 169.8[b]
	2k	CH_3	217.9 (-4.8)	
	2l	$CH_2C_6H_5$	217.2 (-5.5)	
	2m	CO_2CH_3	215.0 (-7.7)	155.2
	2n	CH_3	218.5 (-4.2)	
	2o	$CH_2C_6H_5$	218.0 (-4.7)	
	2p	CO_2CH_3	214.4 (-8.3)	155.8

[a] Figures in parentheses are differential shifts of ketonic carbon in 2h-j relative to cyclopentanone (δ 219.4 ppm[15a]) and in 2k-p relative to 2,2-dimethylcyclopentanone (estimated δ 222.7 ppm, see text); negative values denote shielding effects. [b] Two signals arise from conformational isomerism about the N-CO bond; cf. ref. 36.

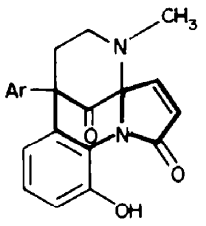
These interpretations are in accord with the CO-stretching wavelengths in the IR spectra of the 3-piperidinones and 3-pyrrolidinones. In the former these are at 5.80 μ, relative to 5.85 μ for cyclohexanone, and in the latter at 5.66–5.70 μ, relative to 5.74 μ for cyclopentanone. These shifts can again be attributed to dipole-dipole interactions.[25] The IR spectral data also indicate that another interpretation that might have been invoked to account for the ^{13}C NMR data, viz. interaction of the unshared pair of electrons on nitrogen with the CO π system, as symbolized by the resonance contributor **20**, is not the major factor in the β-shielding effect of the nitrogen. For although this would account for the ^{13}C NMR spectral observations, it would be expected to result in a shift of the CO-stretching bands to longer wavelengths in the IR spectra. Furthermore, it would be anticipated that the ^{13}C NMR effect would be smaller for N-acyl than for N-alkyl or N-benzyl derivatives. The relative unimportance of the interaction symbolized by **20** is in conformance with theoretical calculations.[38] However, it is possible that such an interaction may contribute to some extent in the case of the N-substituted 3-azacycloalkanones as witnessed by comparison with the corresponding 3-oxacycloalkanones, **21**[26c] and alkyl derivatives of **22**.[39] The CO carbon chemical shifts of these compounds show β-shielding effects relative to the corresponding cycloalkanones that are appreciable (−3 to −5 ppm) but slightly less than those for the analogous N-alkyl-3-azacycloalkanones. If dipole-dipole interaction had been the only factor in causing these effects, it would have been anticipated that the 3-oxa compounds would show the greater effect, because of the greater electronegativity of oxygen. It is possible that the interaction symbolized by **20** plays an additional role in the case of the 3-aza compounds, but not in that of the 3-oxa compounds, because of the greater electronegativity of the heteroatom in the latter.



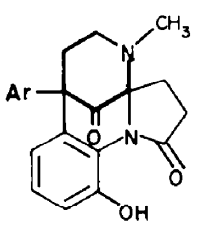
20 **21** **22**

In the two cases, **2e** and **2g**, where comparison data are available,[26b] the presence of the ketonic CO group appears to have a negligible effect on the chemical shifts of the amide or urethane CO carbons. This insensitivity may reflect the additional conjugation of the latter CO groups with the ethoxy and phenyl groups, respectively.

We are now in a position to assess the factors that contribute to the exceptionally high field chemical shift (δ 197.2 ppm) of the ketonic CO carbon in haplophytine (**4**). It may first be noted that this incorporates the tetrahydroindolizine-3,8(2*H*,5*H*)-dione system **17b** (see

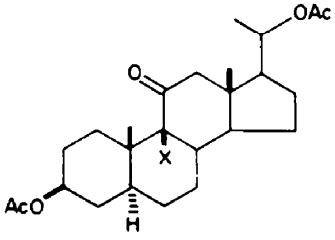


23a(= 4)

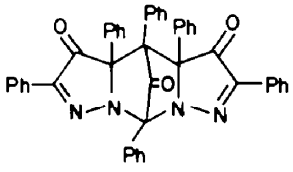


23b(= 4)

