Carbon-13 Nuclear Magnetic Resonance Spectra of Cinchona Alkaloids[1]

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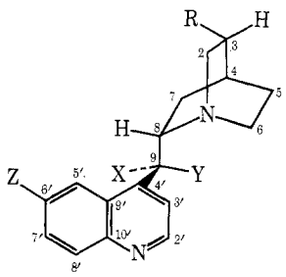
A comparison of the ^{13}C nmr spectra of eight cinchona alkaloids in $CDCl_3$ and in DMSO-d_6 has pointed out some important chemical shift differences which should be useful in the identification of similar compounds. The ^{13}C chemical shifts of carbons 2 and 6 of the quinuclidine ring can be used to distinguish between quinine and quinidine derivatives. Similarly, ^{13}C chemical shifts of C-4′ should provide a means of distinguishing between threo and erythro compounds (quinine and 9-epiquinine derivatives). Solvent studies on these compounds show that intramolecular hydrogen bonding has a large effect on the ^{13}C chemical shifts of the carbons 6, 7, and 4′, indicating that ^{13}C nmr will be a useful tool to study important conformational problems of these and related compounds.

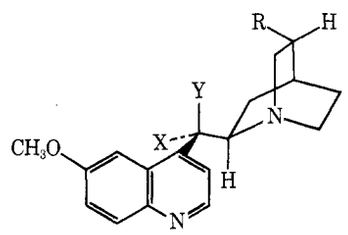
The cinchona alkaloids have been well characterized by structural and stereochemical investigations.[3] In 1971 Roberts and coworkers reported the first ^{13}C nmr chemical shift data on the nonaromatic portion of quinine.[4] More recently Wenkert and coworkers have reported on the ^{13}C nmr chemical shifts for all carbon resonances in quinine, quinidine, and the dihydro derivatives of these two naturally occurring cinchona alkaloids.[5]

In this report we present a study of the ^{13}C nmr spectra of eight cinchona alkaloids, including cinchonidine (I), quinine (II), 9-epiquinine (III), quinidine (IV), 9-epiquinidine (V), dihydroquinine (VI), dihydroquinidine (VII), and dihydro-9-epiquinidine (VIII) (see Chart I). A comparison is made between the ^{13}C nmr chemical shifts of the cinchona alkaloids which have the erythro configuration at the 8,9 positions (I, II, IV, VI, and VII) and the C-9 epimers (III, V, and VIII) which have the threo arrangement. Each of the eight alkaloids were run in $CDCl_3$ and in DMSO-d_6. Solvents effects on the ^{13}C nmr chemical shifts were observed and possible explanations are presented.

Chart I



I, R = ^{10}CH═^{11}CH$_2$; X = OH; Y = Z = H
II, R = CH═CH$_2$; X = OH; Y = H; Z = CH$_3$O
III, R = CH═CH$_2$; X = H; Y = OH; Z = CH$_3$O
VI, R = CH$_2$CH$_3$; X = OH; Y = H; Z = CH$_3$O



IV, R = CH═CH$_2$; X = OH; Y = H
V, R = CH═CH$_2$; X = H; Y = OH
VII, R = CH$_2$CH$_3$; X = OH; Y = H
XIII, R = CH$_2$CH$_3$; X = H; Y = OH

Results and Discussion

Most of the ^{13}C nmr chemical shift assignments for the cinchona alkaloids in Tables I and II were based on empirical correlations which have been summarized in the equations of Lindemann and Adams[6] and of Grant and Paul.[7] Although these equations are for simple paraffins, the qualitative trends found for the ^{13}C shifts in paraffins have been extended to predict the relative order of ^{13}C chemical shifts in other compounds.[8] The most important of these trends are (1) that substitution of a carbon (or a more electronegative atom or group) for a directly attached hydrogen produces a *downfield* shift [*i.e.*, the more carbons which are α to the carbon in question, the more *downfield* the ^{13}C shift (α effect)], (2) that substitution of a carbon or other atom for a hydrogen attached to a carbon α to the carbon in question also produces a *downfield* shift [*i.e.*, the more substitution at the carbon α to the carbon in question, the more *downfield* the ^{13}C shift (β effect)], (3) that hydrogens or other groups that are attached to carbons which are γ to the carbon in question produce an *upfield* shift (γ effect). The α and β effects are presumably through-bond effects while the γ effect is a steric compression effect.[9,10]

