Carbon-13 Magnetic Resonance. Chemical Shift Additivity Relationships in *N*-Methyl-4-piperidones

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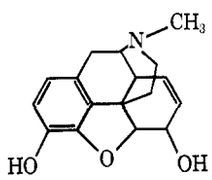
Natural abundance carbon-13 spectra of a series of substituted 4-piperidones (and some pertinent piperidines) in free base, hydrochloride, and methiodide salt forms have been determined and the observed chemical shifts analyzed in terms of the conformational properties of the molecules. Additivity parameters have been derived for the substituents and are compared with similar parameters obtained for the methylcyclohexanes, cyclohexanones, and 1,3-dioxanes. The reduced magnitude of the substituent parameters in the present series compared with the cyclohexanes has been attributed to the higher degree of substitution in the ring, since the electronegative N—H and C=O centers are also considered as substituents in the cyclohexane system. Of particular importance are the additivity effects obtained on protonation and methiodation of the nitrogen in these systems. It is suggested that the parameters derived in this study will be valuable in determining stereo-structural activity relationships in the analgesics which may be readily derived from their precursors studied here.

It has been shown that the stereoisomeric forms of many pharmacologically active molecules, which are simple derivatives of morphine (I), differ greatly in their analgesic potency.[2,3]



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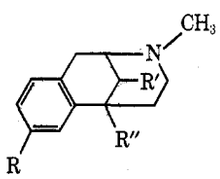

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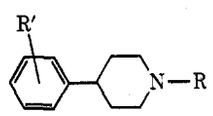
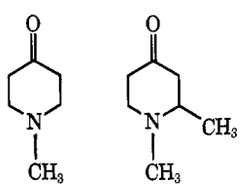


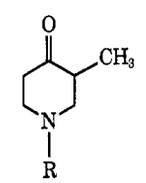
III

It is, therefore, of considerable interest to determine the nature of stereo structural–activity relationships in these types of molecules. Studies concerned with these relationships have employed a variety of accepted methods for structural determination, the most generally useful of which has been proton magnetic resonance (pmr) spectroscopy as indicated by the work of Casy and coworkers.[4-10] Using pmr techniques it has been shown that conformation is a particularly important factor in the determination of the analgesic properties in, for example, the 6,7-benzomorphans (II)[6] and a variety of 4-phenylpiperidine derivatives (III).[4,5]

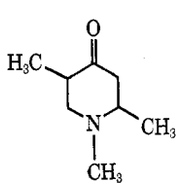
The purpose of the present paper is in part to suggest that the carbon-13 magnetic resonance (^{13}C nmr) technique may also be of considerable value in the determination of conformation in pharmacologically important molecules, particularly in cases where limited resolution of the proton multiplets in the pmr spectra is observed. Recent successes in the application of ^{13}C nmr spectroscopy in conformational analysis of the methylcyclohexanes,[11] the decalins,[12] the perhydroanthracenes and phenanthrenes,[13] the cyclohexanols and derivatives,[14] carbohydrates,[15] the 1,3-dioxanes,[16,17] some cyclic phosphonites,[18] and selected piperidines[19,20] justify this application. We have chosen to demonstrate the potential of the ^{13}C nmr technique for conformational analysis of pharmacologically active molecules by selecting a series of their synthetic precursors, the *N*-methyl-4-piperidones (IV–VII), and related



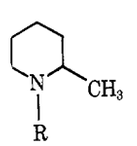
IV V



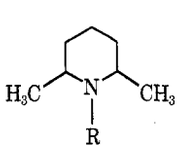
VIa, R = CH_3
b, R = CH_2Ph



VII



VIIIa, R = H
b, R = CH_3



IXa, R = H
b, R = CH_3

compounds VIII and IX along with their hydrochlorides and methiodides.

The conformational features of the *N*-alkyl-4-piperidones to be discussed have been defined using other techniques.[8-10] Consequently, we will use these results to confirm the general trends observed in the present

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(2) *E.g.*, N. B. Eddy and E. L. May in "Synthetic Analgesics," Part IIB, Pergamon Press, Oxford, 1966.

(3) *E.g.*, A. H. Beckett and A. F. Casy, *J. Pharm. Pharmacol.*, **6**, 986 (1954).

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(9) M. M. A. Hassan and A. F. Casy, *Org. Magn. Resonance*, **1**, 389 (1969).