23a), whose ketonic CO carbon has been found to have a chemical shift of δ 205.8 ppm. This CO group also forms part of an N-methyl-3-piperidinone system that has been found to result in an upfield shift of the CO carbon signal of ~ -6 ppm in the parent system. Alternatively, of course, this system (δ 205.9 ppm) may be taken as the point of departure (see **23b**) and the effects of the lactam nitrogen assessed from the shielding effect of the lactam nitrogen in **17b** (~ -6 ppm). In relation to the latter dissection it may be noted that the ketonic CO carbon chemical shift of **24a** has been observed to be shifted upfield by ~ -5 ppm upon introduction of an axial α-



24a: X = H
24b: X = $NHCOCH_3$
24c: X = $NHCO_2CH_3$



25

carboxamido or α-carbomethoxyamido substituent as in **24b** and **24c**.[40] The geometrical relationship of the C.9–N bond and the ketonic CO bond in these compounds is analogous to that of the corresponding bonds in **23b**. Thus the effect of the two N atoms in 4 may be estimated to result in a chemical shift of $\delta \sim 200$ ppm for the ketonic CO carbon. As in the case of the simpler system discussed earlier, the N substituents also exert a considerable effect on the IR ketonic CO stretching band, which occurs at $\sim 5.72\ \mu$,[m] an extraordinarily short wavelength for a 6-membered cyclic ketone. This very large hypsochromic shift in the case of **4** is attributed to the combined electrostatic effects of both of the N atoms.

Further, secondary factors that would account for an additional upfield shift of the ketonic CO carbon in the ^{13}C NMR spectrum of **4** are as follows: (i) enhancement of the electrostatic effect of the lactam nitrogen because of its interaction with the aromatic ring I, (ii) homoconjugation[n] of the ketonic CO group with the aromatic ring I, and (iii) homoconjugation of this group with the aromatic substituent designated as Ar in **4**. Deshielding effects that could partially counteract these may be associated with (i) the β-effect of the Ar group as an α-substituent, which would, however, be partially compensated by a strong countervailing γ-effect and (ii) the incorporation of the ketonic CO group at the C.9 position of a bicyclo[3.3.1]nonane type system [*cf* **6** (216.8 ppm) with cyclohexanone (212.0 ppm)]. It is clear that no quantitative assessment can be made of the magnitude of these various additional factors, but it can be concluded that a combination of these together with the major electrostatic effects of the N atoms can account for the chemical shift of the ketonic CO carbon of **4**. In conclusion, we draw attention to compound **25**, which shows CO carbon signals at δ 191.3 and 193.0 ppm.[41] Although individual assignments have not been made, either signal is at extraordinarily high field for a bicyclo[heptan-7-one derivative. It is of interest that several of the factors that we have invoked to account for the ketonic CO carbon chemical shift in **4** are operative also in the case of **25**.

Chemical shifts of sp^3 *carbon atoms*[o]

The chemical shifts of the sp^3 carbons in the ^{13}C NMR spectra of compounds **1**, **15**, **16** and related bicyclo[2.2.2]-octane derivatives are recorded in Tables 8–10. The assignments are based on the multiplicities of the signals in off-resonance single frequency decoupled spectra, on comparison of the spectra with each other and with the spectra of related compounds reported by other workers, and on known types of substituent effects. In the case of the methylene carbons of the hydroxy and acetoxy compounds in Table 9, the assignment must be considered as tentative. We shall not discuss the chemical shifts of the sp^3 carbons in detail, but we draw attention to the following aspects:

(i) The α deshielding effect of a 1-Me substituent on C.1 in bicyclo[2.2.2]octanone and its derivatives is small (< 1.5 ppm) and often negligible; the β deshielding effect at C.6 and C.7 is larger (4.5–9 ppm) and is dependent on the hybridization of these carbons and the nature of their substituents, if any.

(ii) Comparison of bicyclo[2.2.2]octanones with the corresponding bicyclo[2.2.2]octenones shows that the presence of the Δ^5 ethylenic double bond shields C.3 (-3 to -5 ppm) and CH_3(1) (~ -2.5 ppm), while it deshields C.1 (5.5–7 ppm) and C.4 (3–5 ppm).