The structures and the numbering system for the cinchona alkaloids are shown in Chart I. The ^{13}C chemical shifts for the alkaloids are given in Tables I and II. In each case a noise-decoupled and single-frequency off-resonance decoupled (SFORD) spectrum were obtained. The multiplicities generated in the SFORD spectra enabled distinction between methyl, methylene, methine, and quaternary carbon resonances. As is apparent from Tables I and II, the ^{13}C resonances of the cinchona alkaloids can be grouped into two main regions which correspond to the quinuclidine ring and the quinoline ring of the molecule. The assignments of these two heterocyclic rings will be considered in turn.

Quinuclidine Ring. There are seven separate signals in the 20–60 ppm ^{13}C chemical shift region relative to internal TMS. These have been assigned to the seven carbons in the quinuclidine ring for each of the eight cinchona alkaloids listed in Tables I and II. Off-resonance experiments performed on each of these compounds in $CDCl_3$ and in DMSO-d_6 gave a ^{13}C nmr spectrum with three doublets and four triplets for the seven signals. The doublet resonances are for carbons 3, 4, and 8 and can be readily assigned, since they have markedly different ^{13}C chemical shifts which are in the same order (*i.e.*, $\delta_{C\text{-}4} < \delta_{C\text{-}3} < \delta_{C\text{-}8}$), but at lower fields than the corresponding ^{13}C shifts in unsubstituted quinuclidine.[11] The chemical shifts for carbons 3, 4, and 8 are about the same for the

Table I
Carbon-13 Chemical Shifts for Some Cinchona Alkaloids in $CDCl_3$[a,b]

Identification and multiplicity of carbon[c,d]		Cinchonidine (I)	Quinine (II)	Epiquinine (III)	Quinidine (IV)	Epiquinidine (V)	Dihydroquinine (VI)	Dihydroquinidine (VII)	Dihydroepiquinine (VIII)
2	t	56.81	56.86	55.25	(49.85)	49.07	58.38	(50.88)	(49.07)
3	d	39.77	39.76	39.62	39.96	38.83	37.36	37.22	37.07
4	d	27.76	27.71	27.76	28.11	27.23	28.11	26.97	27.22
5	t	27.46	27.46	27.08	26.24	26.54	27.42	26.14	25.56
6	t	43.04	43.00	40.55	(49.42)	46.72	43.15	(49.95)	(48.87)
7	t	21.19	21.44	24.92	20.76	23.84	21.05	20.37	23.70
8	d	60.24	59.85	61.32	59.55	62.11	59.66	59.60	61.91
9	d	71.46	71.51	71.17	71.51	69.94	71.56	71.46	70.24
10	d	141.61	141.66	141.18	140.54	140.05	25.31 (t)	24.92 (t)	25.56 (t)
11	t	114.13	114.08	114.33	114.23	114.48	11.84 (q)	11.79 (q)	11.74 (q)
CH_3O	q		55.44	55.74	55.34	55.20	55.49	55.30	55.15
2′	d	149.75	147.01	147.30	147.06	147.35	147.06	147.06	147.35
3′	d	122.85	121.09	121.04	121.09	121.43	121.04	121.09	121.33
4′	s	149.75	148.33	(144.26)	148.18	(144.56)	148.43	148.73	(144.75)
5′	d	118.10	101.40	102.47	101.25	101.89	101.49	101.15	102.08
6′	s	126.38 (d)	157.44	157.25	157.34	157.25	157.44	157.34	157.25
7′	d	128.78	118.30	119.87	118.25	118.34	118.55	118.25	119.82
8′	d	129.46	130.89	131.33	130.94	131.43	130.93	130.89	131.42
9′	s	125.49	126.43	127.95	126.33	127.85	126.43	126.43	127.90
10′	s	147.84	143.67	(144.61)	143.63	(144.85)	143.72	143.63	(144.61)