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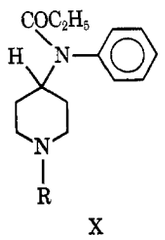
TABLE I

CARBON-13 CHEMICAL SHIFTS IN *N*-ALKYL-4-PIPERIDONES[a]

Structure	Form	Solvent	Carbon position C-2	C-3	C-4	C-5	C-6	C-1′	C-2′	C-3′ or C-5′
IV		Neat	55.40	40.89	206.22	40.89	55.40	45.14		
IV	HCl	$CHCl_3$	52.03	38.39	203.08	38.39	52.03	42.20		
IV	CH_3I	DMSO	60.58	35.92	201.65	35.92	60.58	51.83		
IV	CH_3I	H_2O	61.11	33.12	101.72	33.12	61.11	52.09		
V		Neat	58.81	48.88	207.29	41.38	54.87	41.59	19.69	
V	HCl	$CHCl_3$/DMSO[b]	58.68	44.60	202.47	37.29	51.80	(~39.5)	17.30	
V	CH_3I	DMSO	65.88	42.89	201.07	35.57	60.93	57.82 46.21	14.94	
V	CH_3I	H_2O	66.20	42.89	89.90	35.57	62.44	52.87	14.40	
VIa		Neat	63.40	43.83	207.77	40.57	56.20	45.10		11.89
VIa	HCl	$CHCl_3$	60.44	40.74	203.81	37.34	53.09	43.10		10.89
VIa	CH_3I	DMSO	65.75	38.58	203.56	35.60	61.10	55.53 48.29		10.78
VIa	CH_3I	H_2O	67.00	39.40	92.75	35.94	62.27	56.98 49.54		11.00
VIb		Neat	61.41	40.41	207.89	43.75	60.53	(53.41)[c]		11.93
VIb	HCl	$CHCl_3$	56.30	37.25	204.00	40.75	60.36	(51.17)[c]		11.00
VIb	CH_3I	$CHCl_3$	63.94	35.69	203.81	36.68	70.18	58.12 (59.01)[c]		10.95
VII		Neat[d]	59.78	48.60	207.41	44.03	63.95	41.04	20.84	11.14
VII	HCl	$CHCl_3$	59.82	45.46	203.30	41.48	60.89	39.93	17.90	10.66
VII	CH_3I	DMSO	67.18	42.96	203.40	39.22	67.18	53.02 51.66	15.60	10.66
VII	CH_3I	H_2O	67.00	43.06	92.31	39.88	68.07	54.00	15.54	10.72

[a] Given in parts per million downfield relative to TMS. [b] Low solubility necessitated use of mixed solvent. C-1′ line obscured by solvent peak. [c] Parentheses indicate that this is the shift for the methylene carbon in the benzyl derivatives. Phenyl ring carbons were found at 138.53 (α-C), 128.70 (*o*-C), 128.30 (*m*-C), and 127.11 ppm (*p*-C) in the free base VIb, and at 129.60 (α-C), 130.71 (*o*-C), 128.53 (*m*-C), and 127.37 ppm (*p*-C) in its hydrochloride. The phenyl ring region in the methiodide of VIb was not investigated. [d] It has been shown (ref 10) that VII exists as an approximately 90:10 equilibrium mixture in which the major isomer has the *trans*-2,5-dimethyl configuration with the *N*-methyl group equatorial. These results are for the major isomer.

work. Currently we are attempting to apply the fundamental data derived herein and have obtained some success in the conformational analysis of several 4-phenylpiperidine and fentanyl type (X) analgesics,



X

which are derived from the above piperidones. This work will be the subject of further publications.

Experimental Section

Carbon-13 spectra were determined using a Varian Associates HA-100D-15 spectrometer operating at 25.14 MHz. For carbon-13 determinations this instrument features a Varian V-3530 rf/af sweep unit. Fixed frequency audio modulation for the signal oscillator was obtained from a Hewlett-Packard 5100B–5110B frequency synthesizer system. Broad-band proton decoupling at approximately 100 MHz was achieved using a Varian V3512-1 heteronuclear decoupler. Frequency swept spectra were obtained by applying pulses from the digital recorder to drive a Varian C-1024 time averaging device and the rf sweep. Where long-term spectral accummulation was necessary, the C-1024 was used in the internal trigger mode. The sweep width (2.0–2.5 KHz) was calibrated using a Hewlett-Packard 3735 electronic counter and measured to ±0.25 Hz end to end. All samples were contained in precision-ground 12-mm-o.d. tubes, and a 5-mm capillary containing carbon-13 enriched methyl iodide was added to provide the lock signal.

