HETEROCYCLES, Vol. 14, No. 10, 1980

CARBON-13 NMR ANALYSIS OF SOME 4-QUINAZOLINONE ALKALOIDS AND RELATED COMPOUNDS

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Abstract - Carbon-13 NMR Spectra of some 4-quinazolinones, which *indicate the predominent tautomeric forms of these compounds,* have been determined.

4-Quinazolinone alkaloids occur widely in nature.[2] These alkaloids have been encountered in plant families such as Saxifragaceae, Acanthaceae, and Rutaceae, in Glomeris marginata, an arthropoda,[3] as well as in micro-organisms.[4] The well known tautomeric nature of these relatively simple compounds is responsible for their unpredictable chemical behavior. There has been much controversy over the structures of several 4-quinazolinone alkaloids[5,7,8] which could not be resolved by chemical degradation, UV and IR spectra, or even synthesis. Consequently, tedious and extensive investigations were necessary to resolve such controversy.[6,9,10] So far, carbon-13 NMR spectroscopy has not been used for characterizing these compounds. In this communication, we wish to report the carbon-13 NMR analysis of several naturally occurring simple 4-quinazolinone alkaloids and related compounds. These data will prove very useful for correct structure elucidation of this class of compounds, especially in the determination of their most predominent tautomeric forms.

The chemical shifts of compounds 1-10 are listed in Table 1. The assignments of the chemical shifts of the various carbons in these compounds were made with the aid of direct analysis of the non-protonated centers, complete and partially decoupled spectra, substitutions at various positions of the heterocyclic ring and comparison with the spectra of similar systems.

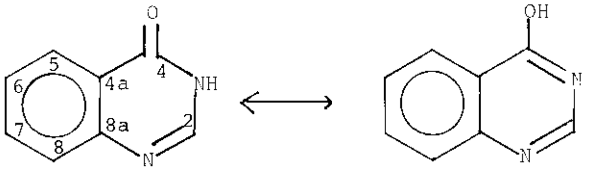
The chemical shifts of the ring B carbons in all the compounds and those of the benzyl group in (8) and (9) were assigned by comparison with the spectra of flavone.[11] The triplet at 43.7 ppm in the spectrum of arborine (9) is obviously due to the CH_2 of the benzyl group and this rules out the alternative

Table 1. Carbon-13 Chemical Shift Assignments of Some 4-Quinazolinones.[a,b]

Carbon	1	2	3	4	5	6	7	8	9	10
2	146.6	154.8	152.1	154.4	149.4	162.3	155.7	155.6	162.3	161.9
4	165.7	168.9	159.2	161.9	161.7	168.5	161.4	161.8	168.5	167.7
5	128.9	127.2	129.2	126.7	128.1	128.5	128.4	128.5	128.5	127.1
6	128.0	126.4	127.5	126.3	127.4	127.5	126.5	126.5	127.6	125.9
7	135.4	134.3	136.3	134.3	134.4	133.8	134.2	136.6	133.8	135.5
8	127.6	115.7	118.4	125.9	127.2	114.0	126.2	124.4	114.0	115.8
4a	123.6	119.9	120.6	120.8	123.1	120.1	120.3	120.6	120.1	119.3
8a	149.4	140.2	138.8	149.2	148.5	141.6	147.2	148.9	141.6	141.5
N-1-CH_3	-	37.0	39.6	-	-	34.9	-	-	34.9	34.0
N-2-CH_3	-	-	-	-	33.9	-	30.6	-	-	-
1'	-	-	-	-	-	-	-	134.3	134.7	-
2', 6'	-	-	-	-	-	-	-	125.0	125.9	-
3', 5'	-	-	-	-	-	-	-	128.1	128.1	-
4'	-	-	-	-	-	-	-	130.7	129.2	-
C-2-$\underline{C}H_3$	-	-	-	21.4	-	23.5	23.5	-	-	-
C-$\underline{C}H_2$-ph	-	-	-	-	-	-	-	42.0	43.7	-
C-2-$\underline{C}H_2$-CH_3	-	-	-	-	-	-	-	-	-	28.3
C-2-CH_2-$\underline{C}H_3$	-	-	-	-	-	-	-	-	-	10.7

[a] Chemical shifts in ppm downfield from TMS. The solvent is DMSO-d_6.

[b] The spectra were taken at 22.6 MHz in the Fourier Mode using a Brucker HX-90 instrument.



