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Carbon-13 Nuclear Magnetic Resonance of Some Derivatives of 3-Methyl-4,1-benzoxazepine-2,5-dione

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Summary. ^{13}C chemical shift assignment of seven N-derivatives of 3-methyl-4,1-benzoxazepine-2,5-dione is reported. The assignment has been done with the help of J-modulated spectra and by comparison with the values of resembling segments reported in the reference. It has been found that the substituent on nitrogen atom has no significant effect on the ^{13}C chemical shift of the skeleton.

Keywords. Benzoxazepinedione; Seven membered heterocycles; ^{13}C NMR analysis.

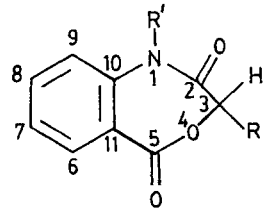
^{13}C-NMR einiger Derivative des 3-Methyl-4,1-benzoxazepin-2,5-dions

Zusammenfassung. Es werden die ^{13}C-NMR-Verschiebungszuordnungen von sieben N-Derivaten von 3-Methyl-4,1-benzoxazepin-2,5-dionen diskutiert. Die Zuordnungen erfolgten über J-modulierte Spektren und Vergleich von entsprechenden Literaturdaten ähnlicher Molekülsegmente. Es zeigte sich, daß die Substitution am Stickstoff keinen signifikanten Einfluß auf die ^{13}C-chemischen Verschiebungen der Skelettkohlenstoffatome hat.

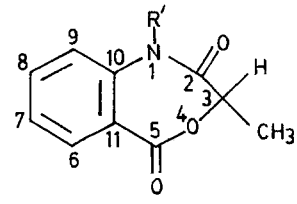
Benzoxazepinediones are synthetic heterocyclic compounds which may have different positions of nitrogen and oxygen atoms in the ring [1–8]. Some compounds of this class are reported to have wide ranging medicinal importance [9–13]. Inspite of the fact that these compounds are synthetic on one hand and have considerable medical significance on the other, only few of their derivatives have been reported in the Ref. [1–13]. Even for the reported compounds detailed study of proton NMR in general and ^{13}CNMR in particular is almost lacking. These facts stimulated us to undertake a systematic study of some selected compounds and a series of their derivatives. The scope of our investigation includes synthesis, structure elucidation, observation of biological activity and physico-chemical characterization. However, as a part of the study we report in this paper a comparative ^{13}C chemical shift assignment of seven derivatives of 3-methyl-4,1-benzoxazepine-2,5-dione (*MBOAD*).

4,1-Benzoxazepine-2,5-diones (*BOAD*) have a general formula given by the structure **I**. Although a number of derivatives may be synthesized by different

combinations of the substituents R and R′ but limited information on only few of them is available [1, 4, 5, 7, 12]. By varying the substituent R′ on the nitrogen atom and keeping R as CH_3, derivatives **IIa–g** were synthesized.



Structure I (BOAD)



Structure II (MBOAD)

IIa (R′ = H), **IIb** (R′ = CH_3), **IIc** (R′ = C_2H_5) **IId** (R′ = n-C_3H_7), **IIe** (R′ = n-C_4H_9), **IIf** (R′ = CH_2–$CH{=}CH_2$), **IIg** (R′ = CH_2–Ph)

In establishing the structures of the derivatives UV, IR, mass spectrometry and elemental analysis were employed [14].

For each compound **IIa–g** the number of peaks in the ^{13}CNMR spectrum was in exact agreement with the proposed number of carbon atoms in it. The

Table 1. ^{13}C-Chemical shift assignments[a] of *MBOAD*

C-atom[b]	N-Substituent R′						
	H	CH_3–	C_2H_5–	n-C_3H_7–	n-C_4H_9–	$CH_2{=}CH{-}CH_2$–	$C_6H_5{-}CH_2$–
CH_3	15.20	15.59	15.44	15.48	15.46	15.49	15.59
C-3	71.67	71.89	72.06	72.18	72.01	71.97	72.03
C-2[c]	170.0	168.91	168.26	168.40	168.25	168.23	168.79
C-5[c]	168.08	168.30	167.95	168.32	168.22	168.17	168.18
C-6	133.39	132.28	132.24	132.19	132.15	132.28	132.34
C-7	125.30	126.21	126.57	126.65	126.61	126.55	126.74
C-8	134.89	134.51	134.51	134.45	134.41	134.41	134.39
C-9	121.71	122.35	122.90	123.27	123.19	122.79	123.12
C-10	138.24	141.10	140.67	140.58	140.49	140.95	140.62
C-11	123.0	125.52	126.81	126.85	126.76	126.18	126.62
C′-1	–	34.99	42.97	48.64	46.60	50.33	50.61
C′-2	–	–	13.56	21.53	30.32	134.0	138.0
C′-3	–	–	–	11.15	20.21	117.43	129.36[d]
C′-4	–	–	–	–	13.79	–	128.05[d]
C′-5	–	–	–	–	–	–	127.90[d]