The majority of compounds studied were freshly prepared and purified by techniques previously described.[8-10] The parent *N*-alkyl compounds were run as neat liquids containing 10% tetramethylsilane (TMS) as internal reference. Their hydrochlorides were studied as solutions in chloroform, also containing TMS as reference, and the methiodides in freshly distilled *dry* dimethyl sulfoxide which also served as reference. (TMS–DMSO, 41.17 ppm.) Solutions of the methiodides in water produced the geminal diols of the 4-piperidones as described in the literature.[8-10] In these cases 10% *p*-dioxane was added as internal reference (TMS–dioxane, 67.12 ppm). In all cases chemical shifts were calculated relative to TMS.

Results

The observed carbon-13 chemical shifts in the *N*-alkyl-4-piperidones IV–VII and their hydrochlorides, methiodides, and, where appropriate, their 4,4-*gem*-diol derivatives, are presented in Table I. Supporting data on 1,2-dimethyl- (VIII) and 1,2,6-trimethylpiperidine (IX) and their hydrochlorides and methiodides are given in Table II. For comparison, data on 2-methyl- (VIIIa) and 2,6-dimethylpiperidine (IXa) are also given in Table II. The choice of solvents shown in Tables I and II was dictated by the solubility of the various species and enabled comparison with the earlier proton data.[8-10] In general solvent effects on carbon-13 chemical shifts are considered sufficiently small (~0.5 ppm) to be insignificant[11-19] unless conformational changes occur in different solvents. The earlier pmr studies[8-10] indicate that no conformational changes occur in the systems presently being described.

Assignment of the carbon-13 resonances to the appropriate carbon position in the compounds studied was made using conventional techniques.[21] In the

(21) See, for example, A. J. Jones, D. M. Grant, and K. F. Kuhlmann, *J. Amer. Chem. Soc.*, **91**, 5013 (1969), and ref 16.

TABLE II

CARBON-13 CHEMICAL SHIFTS IN 2-METHYL- AND 2,6-DIMETHYLPIPERIDINES[a]

Structure	Form	Solvent	Carbon position C-2	C-3	C-4	C-5	C-6	C-1′	C-2′ or C-6′
VIIIa		Neat	53.37	35.99	26.33	27.48	48.20		24.02
VIIIb		Neat	59.30	34.76	24.98	26.41	57.03	42.99	20.24
VIIIb	HCl	$CHCl_3$	61.45	31.54	22.15	23.39	56.04	41.00	17.86
VIIIb	CH_3I	DMSO	69.75	29.74	22.09	23.20	67.01	55.31	16.81
								44.18	
IXa		Neat	52.74	34.48	25.41	34.48	52.74		23.35
IXb		Neat	59.54	35.28	25.02	35.28	59.54	37.86	21.83
IXb[b]	HCl	$CHCl_3$	61.69	31.86	22.27	31.86	61.69	36.39	18.30
IXb	CH_3I	DMSO	70.62	28.98	22.86	28.98	70.62	50.23	16.57
								36.07	

[a] Given in parts per million downfield relative to TMS. [b] Studied as a mixture. The minor isomer (*ca.* 30%) exhibited resonances at 59.50 (C-2,6), 24.74 (C-3,5), 24.32 (C-4), 31.86 (C-1′), and 17.46 ppm (C-2′, 6′).

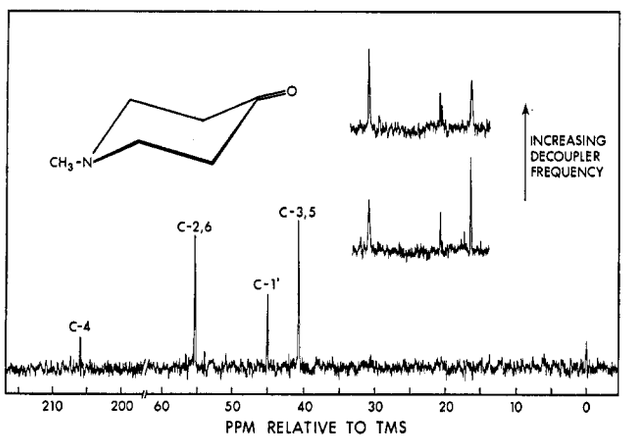


Figure 1.—The natural abundance carbon-13 magnetic resonance spectrum of *N*-methyl-4-piperidone (IV). Insets show the effects of stepping the ^1H decoupler frequency in the selective decoupling experiment.