[a] Chemical shifts are in parts per million relative to tetramethylsilane. [b] Uncertain assignments are shown along with the next nearest uncertain chemical shift in parentheses. [c] Numbering of carbon is shown in Chart I. [d] Signal multiplicity obtained from single frequency off-resonance experiments; s = singlet, d = doublet, t = triplet, q = quartet.

eight cinchona alkaloids listed in Tables I and II and are in close agreement with those reported for quinine in $CDCl_3$ by Roberts and coworkers[4] and with the chemical shifts for the same carbon resonances of quinine, dihydroquinine, quinidine, and dihydroquinidine in chloroform reported by Wenkert and coworkers.[5]

The four triplet resonances observed in the off-resonance spectrum are for carbons 2, 5, 6, and 7 and have been assigned by comparing the ^{13}C chemical shifts for the eight cinchona alkaloids and quinuclidine in $CDCl_3$ and in DMSO-d_6. Since carbons 2 and 6 are α to the quinuclidine nitrogen, they will be shifted downfield relative to carbons 5 and 7, and thus the problem is to assign C-2 in comparison to C-6 and C-5 in comparison to C-7. Any difference in chemical shifts for carbons 2 and 6 should depend on the following: (a) C-2 is α to the quinuclidine nitrogen and to the tertiary C-3 while C-6 is α to the nitrogen and to the secondary C-5 and thus C-2 should be more downfield, and (b) depending on the configuration at C-8, C-2 or C-6 will experience an upfield shift (γ effect) from substituents on C-9 which relies on the proximity of these centers (see Chart I). In cinchonidine (I), quinine (II), 9-epiquinine (III), and dihydroquinine (VI) models show that C-2 does not interact sterically with substituents on C-9 and thus by (a) would be shifted downfield relative to C-2 in unsubstituted quinuclidine[11] ($\delta_{C\text{-}2}$ 48.7 ppm). On the other hand, C-6 can interact sterically with the C-9 substituents and should be shifted upfield (γ effect). Thus, the triplet signals in the 55–58-ppm region have been assigned to C-2 and the triplet signals in the 40–43-ppm region to C-6 for compounds I, II, III, and VI.

In quinidine (IV), 9-epiquinidine (V), dihydroquinidine (VII), and dihydro-9-epiquinidine (VIII) the shifts for C-2 relative to the shift for C-2 in unsubstituted quinuclidine should be downfield by (a) and upfield by (b). Models show that C-6 should not experience a γ effect and thus should have a chemical shift approximately the same as that of C-2 in unsubstituted quinuclidine. The ^{13}C nmr spectrum of each of these compounds shows two triplet resonances in the 46–49-ppm region which have been assigned to carbons 2 and 6. It is not possible to specifically assign these two signals for compounds IV, VII, and VIII.

Similar reasoning can be used to assign carbons 5 and 7. Carbon 5, which is α to one tertiary carbon, should experience no γ effect from either the olefinic group or from substituent groups at C-9, whereas C-7, which is α to two tertiary carbons, should experience a γ effect from both groups. For each of the cinchona alkaloids listed in Tables I and II there is a triplet signal in the 26–28-ppm region of the ^{13}C nmr spectrum. This value is approximately the same as that of C-2 in unsubstituted quinuclidine (δ 27.7 ppm)[11] and has been assigned to C-5 which, for reasons cited above, should be very similar to C-2 of quinuclidine. The triplet signal in the 21–24-ppm region of the ^{13}C nmr spectrum of each compound has, therefore, been assigned to C-7. This is consistent with the reasons cited, since one would expect a net upfield shift of the C-7 resonance if the γ effect from either or both groups is greater than the influence of an additional α tertiary carbon. It should be noted that our assignments for C-5 and C-7 are reversed from those reported by Roberts and coworkers[4] for quinine but are in agreement with those reported by Wenkert and coworkers.[5]