(iii) The C.3 signal of 3-hydroxybicyclo[2.2.2]octan-2-one is shifted slightly (-0.5 ppm) upfield in 3-hydroxy-3-methylbicyclo[2.2.2]octan-2-one; this may be compared with the downfield shift (2.1 ppm) of the C.2 signal of 2-methylbicyclo[2.2.2]octan-2-ol relative to that of bicyclo[2.2.2]octan-2-ol[28b] and the downfield shifts of the C.2 signals of *endo*-2-methyl-*exo*-2-norbornanol and *exo*-2-methyl-*endo*-2-norbornanol relative to those of their

[m] The exact position is uncertain because of overlap with another carbonyl-stretching band; in haplophytine derivatives where such overflap does not occur, the band is at $\sim 5.75\ \mu$.

[n] As in the case of the β,γ-unsaturated ketones discussed earlier a significant upfield shift may be expected to result from the presence of the aromatic ring, although this may be only due in part to homoconjugation.

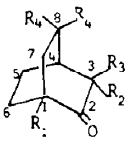
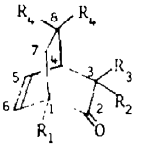
[o] Only the sp^3 carbon ^{13}C NMR chemical shifts of the bicyclo-[2.2.2]octane derivatives are referred to here; those of the 3-azacycloalkanones[3c,42] will be discussed elsewhere in relation to their other spectroscopic properties.

Table 8. ^{13}C NMR chemical shifts of sp^3 carbons in keto lactones **1** and **15**[a]

	δ^{CDCl_3}									
	1a	1b[b]	1c	1d	1e	1f	1g	1h	1i[c]	15[d]
C.1	48.8	54.0	54.2	55.9	55.5	54.1	51.4	50.4	48.9	42.2
C.3	80.3	78.0	80.2	80.1	79.6	79.5	80.0	79.9	80.0	85.2
C.4	46.7	53.2	46.9	45.6	46.4	46.7*	46.2*	47.4	47.7*	43.5
C.7	36.9	43.8	50.6*	51.9*	43.1	50.7	49.5	52.5	48.0*	33.2*
C.8	40.4	48.1	49.9*	51.4*	49.4	47.7*	45.3*	44.5	42.3	40.1
$CH_3(1)$	17.1	15.8	15.9	16.5	-	17.5	16.0	15.2	-	19.8
$CH_3(3)$	17.9	18.0	18.3	17.9	17.7	18.0	18.1	18.3	18.1	15.4
OCH_3	-	-	-	-	-	-	52.5	53.7	52.7	-

[a]Assignments are in accord with the multiplicities in single frequency off-resonance decoupled spectra: the assignments of signals for a given compound that are marked with asterisks may be interchangeable. [b]Signals at δ 10.7 and 17.5 ppm are assigned to $CH_3(7)$ and $CH_3(8)$, respectively. [c]Assignment of C.1 signal is based on the spectrum of 1i-1,5-d_2; see text. [d]Signals at δ 15.3 and 33.4* ppm are assigned to C.5 and C.6, respectively.

Table 9. ^{13}C NMR chemical shifts of sp^3 carbons in bicyclo[2.2.2]octan-2-ones and bicyclo[2.2.2]oct-5-en-2-ones