symmetrical molecules, *N*-methyl-4-piperidone (IV) and 1,2,6-trimethylpiperidine (IXb), the double intensity of the resonances due to the equivalent carbons C-2,6, C-3,5, and C-2′,6′ (where *n*′ refers to the substituent carbon at the appropriate position *n* on the piperidine ring) enabled their distinction compared with the single intensity of the resonances due to C-1′ and C-4. The distinction of C-4 from C-1′ in the piperidones arises from observation of the typical low-field carbonyl shift (~204 ± 3 ppm) at C-4. In IXb the off-resonance decoupled spectrum exhibited a triplet about the higher field resonance of the pair attributable to C-1′ or C-4 and a quartet about the highest field resonance (21.8 ppm) attributable to the C-2′,6′ methyl carbon atoms. The carbon-13 spectrum of *N*-methyl-4-piperidone (IV) is shown in Figure 1. Figure 1 also shows the results of a selective decoupling experiment which established the order of the chemical shifts given in Table I for the compound IV.

For purposes of assignment the remaining molecules in this study (V–VII in Table I and VIII in Table II) form a second group which due to the absence of symmetry exhibits carbon-13 resonances of approximately equal intensity for each of the carbon atoms in the molecule. Many of the spectral assignments for these methyl-substituted systems were first suggested from substituent parameter considerations and were then confirmed where possible using off-resonance or selective proton decoupling techniques.

An additional factor, which aided the assignments for all bases was the consistent trend observed in the carbon-13 resonances on protonation or methiodation. Approximate parameters for the effects of protonation and for methiodation were also used in the initial interpretation of the spectra of the corresponding derivatives. Some precedence for this approach was set in the work of Duch and Grant[19] on the piperidine hydrochlorides. With only minor exceptions the results given in Tables I and II add further validity to this procedure.

All further assignments were made in a relatively routine manner and do not warrant detailed discussion.

Discussion

In the previous section attention has been focussed on the use of additivity relationships to provide a mechanism for initial spectral interpretation in systems related by structure and conformation. Spectroscopic methods were used to confirm many of the suggested assignments. The overall objective is to provide a set of general and reliable additivity parameters which would provide a direct mechanism for determining structure and conformation for any particular class of molecules.

The carbon-13 additivity relationships derived from the methylcyclohexanes by Dalling and Grant[11] have provided a most important foundation for studies concerned with structure and conformation in compounds containing saturated six-membered rings. A number of recent applications[12-19,22] have used these parameters in assigning carbon-13 spectra of relatively complex molecules. It has become increasingly clear from the observed trends that additional or modified parameters are valuable in systems containing substituted cyclohexanes. Introduction of an electronegative but isoelectronic NH– group in place of a CH_2 group, as in the piperidines, appreciably changes the local charge density of the adjacent carbon atoms.[23] The consequent deshielding, in comparison with the alicyclic analogs, is apparent from the downfield shift (20.6 ppm) at C-2,6 in piperidine compared with cyclohexane.[11,19,20] In the 4-piperidones similar effects are expected as a consequence of the relatively electronegative carbonyl group at C-4. The adjacent (α-C) carbon atoms C-3,5 shift downfield 14.7 ppm in *N*-

(22) H. J. Reich, M. Jautelat, M. J. Messe, F. J. Weigert, and J. D. Roberts, *J. Amer. Chem. Soc.*, **91**, 7445 (1969).

(23) G. E. Maciel and G. B. Savitsky, *J. Phys. Chem.*, **69**, 3925 (1965).

methyl-4-piperidone[24] compared with *N*-methylpiperidine.[19,20] This downfield shift is similar to that noted at the α carbon in cyclohexanone (13.6 ppm)[25] compared with cyclohexane[11] and may be considered characteristic for an α-C-carbonyl substituent effect. The chemical shifts of the carbonyl at C-4 (204 ± 3 ppm) and other cyclanones (211 ± 4 ppm)[26] are similar but differ from that of the carbonyl carbon in the 2-piperidones (170 ± 3 ppm).[27] This latter value has been noted in several nucleoside bases[28] and is indicative of the amide character of these carbon atoms.

