Carbon-13 Nuclear Magnetic Resonance Spectra of
1,2,3,4-Tetrahydroquinazoline and Some 3-Benzyl Derivatives

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The concerted use of the $^1H/^{13}C$ shift correlation with full $^1H/^1H$ decoupling and the modified COLOC sequence for long-range X/H correlation 2D nmr spectroscopy allows the total assignment of the ^{13}C nmr resonances of 1,2,3,4-tetrahydroquinazoline and 3-benzyl-1,2,3,4-tetrahydroquinazoline. From these data, the ^{13}C nmr chemical shifts of a series of 3-benzylsubstituted-1,2,3,4-tetrahydroquinazolines are deduced.

Introduction.

We have synthesized in our laboratory a new series of 3-substituted-1,2,3,4-tetrahydroquinazoline derivatives [1]. They show an *in vitro* antiaggregant activity, comparable to and sometimes greater than the inhibiting power of aspirin; the structure of these molecules had to be determined. The concerted use of Reynold's $^1H/^{13}C$ 2D nmr shift correlation with full $^1H/^1H$ decoupling [2] and Krishnamurthy's modified COLOC sequence for long-range $^1H/^{13}C$ correlation [3], applied to compound **1**, permits a complete assignment.
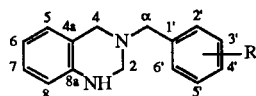

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1  R = H        6  R = 2'CH3
2  R = 2'F       7  R = 4'CH3
3  R = 4'F       8  R = 2'OCH3
4  R = 2'Cl      9  R = 4'OCH3
5  R = 4'Cl
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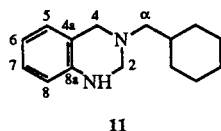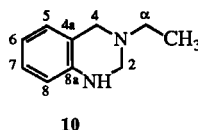
These two-dimensional $^1H/^{13}C$ nmr methods are also employed to establish the structure of the 1,2,3,4-tetrahydroquinazoline nucleus itself.
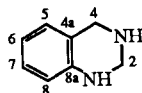
This study is one of the few applications [4,5] of these two recently published methods.

Results and Discussion. ^1H and ^{13}C-NMR Studies.

The ^1H nmr spectrum of compound **1-9** in deuteriochloroform at 200 MHz consisted of three singulets, a broad signal around 4 ppm and a complex pattern between 7.5-6 ppm.

The broad signal corresponded to the NH proton which was exchangeable with deuterium oxide. The use of deuterated dimethylsulfoxide shifted the NH proton to about 6 ppm, but did not make it possible to observe the coupling with vicinal protons (H.2). Thus, the three methylene group singulets could not be differentiated.

For compound **1**, two series of signals could be distinguished in the complex pattern; one due to the H.5, H.6, H.7, H.8 quinazoline protons and the other to the aromatic protons of the benzylic group. The multiplicity of the signals made it possible to distinguish the H.5, H.8 protons (doublet) and the H.6, H.7 protons (triplet), but the exact assignment of each one remained ambiguous.

The direct analysis of the ^{13}C nmr proton noise decoupled and DEPT spectra of compounds **1-9** showed three CH_2 carbons. The first signal at 60 ppm was assigned to the methylene C.2, according to the relative deshielding induced by the proximity of two nitrogen atoms, whereas the other two at about 50 ppm were associated with the methylene C.4 and C.α. However, these also remained a doubt about the assignment, except for the fluorobenzyl derivative **2** where we observed the following $^{19}F/^{13}C$ couplings: $^1J = 246.6$ Hz; $^2J_{F.C1'} = 14.7$ Hz; $^2J_{F.C3'} = 21.9$ Hz; $^3J_{F.C\alpha} = 2.5$ Hz; $^3J_{F.C4'} = 8.5$ Hz; $^3J_{F.C6'} = 3.6$ Hz.

For the aromatic part, we observed two quaternary carbons at constant chemical shifts (142-143 ppm and 119-120 ppm). These carbons were assigned to the C.8a and C.4a carbons respectively. The other quaternary carbons had chemical shifts depending on the nature and the position of the benzylic ring substituant.