	δ^{CDCl_3}										
											
	R_1 = H[b]	CH_3	CH_3	H	CH_3	H	H	H[b]	CH_3	CH_3	CH_3
	R_2 = H	H	H	OAc	OAc	OH	OH	H	H	H	OAc
	R_3 = H	H	H	H	CH_3	H	CH_3	H	H	H	CH_3
	R_4 = H	H	CH_3	H	H	H	H	H	H	CH_3	H
C.1	42.3	42.4	44.3	42.0	42.3	41.3	41.8	48.6	49.0	50.6	48.3
C.3	44.7	44.5	41.9	75.8	83.9	76.1	75.6	40.5	40.5	36.8	79.7
C.4	27.9	28.1	39.1	33.5	35.2	35.0	38.2	32.4	32.3	44.3	39.4
C.5	24.7	25.5	22.8	19.8	21.8	19.4	21.9*	-	-	-	-
C.6	23.4	30.9	29.3	25.6	31.0*	26.8	25.4	-	-	-	-
C.7	23.4	30.9	47.6	23.0	30.1*	23.1	22.1*	22.5	30.3	47.2	29.0
C.8	24.7	25.5	31.3	21.3	19.0	21.2	20.6	24.3	26.0	35.4	19.9
$CH_3(1)$	-	20.2	20.3	-	20.3	-	-	-	17.6	17.6	17.8
$CH_3(3)$	-	-	-	-	21.5	-	23.3	-	-	-	22.0*
$CH_3(8)$	-	-	30.0,30.4	-	-	-	-	-	-	28.8,31.7	-
CH_3CO	-	-	-	20.8	22.3	-	-	-	-	-	22.3*

[a]See footnote a in Table 8. [b]Cf. ref. 15c.

Table 10. ^{13}C NMR chemical shifts of sp^3 carbons in compounds **16**

	δ^{CDCl_3}										
	16a	16b	16c	16d	16e	16f	16g[b]	16h	16i	16j[c]	16k
C.1	43.9	44.9	49.9	50.4	50.3	44.2	47.4	55.9	57.2	57.2	56.7
C.3	73.7	80.2	70.7	77.0	79.4	40.9	37.8	75.4[d]	67.8	67.9	68.4
C.4	40.0*	39.0	44.8	43.2*	42.6	30.8	41.0*	45.1	48.4	48.5	51.7
C.5	17.9	18.7	-	-	-	24.3	31.4	-	-	-	-
C.6	25.1	26.1	-	--	-	30.4	47.7	-	-	-	-
C.7	46.0	46.2	46.5	47.0	49.5	47.5	46.6	-	-	-	-
C.8	40.8*	41.8	42.0	42.5*	44.5	44.2	42.2*	-	-	-	-
$CH_3(1)$	16.9	17.2	14.5	14.7	15.6	17.5	17.5	15.2	14.9	14.9	14.2
$CH_3(3)$	23.1	21.8*	25.4	23.4	21.7[e]	-	-	22.0*	26.8	26.8	27.1
CH_3CO	-	21.1*	-	21.2	21.7[e]	-	-	22.5*	-	-	-
CH_3O	-	-	-	-	-	-	-	-	52.1	-	48.5

[a]See footnote a in Table 8. [b]Signals at δ 29.0 and 29.8 ppm are assigned to $CH_3(5)$. [c]Signals at δ 14.2 and 61.0 ppm are assigned to the ethoxyl carbon atoms. [d]Signal is considered to be superimposed on $CDCl_3$ signal. [e]Superimposed signals.

parent 2-norbornanols (3.2 and 4.3 ppm, respectively).[21b] A similar geminal effect has been observed in the case of 3,3-dimethylbicyclo[2.2.2]octan-2-one, whose C.3 signal is shifted to higher field (−1.3 ppm) relative to that of 3-methylbicyclo[2.2.2]octan-2-one.[15c,21a] It is of particular interest that one of the methylene carbon signals of 3-hydroxybicyclo[2.2.2]octan-2-one is shifted to lower field relative to the C.5–8 methylene carbon signals of bicyclo[2.2.2]octan-2-one. This has been assigned to C.6 since this corresponds to the only one of the C.5–8 signals in bicyclo[2.2.2]octan-2-ol that undergoes such a shift relative to bicyclo[2.2.2]octane.[21a] In the latter case the differential shift is only 0.4 ppm, whereas in the former it is ≥ 2.1 ppm. Although full analysis must await unambiguous assignments of the methylene carbon signals of the former compound and related compounds (*vide supra*) it can be suggested that dipolar interactions and/or H-bonding effects in the α-ketol and its congeners affect their ^{13}C NMR spectra because of the influence they exert on the conformation of the bicyclo[2.2.2]octan-2-one system.