The effect of methyl substitution has been characterized in the methylcyclohexanes,[11,13] selected piperidines,[19] and some 1,3-dioxanes.[16,17] Table III provides

TABLE III

SUBSTITUENT PARAMETERS OBSERVED IN SIX-MEMBERED RING ALICYCLICS AND DERIVATIVES[a]

	Substituent parameter derived from				
Substituent	Cyclohexanes (ref 11, 13)	Cyclohexanones (ref 25)	1,3-Dioxanes (ref 16, 17)	Piperidines (ref 19, 20 and present work)	4-Piperidones (present work)
$NH_{C-\alpha}$[b]				20.6	(20.6)
$C{=}O_{C-\alpha}$[b]		13.3			14.7
$CH_{3C-\alpha_e}$[b]	5.96	5.4	4.6	5.4	3.7
$CH_{3C-\beta_e}$[b]	9.03	8.2	6.7	8.5	7.9
$CH_{3C\gamma-a}$[b]	4.5		7.5		
$NCH_{3C-\beta_e}$[b]				8.9[d]	(8.9)
$CH_3NH_{C-\alpha}$[c]				−2.5[e]	−3.1[e]
$CH_3NH_{C-\beta}$[c]				−4.9	−2.8
$CH_3NH_{C-\gamma}$[c]				−3.5	−3.7
$CH_3NCH_{3C-\alpha}$[c]				10.5[d]	4.6
$CH_3NCH_{3C-\beta}$[c]				−4.8[d]	−4.9
$CH_3NCH_{3C-\gamma}$[c]				−2.5[d]	−4.3

[a] Given in parts per million. Negative sign indicates upfield shift. [b] Parameter derived with respect to cyclohexane. [c] Parameters derived with respect to free base. [d] Derived from data obtained in the present work. [e] Parameter does not include data from 2-methyl derivatives in which opposite effects were observed.

a summary of the average substituent shifts (for methyl and other substituents relevant to the present discussion) observed in most of the six-membered ring systems studied to date. This summary is by no means comprehensive, and the paucity of data coupled with solvent shifts suggests that these parameters are accurate to one significant figure. However, for a given series of compounds it is determination of the order more than the absolute magnitude of the calculated shifts that is of primary significance in the use of these parameters. Downfield shifts of approximately 6.0 ppm are observed at the carbon site at which equatorial methyl substitution occurs, while concomitant downfield shifts of 9.0 ppm are found at the adjacent β position in the methylcyclohexanes.[11] Shifts of carbon atoms further removed from the site of substitution are sufficiently small to be neglected. Substitution of a methyl group at C-3 (≡C-5) in the *N*-methyl-4-piperidones VIa and VII results in an average downfield C-α_e shift of only 3.0 ppm. The corresponding shift at C-2 in the 4-piperidone V is 3.4 ppm, while in the model piperidine systems VIIIb and IXb the average downfield shift at C-2 is 2.7 ppm compared with *N*-methylpiperidine.[19,20] In 1,2,5-trimethyl-4-piperidone (VII) the C-α value is 4.38 ppm. These values provide an average C-α_e methyl substituent shift of only 3.7 ppm as given in Table III. Sizable terms are required to correct the cyclohexane C-α_e parameter where substitution occurs at a carbon site adjacent to a higher order (tertiary or quaternary) substituted center such as carbonyl. Similar correction terms were considered necessary to account for the chemical shifts in the branched alkanes compared with their linear analogs.[29] In general, the 6.0-ppm C-α_e substituent parameter in the methylcyclohexanes may be reduced to 2.5 ppm when substitution occurs adjacent to higher order substituted centers.[30] A correction term for C-α_e near to −3.0 ppm seems appropriate where this center is carbonyl, while approximately −1.5 ppm would seem appropriate to the NH group. The relative magnitude of these two correction terms also invalidates the possibility that the electronegativity of the adjacent center attenuates the C-α_e parameter. The low C-α_e value (2.7 ppm) in VII, VIIIb, and IXb presumably arises since steric interactions between the 1- and 2-methyl groups would raise the chemical shift at C-2 and consequently compensate for the lowering *via* the substituent effect.

The C-β_e parameter observed in the methylcyclohexanes (9.0 ppm)[11,13] is attenuated by an adjacent carbonyl or piperidine–nitrogen center. The C-β_e value given in Table III for the 4-piperidones does not include the C-β_e contributions observed at C-4 in the 3-methyl- (VIa) and 1,2,5-trimethyl-4-piperidone (VII), where the carbonyl carbon is shifted downfield 1.32 ppm relative to *N*-methyl-4-piperidone (IV). This shift is close to the corresponding β-carbonyl site in 2-methylcyclohexanone (downfield, 1.5 ppm)[25] compared with cyclohexanone. These modified C-β shifts suggest that the carbonyl oxygen compensates for the lowering in electron density at the carbonyl carbon by donating electrons when methyl (or alkyl) substitution occurs at adjacent sites. This may be a mechanism by which the C-α and C-β methyl substituent parameters are generally lowered in the presence of electronegative centers. The C-β_e parameter follows the same trends in *N*-methyl and *C*-methyl derivatives. Thus the shifts at C-2 or C-6 in *N*-methylpiperidine,[19,20] 1,2-dimethylpiperidine (VIIIb), and 1,2,6-trimethylpiperidine (IXb) give an average C-β_e parameter of 8.9 ppm. This parameter may be the same in the 4-piperidones, though in the *N*-methyl-2-piperidones[27] it is approximately 5 ppm.