A comparison of the ^{13}C chemical shifts assigned for the quinuclidine rings in cinchonidine (I), quinine (II), and 9-epiquinine (III) in $CDCl_3$ shows that the shifts for I and II are almost identical, but that they differ from those of III for the 2, 6, 7, and 8 carbons. Since compounds I and II differ from III in the configuration at C-9, the chemical shift differences seem likely due to intramolecular hydrogen bonding of the hydroxyl group at C-9 with the nitrogen in the quinuclidine ring. In order to test this hypothesis the spectra of the compounds were obtained in DMSO-d_6 (Table II). A comparison of the shifts in Table I with those in Table II shows that there is a substantial change with solvent in the ^{13}C shift for carbons 6 and 7 in cinchonidine and quinine (erythro isomers) and that these values approach those for carbons 6 and 7 in 9-epiquinine (threo isomer) which does *not* show any solvent effects. There is also a smaller change in the ^{13}C chemical shifts with solvent for carbons 2 and 8 of cinchonidine and quinine as compared to the same carbons of 9-epiquinine. Chemical shifts in Tables I and II show a similar difference between quinidine and 9-epiquinidine as well as be-

Table II
Carbon-13 Chemical Shifts for Some Cinchona Alkaloids in DMSO-d_6[a]

Identification and multiplicity of carbon[a]		Cinchonidine (I)	Quinine (II)	Epiquinine (III)	Quinidine (IV)	Epiquinidine (V)	Dihydroquinine (VI)	Dihydroquinidine (VII)	Dihydroepiquinidine (VIII)
2	t	56.11	55.96	55.47	(49.20)	49.34	57.73	50.23	48.71
3	d	39.60	39.60	39.31	39.89	39.30	37.24	37.20	36.90
4	d	27.55	27.86	27.40	27.94	28.03	28.23	27.25	26.96
5	t	27.55	27.50	27.16	26.37	26.76	27.25	26.13	(25.69)
6	t	41.76	41.85	40.67	(48.56)	47.24	42.05	49.35	48.71
7	t	24.46	23.92	24.61	23.28	24.22	23.48	23.09	23.48
8	d	60.96	60.62	60.91	60.61	62.19	60.47	60.76	61.60
9	d	71.25	70.95	70.02	70.91	69.39	71.00	70.76	69.04
10	d	142.58	142.53	142.04	141.37	141.35	25.31 (t)	25.05 (t)	(25.10) (t)
11	t	114.11	114.02	114.07	114.41	115.04	12.01 (q)	11.97 (q)	11.87 (q)
CH_3O	q		55.47	55.47	55.47	56.01	55.47	55.38	55.37
2′	d	150.07	147.48	147.43	147.52	148.02	147.43	147.43	147.48
3′	d	(124.16)	120.93	121.07	120.97	121.86	120.87	120.93	121.27
4′	s	150.61	149.24	145.56	149.46	146.79	149.33	149.58	146.15
5′	d	119.16	102.50	102.95	102.50	103.04	102.50	102.46	102.70
6′	s	126.12 (d)	156.84	156.88	156.83	157.47	156.83	156.79	156.58
7′	d	128.76	119.11	120.24	119.01	120.68	119.01	118.92	120.14
8′	d	129.74	131.16	131.16	131.16	131.75	131.16	131.11	131.21
9′	s	(126.12)	127.05	127.67	127.10	128.22	127.05	127.10	127.69
10′	s	147.92	143.95	144.15	143.95	144.69	143.99	143.90	144.15

[a] See footnotes to Table I.

tween dihydroquinidine and dihydro-9-epiquinidine. The larger solvent effect on the chemical shifts of the erythro isomers when compared to the corresponding threo isomer is attributed to differences in intramolecular hydrogen bonding between the 9-hydroxyl group and the quinuclidine nitrogen. In the case of the erythro isomers, DMSO-d_6, a solvent known to be a good hydrogen-bond acceptor, can hydrogen bond to conformers not involved in intramolecular hydrogen bonding and might successfully compete for protons in conformers that are involved in weak intramolecular hydrogen bonding. Conversely, the strength of the intramolecular hydrogen bond in the case of threo isomers must be great enough to prevent disruption by the DMSO-d_6.