EXPERIMENTAL

The preparation of compounds **1a–i** and **15**[2] and compounds **2b**, **2c**, **2d**, **2g**, **17a** and **17b**[3b] has been described, as has the isolation of **4**.[3a] The preparation of compounds **2b–p**,[3c] **16a–l**.[34,35] and the compounds whose spectra are listed in Table 9 will be described elsewhere.

The ^{13}C NMR spectra of these compounds were obtained with Varian CFT-20 or XL-100 spectrometers in the Fourier transform mode with proton noise decoupling and, in most cases, with off-resonance single frequency decoupling. These spectra were recorded in $CDCl_3$ solutions (5–10%) with TMS as internal reference, unless otherwise stated. The spectra of the other compounds in Tables 1–10 are from the references cited.

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REFERENCES

[1]P. Yates, H. Auksi, J. A. Gosbee, G. E. Langford and F. N. MacLachlan, *Org. Magn. Res.* **14**, 153 (1980).
[2]P. Yates and H. Auksi, *Can. J. Chem.* **57**, 2853 (1979).
[3a]P. Yates, F. N. MacLachlan, I. D. Rae, M. Rosenberger, A. G. Szabo, C. R. Willis, M. P. Cava, M. Behforouz, M. V. Lakshmikantham and W. Zeiger, *J. Am. Chem. Soc.* **95**, 7842 (1973); P.-T. Cheng, S. C. Nyburg, F. N. MacLachlan and P. Yates, *Can. J. Chem.* **54**, 726 (1976); [b]P. Yates and F. N. MacLachlan, *J. Indian Chem. Soc.* **55**, 1116 (1978); [c]J. A. Gosbee, M.Sc. Thesis, University of Toronto (1978).
[4]S. H. Grover, D. H. Marr, J. B. Stothers and C. T. Tan, *Can. J. Chem.* **53**, 1351 (1975).
[5a]J. B. Stothers, *Carbon-13 NMR Spectroscopy*, pp. 280–285. Academic Press, New York (1972); [b]*Ibid.* pp. 65–68.
[6]G. B. Savitsky, K. Namikawa and G. Zweifel, *J. Phys. Chem.* **69**, 3105 (1965).
[7]D. H. Marr and J. B. Stothers, *Can. J. Chem.* **45**, 225 (1967); Gurudata and J. B. Stothers, *Ibid.* **47**, 3601 (1969).
[8a]E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison, *Conformational Analysis*, p. 196. Wiley, New York (1965); [b]H. C. Brown and K. Ichikawa, *Tetrahedron* **1**, 221 (1957).
[9]H. H. Günthard and T. Gäumann, *Helv. Chim. Acta* **34**, 39 (1951); R. Arndt, H. H. Günthard and T. Gäumann, *Ibid.* **41**, 2213 (1958).
[10]C. A. Coulson and W. E. Moffitt, *Phil. Mag.* **40**, 1 (1949); P. D. Bartlett and M. Stiles, *J. Am. Chem. Soc.* **77**, 2806 (1955).
[11]L. J. Bellamy, *Advances in Infrared Group Frequencies*, pp. 132–134. Methuen, London (1968).
[12a]J. B. Stothers, J. R. Swenson and C. T. Tan, *Canl J. Chem.* **53**, 581 (1975); [b]A. Heumann and H. Kolshorn, *Tetrahedron* **31**, 1571 (1975).
[13]P. von R. Schleyer, *J. Am. Chem. Soc.* **86**, 1854 (1964); G. L. Buchanan, *Topics in Carbocyclic Chemistry* (Edited by D. Lloyd), Vol. 1, p. 219. Logos Press, London (1969).
[14]J. B. Grutzner, M. Jautelat, J. B. Dence, R. A. Smith and J. D. Roberts, *J. Am. Chem. Soc.* **92**, 7107 (1970).
[15a]J. B. Stothers and C. T. Tan, *Can. J. Chem.* **52**, 308 (1974); [b]J. B. Stothers, C. T. Tan and K. C. Teo, *Ibid.* **51**, 2893 (1973); [c]K. R. Stephens, J. B. Stothers and C. T. Tan, *Mass Spectrometry and NMR Spectroscopy in Pesticide Chemistry* (Edited by R.