Moreover, in one-dimensional ^{13}C nmr, it was very difficult to differentiate unequivocally the CH carbons because they resonated in a narrow range.

With regard to the ambiguity of the general ^1H and ^{13}C assignment, we used two-dimensional $^1H/^{13}C$ nmr experiments, applied to the model compound **1**: the 3-benzyl-1,2,3,4-tetrahydroquinazoline.

First, the use of the heteronuclear two-dimensional

Table 1

One-bond and Long-range 2D ^{1}H/^{13}C Correlations for

3-Benzyl-1,2,3,4-tetrahydroquinazoline

^{13}C δ ppm	Type	one-bond connected protons (δ ppm)	long-range connected protons (δ ppm)	Assignment
53.23	CH$_2$	3.82	3.71-3.98-6.84 [a]	C.4
57.13	CH$_2$	3.70	3.83-3.98-7.36 [a]	C.α
62.87	CH$_2$	3.98	3.70-3.83	C.2
115.05	CH	6.51	6.67	C.8
118.22	CH	6.68	3.83 [a] -6.50	C.6
119.97	Q	–	3.83-6.51 [a] -6.68 [a]	C.4a
127.17	CH	7.01-7.25	6.84-7.36	C.4'-C.7
127.51	CH	6.84	3.83-7.00 [a]	C.5
128.30	CH	7.31	7.32	C.3'-C.5
129.03	CH	7.36	3.70-7.24 [a]	C.2'-C6'
138.49	Q	–	3.70-7.32	C.1'
142.79	Q	–	3.84-3.98-6.84-6.99 [a]	C.8a

[a] Weak intensity correlation.

^{1}H/^{13}C shift correlated spectra for directly-bonded carbons and hydrogens with full elimination of proton-proton coupling [2], allowed chemical shift correlations to appear *via* single sharp peaks with $F_1 = δ$ ^{1}H and $F_2 = δ$ ^{13}C. This gave maximum signal/noise and accuracy in determining proton shifts.

Secondly, the long-range two-dimensional heteronuclear chemical shift correlation COLOC-S [3], which employs ^{1}H/^{13}C coupling *via* two and three bonds, was applied with advantage for the assignment of quaternary carbons. This method provides a selective long-range correlation 2D nmr spectra, without responses due to the directly attached protons.

The concerted use of these methods proved particularly helpful for the complete assignment of the 1,2,3,4-tetrahydroquinazoline skeleton. Results are given in Table 1.

The direct ^{1}H/^{13}C correlation spectrum allowed us to know, for each carbon atom, the chemical shift of the directly-bonded protons (Figure 1).