An alternate explanation for the solvent effect is that the erythro isomers have conformers which participate in intramolecular hydrogen bonding, while intramolecular hydrogen bonding does not occur in the case of the threo isomers. This explanation does not appear to us to be as likely as the first, since molecular models[12] reveal that intramolecular hydrogen bonding should be strongly opposed in the case of the erythro isomers by interference between the bulky quinoline and quinuclidine systems, and thus the conformer population is dominated by nonhydrogen-bonded species. However, in the threo isomers the same steric factors favor conformers which place the hydroxyl group and nitrogen proximate in space. In addition, the larger basicity of the 9-epi compounds compared to the natural alkaloids has been attributed to the more favorable intramolecular hydrogen bonding, possibly with participation of solvent, in the case of the epi isomers.[3]

Quinoline Ring. There are nine separate ^{13}C resonances for the quinoline ring for each of the cinchona alkaloids in Tables I and II. Relative to internal TMS these signals are in the 100–160-ppm region. Off-resonance experiments on each of these compounds in $CDCl_3$ and in DMSO-d_6 resulted in a ^{13}C spectrum having four singlets and five doublets.[13] The singlet resonances are for carbons 4′, 6′, 9′, and 10′. For each of the compounds II–VIII in $CDCl_3$ and in DMSO-d_6 the signal at ~157 ppm has been assigned to C-6′, since a directly bonded OCH_3 group produces a large downfield shift[14] and since this signal is absent in the ^{13}C nmr spectrum of cinchonidine (I), where there is no OCH_3 group at C-6′. For each of the compounds II–VIII the singlet resonance in the 126–127-ppm region has been assigned to C-9′ because the ^{13}C resonances for carbons 4′ and 10′ should be at much lower fields.[15]

The task then becomes one of assigning C-4′ as compared to C-10′. This was accomplished by comparing the ^{13}C shifts for quinine (II) with 9-epiquinine (III), quinidine (IV) with 9-epiquinidine (V), and dihydroquinidine (VII) with dihydro-9-epiquinidine (VIII). In the ^{13}C nmr spectrum of each of the erythro compounds (II, IV, VI, VII) there are singlets at ~148 and at ~144 ppm while for the threo compounds (III, V, VIII) there are two singlets at ~143–144 ppm. Since, as previously discussed, differences in intramolecular hydrogen bonding result in a difference in the ^{13}C chemical shifts for carbons 2, 6, 7, and 8 for the erythro compounds as compared to the threo compounds, it is very probable that intramolecular hydrogen bonding would also effect the chemical shift of the C-4′. It is also unlikely that this effect would show up at C-10′, and therefore the ^{13}C chemical shift for C-10′ should have approximately the same value in all the compounds. The singlet at ~148 ppm has been assigned to C-4′ and the singlet at ~144 ppm to C-10′ for each of the erythro compounds. It is not possible from these data to specifically assign C-4′ and C-10′ in the threo compounds.

The five doublet signals for carbons 2′, 3′, 5′, 7′, and 8′ in each of the cinchona alkaloids in $CDCl_3$ and in DMSO-d_6 have been assigned on the basis of the following arguments. (a) C-2′ which is α to the quinoline nitrogen is at low field and has approximately the same chemical shift as C-2′ in quinoline (~150 ppm).[16] (b) C-3′ should have about the same chemical shift in cinchonidine and the other cinchonia alkaloids. (c) C-5′ and C-7′ are ortho to the OCH_3 group and, therefore, should be substantially *upfield*[14] from their positions in cinchonidine (with no OCH_3 at C-6′). Carbon 5′ should be at a higher field than C-7′ since it can interact sterically with substituents on C-9′. (d) C-8′ (and C-9′) should be only slightly *downfield*[14] from their positions in cinchonidine since they are meta to the OCH_3 group. There is very close agreement between the ^{13}C chemical shifts reported in Table I for the quinoline ring carbons with those reported by Wenkert for compounds II, IV, VI, and VII.[5]

Other Assignments. With signal multiplicity data obtained from off-renance experiments, the assignments for carbons 9, 10, 11, and OCH_3 were straightforward and consistent with ^{13}C chemical shifts reported for similar carbon groups.