Haque and F. J. Biros), pp. 179–196. Plenum Press, New York (1974).
[16]F. W. Vierhapper and R. L. Willer, *Org. Magn. Res.* **9**, 13 (1977).
[17]M. Christl, H. J. Reich and J. D. Roberts, *J. Am. Chem. Soc.* **93**, 3463 (1971).
[18]R. L. Cargill, D. F. Bushey and P. D. Ellis, *J. Org. Chem.* **39**, 573 (1974).
[19]D. K. Dalling and D. M. Grant, *J. Am. Chem. Soc.* **89**, 6612 (1967); **94**, 5318 (1972).
[20]H-J. Schneider and V. Hoppen, *J. Org. Chem.* **43**, 3866 (1978).
[21a]J. B. Stothers and C. T. Tan, *Can. J. Chem.* **54**, 917 (1976); [b]J. B. Stothers, C. T. Tan and K. C. Teo, *Ibid.* **54**, 1211 (1976).
[22]H. Duddeck and P. Wolff, *Org. Magn. Res.* **9**, 528 (1977).
[23]F. C. Brown and D. G. Morris, *J. Chem. Soc.* Perkin II, 125 (1977).
[24]E. Wenkert, A. O. Clause, D. W. Cochran and D. Doddrell, *Chem. Comm.* 1433 (1969).
[25]R. N. Jones, D. A. Ramsay, F. Herling and K. Dobriner, *J. Am. Chem. Soc.* **74**, 2828 (1952).
[26a]J. B. Lambert, D. A. Netzel, H. Sun and K. K. Lilianstrom, *Ibid.* **98**, 3778 (1976);[b]J. A. Hirsch and E. Havinga, *J. Org. Chem.* **41**, 455 (1976); [c]J. A. Hirsch and A. A. Jarmas, *Ibid.* **43**, 4106 (1978).
[27]E. L. Eliel, W. F. Bailey, L. D. Kopp, R. L. Willer, D. M. Grant, R. Bertrand, K. A. Christensen, D. K. Dalling, M. W. Duch, E. Wenkert, F. M. Schell and D. W. Cochran, *J. Am. Chem. Soc.* **97**, 322 (1975).
[28a]P. J. Garratt and R. Riguera, *J. Org. Chem.* **41**, 465 (1976); [b]R. Riguera and P. J. Garratt, *An. Quim.* **74**, 216 (1978).
[29]I. Morishima, K. Okada, T. Yonezawa and K. Goto, *J. Am. Chem. Soc.* **93**, 3922 (1971).
[30]A. Heumann and H. Kolshorn, *J. Org. Chem.* **44**, 1575 (1979).
[31]S. Berger, *Ibid.* **43**, 209 (1978).
[32]J.-C. Jacquesy, R. Jacquesy and J.-F. Patoiseau, *Tetrahedron* **32**, 1699 (1976).
[33]P. Natalis, *Bull. Soc. Roy. Sci. Liège*, **29**, 37 (1960).
[34]H. Auksi, Ph.D. Thesis, University of Toronto (1978).
[35]P. Yates and G. E. Langford, *Can. J. Chem.* in press.
[36]J. A. Hirsch, R. L. Augustine, G. Koletar and H. G. Wolf, *J. Org. Chem.* **40**, 3547 (1975).
[37]J. A. Pople and M. Gordon, *J. Am. Chem. Soc.* **89**, 4253 (1967).
[38]C. C. Levin, R. Hoffmann, W. J. Hehre and J. Hudec, *J. Chem. Soc.* Perkin II, 210 (1973).
[39]P. M. Burke, W. F. Reynolds, J. C. L. Tam and P. Yates, *Can. J. Chem.* **54**, 1449 (1976).
[40]O. E. Edwards and Z. Paryzek, *Ibid.* **51**, 3866 (1973).
[41]B. M. Trost and P. J. Whitman, *J. Am. Chem. Soc.* **96**, 7421 (1974).
[42]F. N. MacLachlan, Ph.D. Thesis, University of Toronto (1977).