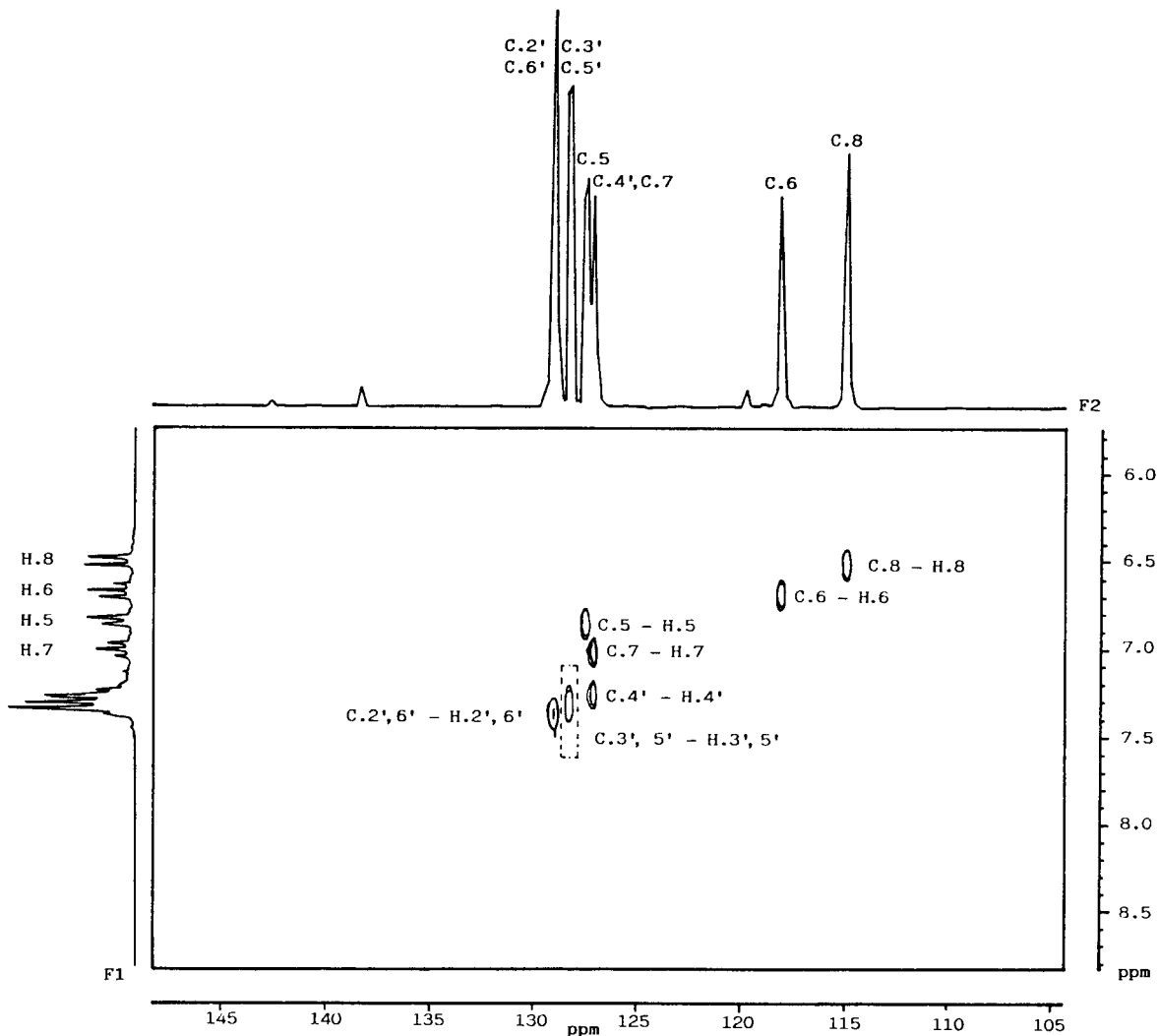Figure 1.   One-bond ^{1}H/^{13}C 2D aromatic correlation by CORFD method-F1 ^{1}H nmr spectrum - F2 ^{13}C projection of the correlations.

The analysis of the long-range correlation spectrum served to identify each carbon (Figure 2). For the aromatic compounds, the [3]J ^{1}H/^{13}C long-range correlation [6] were the most intense. The multiplicity of the H.5, H.8 (doublet) H.6, H.7 (triplet), observed in the one-dimensional ^{1}H nmr spectrum, and the three-bond correlations between the carbon C.4a and the protons H.6, H.8 on one hand and between the carbon C.8a and the protons H.2, H.4, H.5, H.7 on the other, prove the assignment reported in Table 1.

The aromatic carbons of the benzylic substituent are assigned with respect to the one-bond and long-range correlations existing between carbons C.α, H.2', H.6' and C.1', H.3', H.5'.

The two-dimensional ^{1}H/^{13}C experiment was used only for the compound 1 model. The chemical shifts obtained for the benzylic part served as reference for applying an empirical method based on the SCS tabulation of Ewing [7]. We determined the aromatic carbon calculated shifts of the mono-substituted derivatives 2-9. The good agreement between the estimated and experimental values allowed the assignment of the benzylic carbons (Table 2).

Moreover, the quinazoline carbon shifts present a great similitude with the values observed in the unsubstituted model compound 1. Thus, all carbons of derivatives 2-9 can be assigned.