Experimental Section

Nmr Spectra. ^{13}C nmr spectra were determined at 24.92 MHz on a modified JEOL JNM-PS-100 Fourier-transform spectrometer interfaced with a Nicolet 1085 Fourier-transform computer system. Spectra were obtained in either chloroform-*d* ($CDCl_3$) or dimethyl sulfoxide-d_6 (DMSO-d_6) in 10-mm tubes. The spectra were recorded at ambient temperature by using the deuterium resonance of $CDCl_3$ or DMSO-d_6 as the internal lock signal. All proton lines were decoupled by a broad-band (~2500 Hz) irradiation from an incoherent 99.075-MHz source. Interferograms were stored in 8*K* of computer memory (4*K* output data points in the transformed phase corrected real spectrum), and chemical shifts were measured on 5000-Hz sweep width spectra. Typical pulse widths were 12 μsec, and the delay time between pulses was fixed at 1.0 sec. Normally 512 (twice as many for single frequency off-resonance experiments) data accumulations were obtained on a 200 mg/2 ml of solvent sample. The chemical shifts reported are believed accurate to within ±0.05 ppm.

Chemicals. Cinchonidine and quinine were obtained from Sigma Chemical Co. Quinidine was purchased from Aldrich Chemical Co. 9-Epiquinine and 9-epiquininidine were prepared by conversion of the natural alkaloid tosylate.[17] The dihydro alkaloids were prepared by reduction of the corresponding unsaturated alkaloid in ethanol using 10% palladium on carbon catalyst. The melting points and $[\alpha]D$ values of all the compounds synthesized were in agreement with literature values.

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Registry No.—I, 485-71-2; II, 130-95-0; III, 572-60-1; IV, 56-54-2; V, 572-59-8; VI, 522-66-7; VII, 1435-55-8; VIII, 51743-68-1.

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(11) Reference 8, p 54.
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(13) The ^{13}C nmr spectra of cinchonidine in $CDCl_3$ and in DMSO-d_6 contain three singlets and six doublets for the nine carbons of the quinoline ring.
(14) Reference 8, p 81.
(15) For quinoline in $CDCl_3$ the ^{13}C chemical shifts of C-9′ and C-10′ are at 128.0 and 148.0 ppm, respectively, and for 4-methylquinoline in $CDCl_3$ C-9′, C-4′, and C-10′ are at 127.9, 143.9, and 147.7 ppm, respectively.
(16) Reference 8, p 100.
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Reductive Defunctionalization of 1-Substituted Adamantanes in Molten Sodium Tetrachloroaluminate

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The reactivity of a number of substituted adamantanes in molten $NaAlCl_4$ at 175° was assessed. Those substituents with Lewis base character reacted with the melt to give adamantane and chloroadamantane. Neutral and Lewis acid substituents were recovered unchanged. Cyclic voltammetry revealed adamantane and 1-methyladamantane to be electroactive at a tungsten electrode well within the background limits of molten $NaAlCl_4$.

The use of molten salt media to effect a variety of organic transformations both homogeneously and at an electrode has recently been reviewed.[2] No reference was made, however, to the kinds of reactions undergone by aliphatic compounds in these ionic, aprotic solvents. Accordingly, we set out to survey the chemical stability of 1-substituted adamantanes (1-Ad-X) in a nominally 50:50 mol % $AlCl_3$–NaCl melt at 175°. By examining the behavior of a representative number of functionalities in this medium an appreciation of their reactivity or inertness can be achieved.

The availability of monofunctionalized bridgehead adamantanes and their resistance to skeletal rearrangement make them an ideal model system with which to probe the reactivity of different substituents. Indeed, the anodic behavior of a series of 1-Ad-X in acetonitrile has been reported.[3] Of particular interest to us is the feasibility of doing organic electrosythesis in molten salts. Cyclic voltammetry indicates that electrochemically generated oxidation intermediates of aromatic amines,[4] sulfur heterocycles,[5] and polycyclic aromatic hydrocarbons[6] are stabilized by the melt.

While the exact nature of this phenomenon is unknown, it appears that the absence of a nucleophilic organic solvent and the associated trace amounts of water accounts for the greatly extended lifetime of these reactive intermediates. If simple aliphatic cation radicals or cations are similarly stabilized it should be possible to do preparative electrochemistry without the chemical follow-up reactions common to organic solvent–electrolyte media.

Results and Discussion

The results of adding 1-Ad-X to approximately 5 ml of melt are summarized in Tables I–III. Substituents with Lewis base character reacted with the melt to give mixtures of adamantane, chloroadamantanes, hydrogen chloride, and, in two instances, carbon monoxide. Neutral and electrophilic substituents either complexed with the