The effect of the carbonyl group and the *N*-methyl group on the methyl shifts in the compounds studied also warrants consideration. The difference in shift (9.5 ppm) between the 2- and 3-methyls in V, VIa, VIb, and VII is partly attributable to the carbonyl group, since in the piperidines VIII and IX the methyl shifts at C-2′ correspond (approximately 20 ppm relative to TMS) to those in the 2-methyl-4-piperidones. A similar difference (9.0 ppm) was noted for the methyl shift

(24) 4-Piperidone is too unstable to enable spectral determination; hence the shift difference quoted above is for the *N*-methyl derivatives.

(25) F. J. Weigert and J. D. Roberts, *J. Amer. Chem. Soc.*, **92**, 1347 (1970).

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(27) A. J. Jones, unpublished results.

(28) A. J. Jones, D. M. Grant, M. W. Winkley, and R. K. Robins, *J. Amer. Chem. Soc.*, **92**, 4079 (1970); *J. Phys. Chem.*, **74**, 2684 (1970).

(29) D. M. Grant and E. G. Paul, *J. Amer. Chem. Soc.*, **86**, 2984 (1964).

(30) Note that contributions from the carbonyl group on the carbon-13 shift at C-2 in the *N*-methyl-4-piperidones are neglected, since the difference in shift observed for the corresponding positions in cyclohexanone compared with cyclohexane is only −0.3 ppm.

in 2-methylcyclohexanone compared with other methylcyclohexanones[25] and it was suggested that the eclipsing of the 2-methyl and the carbonyl group in the 2-methyl derivative probably gave rise to this difference. From 2-methyl- and 2,6-dimethylpiperidine (VIIIa and IXa) and their *N*-methyl derivatives VIIIb and IXb, it is clear that the *N*-methyl group causes an upfield shift (average, 2.6 ppm) at the 2-methyl carbon as a consequence of steric interactions between these equatorial groups. Similarly, the *N*-methyl group is shifted upfield an average of 4.1 ppm, as indicated in comparing *N*-methyl-4-piperidone (IV) with 1,2-dimethyl- (V) and 1,2,5-trimethyl-4-piperidone (VII). Such steric shifts have been clearly established in the methylcyclohexanes[11,13] and the 1,3-dioxanes[16,17] and their magnitude has in part been related to the interatomic distances between the interacting sites.[31]

In analyzing the data in Tables I and II in relation to N-methylation, one minor anomaly remains. The C-3 and C-5 shifts in 1,2-dimethylpiperidine (VIIIb) are upfield 1.1 ppm of those in 2-methylpiperidine (VIIIa) while in the *N*-methyl compound IXb (compared with IXa) these shifts are of similar magnitude but in the opposite direction. No reasonable explanation of this effect is apparent.