So it now seems interesting to study the influence of the benzylic ring and its substituants on the chemical shifts of the tetrahydroquinazoline nucleus carbons themselves. In fact, no nmr characteristics are as yet published to our knowledge. Thus, we have achieved the two-dimensional ^{1}H/^{13}C nmr spectrum of the 1,2,3,4-tetrahydroquinazoline. The same analysis method allowed us to assign all the carbons and protons; the chemical shifts and the different assignments are shown in Table 3.

Finally, the presence of a benzylic group involves a large unequivalent shift of carbons C.2 (4.77 ppm) and C.4 (6.67 ppm) at a higher frequency. The difference in shift
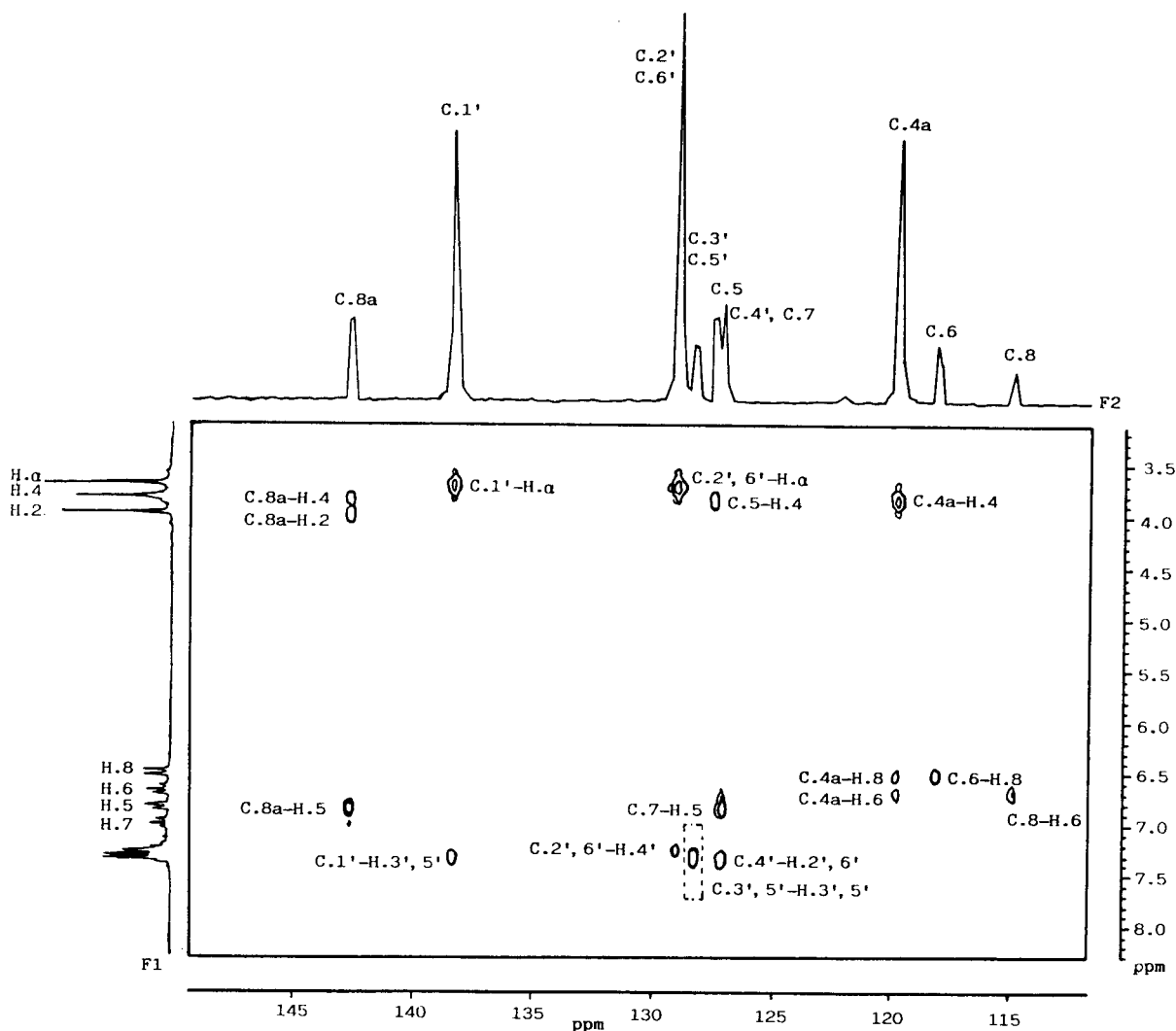