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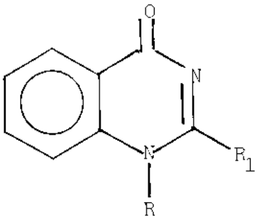
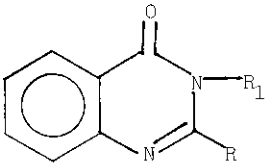


2, R = CH_3; R_1 = H

6, R = R_1 = CH_3

9, R = CH_3; R_1 = CH_2ph

10, R = CH_3; R_1 = CH_2CH_3

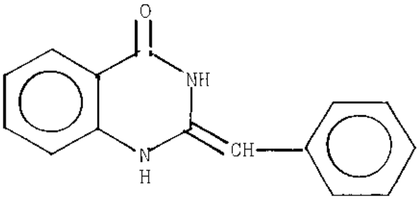


4, R = CH_3; R_1 = H

5, R = H; R_1 = CH_3

7, R = R_1 = CH_3

8, R = CH_2ph; R_1 = H



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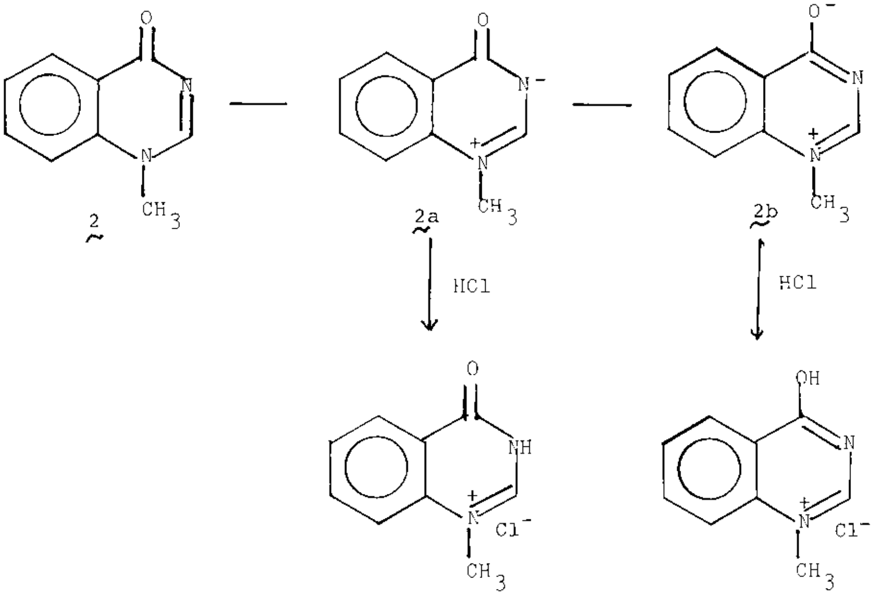

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benzylidine structure (11) suggested for this compound on the basis of chemical evidence.[5]

The characteristic features of the spectra of 4-quinazolinones are the chemical shifts of C-4 and C-8a. Table 1 shows that the chemical shifts of the C-4 in (2), (6), (9) and (10), where the double bond is located between C-2 and N-3 appear at ~ 7 ppm lower fields than those of (5) and (7), where the double bond is located between N-1 and C-2. This is expected,[12] because, in the 3-H, 4-oxo forms (5) and (7), the electron release from N-3 will result in higher electron density at the C-4 relative to the 1-H, 4-oxo forms, (2), (6), (9), and (10). The C-4 chemical shifts of (4) and (8) are very close to those of (5) and (7) suggesting that although (4) and (8) are capable of existing in both 3H, 4-oxo and 1-H, 4-oxo forms, the former is predominant.[10] The spectrum of 1-methyl-4-quinazolinone (glycorine) hydrochloride (3) shows that C-4 shifts to considerably higher field at 159.2 ppm relative to that of the free base (2). It was suggested[6] on the basis of the IR and ^{1}H NMR spectra that the free base (2) goes into zwitterionic forms (2a) and (2b) which are stablized by salt formation. In fact, the C-4 chemical shift of glyocorine hydrochloride is very close to that of (4), (5), (7) and (8). Also, N-1-CH$_3$ in glycorine hydrochloride appears at a relatively low field. Therefore, structure (3) with significant contribution from (12) more accurately represents glycorine hydrochloride.

The C-8a in (4), (5), (7), and (8), appears at a field 7-9 ppm lower than that of (2), (6), (9), and (10). In the 3H, 4-oxo form, a reduced electron density will result at C-8a because of the presence of -N= moiety in the ortho position and possibly because of a significant contribution of the completely conjugated tautomeric form. Also, the higher shielding of C-8a by the substituent at N-1 (γ-effect) possible in (2), (6), (9), and (10) is absent in (4), (5), (7), and (8).

The chemical shifts of the carbons in 4-quinazolinone itself (Table 1) definitely support structure (1) as its predominant form with contributions from (1a).

Table 1 also shows that appropriate shifts are observed for C-2 upon substitution at ring A following the additivity rule.[12]

ACKNOWLEDGEMENTS

Thanks to Profs. R. A. Abramovitch, J. H. Huffman, and A. R. Pinder of the Department of Chemistry and Geology, Clemson Univerity, for a generous supply of chemicals. The use of the facilities for this work during the brief stay of one of us (J.B.) at this Department is also gratefully acknowledged.

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Received, 2nd June, 1980