The effects of protonation and methiodation in the piperidines and 4-piperidones follow additive trends. Table III summarizes the average protonation parameters obtained by Duch and Grant[19] from piperidine and 2-, 3-, and 4-methylpiperidine and similar parameters for the 4-piperidones. Relatively large changes occur for all sites in the molecule and in general all shifts are upfield. The C-2,6 position provides the only exception to these upfield shifts, noticeably in cases where this position is methyl substituted in the protonated series, though invariably in the methiodide series. The $CH_3NH_{C\text{-}\alpha}^+$ parameter given in Table III does not include data for the 2-methyl-substituted piperidines and piperidones. Because quaternization changes the charge at the nitrogen by one electron, the observed effects of protonation or methiodation are remarkably small. The 3–4 ppm observed change represents at most only 2% of the total change possible on addition or subtraction of an electron to the molecular framework.[32] The nitrogen atom probably accounts for most of the charge effect from protonation or methiodation. The electrostatic effect of the positive nitrogen center will be to attract electrons from the carbon framework. Negative charge will build up at C-2,6 and will probably result in an upfield shift of these resonances. However, all C-3,5 and C-4 resonances shift upfield, suggesting buildup of electron charge at these sites also. The effect at C-3,5 can be reconciled by recognizing that the quaternizing substituent takes up the axial position on the nitrogen in the favored chair conformations of most of the piperidines and piperidones studied. Syn-axial 1,3 steric interactions will occur between the axial substituent at the nitrogen and the methylene protons at C-3,5, and upfield shifts commonly found in other molecules[11,16] will occur at these sites. In the minor isomer of the 1,-2,6-trimethylpiperidine hydrochloride (IXb) (see footnote *a*, Table II) in which nitrogen inversion has occurred and the *N*-methyl group is now axial the C-3,5 and *N*-methyl carbons are shifted 7.2 and 4.5 ppm upfield, respectively. The greater steric interference of the methyl group is emphasized. No such steric interactions are likely to occur at C-4 or its substituents in any of the systems studied and it seems unlikely that direct charge-induced effects would be established over the molecular framework. Protonation of the carbonyl oxygen in the 4-piperidones IV–VII could shift the carbon-13 resonance upfield but similar upfield shifts observed in the piperidines VIII and IX exclude this explanation for the shifts at C-4. The shifts at C-4 in the quaternary nitrogen systems present an anomaly when compared with the cyclohexanes.[11,13] Duch and Grant[19] have used an electrostatic field calculation similar to that used by Horsley and Sternlicht[33] to explain the observed effect at C-4 with some degree of success. The similarity in the $CH_3NH_{C\text{-}\gamma}^+$ parameter between the piperidines[19] and 4-piperidones suggests that the effects at C-4 have the same origin and the electric field model provides an acceptable account of the C-4 shifts in these systems. A similar field effect has been invoked to explain the significantly greater $\nu_{C=O}$ stretching frequencies of the hydrochloride salts compared with those of the free bases in the 4-piperidones.[34]

In the 2-methylpiperidones V and VII and piperidines VIII and IX, protonation causes either a negligible or opposite shift (downfield 2.2 ppm) at C-2 compared with the unsubstituted or 3-methyl-substituted systems. From these shift effects it is apparent that the steric interaction between the 2-methyl group and the introduced axial proton results in an inductive effect at C-2 which compensates for the buildup of electron charge at C-2,6 upon protonation. The steric interaction described has been analyzed by Woolfenden and Grant[35] and is further emphasized by the upfield shift (average, 2.95 ppm) of the 2-methyl group in the protonated 2-methyl derivatives studied. On protonation the carbons C-1′ (equatorial *N*-methyl) and C-3′ are shifted upfield 1.76 and 0.80 ppm compared with the corresponding neutral systems. The effects at C-1′ are also presumably steric in origin. In the hydrochloride of *N*-benzyl-3-methyl-4-piperidone (VIb) the shift at C-2 is relatively small, while the α-carbon shift in the benzene ring is upfield 8.9 ppm, presumably because of conjugative interaction between the benzyl group and the nitrogen atom.

From Table III it is clear that in the methiodides of the 4-piperidones or the piperidines the axial methyl substituent at the nitrogen results in a downfield shift (5–10 ppm) at C-2,6, while the shifts for all other carbons are upfield. The parameters given in Table III are for the methiodides compared with the neutral system. The C-α parameter derived from the C-2,6 shifts in the methiodides provides us with an interesting test of the relationships so far derived. If the differ-

(31) The possibility that the magnitude of these shifts may depend on the electronegativity of intervening or adjacent atoms has not been excluded. We thank the referee for bringing this point to our attention.

(32) This argument is based on the general observation that carbon-13 shifts follow the linear relationship between shift and charge which involves a constant 160–200 ppm per electron. See, for example, H. Spiesecke and W. G. Schneider, *Tetrahedron Lett.*, 468 (1961).

(33) W. J. Horsley and H. Sternlicht, *J. Amer. Chem. Soc.*, **90**, 3738 (1968).

(34) A. F. Casy, private communication.

(35) W. R. Woolfenden and D. M. Grant, *J. Amer. Chem. Soc.*, **88**, 1496 (1966).