Figure 2.   Long-range ^{1}H/[13]C 2D aromatic correlation by COLOC-S method-F1 ^{1}H nmr spectrum - F2 ^{13}C projection of the correlations.

Table 2

^{13}C Chemical Shifts (ppm) of Compounds 2-11

Structures: compounds **2-9** (N-benzyl substituted 1,2,3,4-tetrahydroquinazoline with ring positions 2, 4, 4a, 5, 6, 7, 8, 8a, NH, N, α and phenyl 1', 2', 3', 4', 5', 6' bearing R at 3'/4'); compound **10** (N-CH₂-CH₃); compound **11** (N-CH₂-cyclohexyl).

Compound No.	R	C.2	C.4	C.4a	C.5	C.6	C.7	C.8	C.8a	C.α	C.1'	C.2'	C.3'	C.4'	C.5'	C.6'
2	2F	62.89	53.29	119.91	127.35[a]	118.40	127.62[a]	115.27	142.75	49.95	125.41	161.55	115.43	129.00	124.04	131.48
											126.02*	163.78*	115.33*	128.75*	123.89*	130.61*
3	4F	62.70	53.08	119.70	127.35[a]	118.20	127.68[a]	115.10	142.70	56.26	134.31	130.60	115.00	162.17	115.00	130.60
											134.08*	130.61*	115.33*	161.92	115.33*	130.61*
4	2Cl	62.95	53.24	119.69	127.19[a]	118.02	127.52[a]	115.00	142.83	53.78	136.31	134.26	128.27	129.46	126.65	130.70
											138.89*	135.33*	128.70*	128.57*	126.40*	130.43*
5	4Cl	62.62	52.97	119.48	127.24[a]	118.02	127.52[a]	114.90	142.78	56.10	137.12	130.32	128.38	132.69	128.38	130.32
											136.59*	130.43*	128.70*	133.47*	128.70*	130.43*
6	2CH₃[g]	62.90	53.19	120.13	127.25[a]	118.19	127.63[a]	115.06	143.00	54.75	137.60[b]	136.63[b]	130.43[c]	127.25[a]	125.73	129.89[c]
											139.15*	135.25*	128.96*	125.06*	125.26*	128.92*
7	4CH₃[h]	62.68	53.02	119.75	127.14[a]	117.97	127.52[a]	114.90	142.90	56.75	135.39	129.03	129.03	136.58	129.03	129.03
											135.45*	128.92*	128.96*	136.39*	128.96*	128.92*
8	2OCH₃[i]	63.00	53.29	120.13	127.09[a]	117.97	127.52[a]	115.11	143.00	50.87	126.54	157.83	110.36	128.32	120.34	130.54
											124.07*	160.43*	113.88*	128.21*	120.59*	130.34*
9	4OCH₃[j]	62.73	53.13	120.07	127.30[a]	118.35	127.68[a]	115.15	142.94	56.63	130.59	130.38	113.81	159.02	113.81	130.38
											130.78*	130.07*	113.88*	158.57*	113.88*	130.07*
10	-	63.00	53.29	120.02	127.19[a]	118.02	127.46[a]	115.11	143.00	46.93	-	-	-	-	-	-
11	-	63.96	54.09	120.44	127.07[a]	118.01	127.45[a]	115.15	143.04	59.92	-	-	-	-	-	-

*Calculated chemical shifts-[a,b,c] may be interchanged in the same compound. [g] CH₃, 19.15 ppm. [h] CH₃, 21.04 ppm. [i] OCH₃, 55.20 ppm. [j] OCH₃, 55.19 ppm.

Table 3

One-bond and Long-range 2D ^{1}H/^{13}C Correlations for the 1,2,3,4-Tetrahydroquinazoline

^{13}C δ ppm	Type	one-bond connected protons (δ ppm)	long-range connected protons (δ ppm)	Assignment
46.58	CH₂	3.98	4.18-6.85 [a]	C.4
58.16	CH₂	4.17	3.97	C.2
115.27	CH	6.48	3.94 [a] -6.65-6.87 [a] -6.98 [a]	C.8
117.95	CH	6.67	3.98 [a] - 6.47-6.75 [a]	C.6
121.96	Q	-	3.97-6.48 [a]	C.4a
126.35	CH	6.83	3.97-6.98 [a]	C.5
127.11	CH	6.98	3.98 [a] -6.85	C.7
143.28	Q	-	3.96-4.18-6.85-6.98 [a]	C.8a

[a] Weak intensity correlation.

amplitude observed for these two carbons is probably due to a conformational modification of the heterocycle induced by the 3-substituant. There also appears to be a substantial long-range shift effect on carbon C.4a, but which is weaker on the other atoms. The substitution of the benzyl ring or its replacement by an ethyl or cyclohexylmethyl group confirms the above observations in the same manner.

The mean difference of the chemical shifts between derivatives **1-11** and 1,2,3,4-tetrahydroquinazoline (Δ ppm = δ NR - δ NH) are summarized in Figure 3. These values can eventually be used as increments to determine the carbon chemical shifts of the 1,2,3,4-tetrahydroquinazoline 3-substituted by a CH_2-aromatic or CH_2-alkyl group.
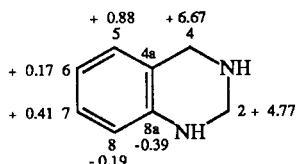

Figure 3. Mean difference of the chemical shifts between derivatives 1-11 and 1,2,3,4-tetrahydroquinazoline (Δ ppm).

EXPERIMENTAL

The compounds studied were prepared from isatoic anhydride according to the reported method [8,9].

The ^{13}C nmr spectra were recorded on a BRUKER WH 90 spectrometer operating in the pulsed Fourier Transform mode at 22.63 MHz. The acquisition parameters were as follows: spectra width 5000 Hz, acquisition time 0.81 s and pulse width 6 μs (corresponding to a 45° pulse).

All compounds were examined in deuteriochloroform solution (10% w/v) containing a few drops of tetramethylsilane (TMS) as internal reference.

The 2D $^1H/^{13}C$ nmr correlations and 1D ^1H spectra for compound 1 and 12 were recorded on a BRUKER AC 200 spectrom-

eter equipped with a 10 mm multinuclear probe (^{13}C 90° pulse width: 13 μs; ^1H 90° pulse width through decoupler coils: 28 μs).

The heteronuclear two-dimensional $^1H/^{13}C$ shift correlated spectra for directly-bonded carbons and hydrogens with full $^1H/^1H$ decoupling along the F1 frequency axis was obtained using the Reynolds sequence [2]: CORrelation with Full Decoupling (CORFD).

The spectrum was acquired with 2024 x 256 data points or data acquisition of 32 scans x 128 increments in t1 and zero filling in the F1 dimension only, and spectra width of 8064 Hz and ±1000 Hz were used in the F2 (^{13}C) and the F1 (^1H) domains respectively. The relaxation delay was 1 s, delay constant T = 3.75 x 10^{-2} s, ½ $^1J_{CH}$ = 4 x 10^{-3} s, refocalisation delay = 2 x 10^{-3} s.

The long-range two-dimensional heteronuclear chemical shift correlation was obtained using a modified version of the COLOC experiment, which is referred to as COLOC-S [3]. The COLOC-S spectrum was run with the same spectra width as the CORFD spectrum. The relaxation delay was 2 s, ½ $^1J_{CH}$ = 3.3 x 10^{-3} s, delay constant T = 5 x 10^{-2} s, reflocalisation delay = 4 x 10^{-2} s.

REFERENCES AND NOTES

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