ence between a methiodide and a corresponding protonated system is an axial methyl substituent then an axial methyl β-substituent parameter at C-2,6 can be derived. In the 4-piperidones an average downfield shift of 7.1 ppm is derived while in the piperidines the corresponding value is 8.1 ppm. The $CH_3NCH_{3\,C\text{-}\alpha}{}^+$ parameter given in Table III for the piperidines (10.5 ppm) was derived from the data on the methiodides of 1,2-dimethyl- (VIII) and 1,2,6-trimethylpiperidine (IX) and consequently comprises an effect from the *N*-methyl-axial substituent (8.1 ppm) and the C-2′ methyl effect for the hydrochlorides (2.2 ppm). The sum of these values (10.3 ppm) is remarkably close to the composite value (10.5 ppm) as given in Table III. Similarly, in the piperidones the corresponding value (4.6 ppm) comprises the axial β-substituent effect (7.1 ppm) and the "charge effect" at C-2,6 (−3.1 ppm) providing the sum 4.0 ppm, also in close agreement with the composite value. These summations add further justification to the parameterization procedure suggested by the results of the present work. The effects of methiodation at the C-3,5 and C-4 sites follow similar trends to the hydrochlorides, though their magnitudes are greater. Further effects are also apparent at the substituent methyl carbons. The *N*-methyl carbons are found downfield 11.2 and 2.1 ppm, on the average, compared with the *N*-methyl carbon in the neutral molecule, while the shift at C-2′ in the 2-methyl-4-piperidones is shifted upfield an average of 4.6 ppm on methiodation. This latter shift is presumably steric in origin (see ref 35). A similar shift effect at C-3′ in the hydrochlorides (0.8 ppm) of the 3-methyl-4-piperidones VI and VII is also observed in the methiodides (0.9 ppm) and is also attributed to the steric effects.

The methiodides of substituted 4-piperidones are generally hydrolyzed in aqueous solution.[9,10] The carbon-13 shifts of the resulting geminal diols are given in Table I and although the upfield shift (approximately 100 ppm) at C-4 is clearly indicative of the change from a carbonyl to a geminal diol center no trends are clear for the other ring carbons.

Conclusions

The substituent additivity parameters summarized in Table III, in addition to the considerations outlined in the Discussion section, should provide a useful basis for the analysis of structure and conformation in more complex molecules. In subsequent studies, to be published, we have used these parameters with some success in order to determine conformations in a series of synthetic analgesics.[36]

Registry No.—IV, 1445-73-4; IV HCl, 34737-83-2; IV CH_3I, 34737-84-3; V, 13669-32-4; V HCl, 34737-86-5; V CH_3I, 34737-87-6; VIa, 4629-80-5; VIa HCl, 4629-76-9; VIa CH_3I, 34737-88-7; VIb, 34737-89-8; VIb HCl, 26822-34-4; VIb CH_3I, 34737-91-2; VII, 20281-02-1; VII HCl, 29849-51-2; VII CH_3I, 34737-92-3; VIIIa, 109-05-7; VIIIb, 671-36-3; VIIIb HCl, 5072-43-5; VIIIb CH_3I, 34737-95-6; IXa, 504-03-0; IXb, 669-81-8; IXb HCl, 5072-29-7; IXb CH_3I, 34737-99-0.

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(36) *E.g.*, A. J. Jones, A. F. Casy, and K. M. J. McErlane, *Tetrahedron Lett.*, 1727 (1972).

Synthesis and Mass Spectra of Some 2-Carbomethoxy-2-carbomethoxymethyl-2,3-dihydro-4(1*H*)-quinazolinones

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A synthesis of 2-carbomethoxy-2-carbomethoxymethyl-2,3-dihydro-4(1*H*)-quinazolinones is described and the major electron impact fragmentation pathways of this series are discussed.

We have recently noted that enamines **1**, prepared by condensation of anthranilamides and dimethyl acetylenedicarboxylate, are versatile precursors of several classes of heterocyclics.[2] Treatment of **1** with NaOMe in xylene produces a new class of benzodiazepinediones **4**, which are labile in alcohol. The reaction of **1** with NaOMe in MeOH leads directly to maleimides **2** and quinazolinones **3**, which can also be obtained in the same ratio in a separate experiment as the ring contraction products of the benzodiazepinediones, thus pointing toward **4** as a possible intermediate.

The isolation of pure quinazolinones by this technique is tedious, since careful fractional separation from the maleimide coproducts is necessary, and only three quinazolinones (**3a–c**) were prepared by this route. With an *N*-methyl group on either the amide or amino nitrogen of the anthranilamide, steric hindrance apparently prevents formation of a benzodiazepinedione intermediate and only quinazolinone (**3d** or **3e**) (not admixed with maleimide) results in base-catalyzed cyclization of the corresponding adduct.

We have now found that the quinazolinones **3** can be obtained uncontaminated by benzodiazepine or maleimide coproducts, by simple thermolysis of the enamino adducts **1**. The quinazolinones obtained displayed two saturated ester carbonyls in their ir spectra between 1725 and 1750 cm^{-1} and a characteristic CH_2 resonance

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