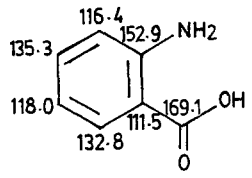
[a] δ-Values in ppm relative to *TMS* in actone-d_6 at 25 °C

[b] For the substituent R′, the C-atom directly attached to the N-atom is numbered as C′-1 and the next adjacents as C′-2, C′-3 etc.

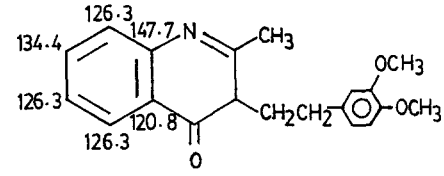
[c] The signal assignments for C-2 and C-5 are interchangeable

[d] Interchangeable

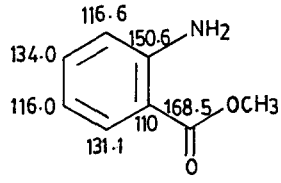
chemical shift assignments are collected in Table 1. The assignments have been made with the help of J-modulated spectra and by comparison with the chemical shift values of resembling segments reported in the Ref. [15–19].



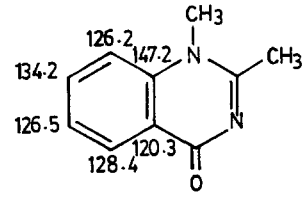
(A)



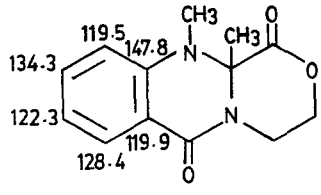
(D)



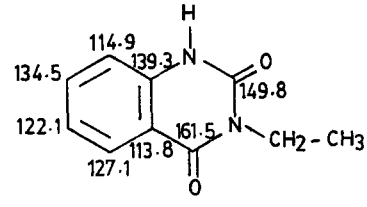
(B)



(E)



(C)



(F)

The aromatic carbons of the compounds **IIa–g** resonate in the region between 121 and 141 ppm. C-10 and C-11 being the quaternary carbon atoms, may be readily recognized from the relative phase (negative sign) of their signals. The simplest model compounds to be compared are *o*-aminobenzoic acid (A) and its methyl ester (B). The assignments given in the Ref. [15, 16] show that the carbon directly attached to the nitrogen atom resonates at a downfield position. This is further confirmed from studies on quinazolone lactone (C) [17] on derivatives of 2-methyl-4-quinazolone (D) [18] and from the investigation of 4-quinazolinone (E) [19]. Accordingly C-10 resonates near 140 ppm and C-11 around 126 ppm in our compounds. The most relevant model compound to be compared is 2,4-quinazolinedione (F) reported earlier [16] in which the carbon atom directly attached to nitrogen also resonates at 140 ppm. Out of the other four aromatic carbons, the

one *meta* to N-substitution is considered to resonate at the lowest field. This may be due to the inductive effect imparted by the nitrogen atom. In all the given model compounds (A–F) this particular carbon resonates around 134.5 ppm, thus the peak around 134.5 ppm in our compounds is assigned to C-8. Following the sequence of chemical shift values in these model compounds and especially that of (F), the assignment of other aromatic carbons has been done as given in Table 1.

Although the substituents R′ are of quite different nature, there seems to be no significant effect imparted by them on the chemical shifts of the skeletal carbon atoms. However, in the case of **IIa** (R′ = H), some of the resonance lines are shifted by 1 to 4 ppm as compared to the other compounds. This may be attributed to the fact that the compound **IIa** via its N–H is capable of making intermolecular H-bonds with the solvent molecules, as well as intramolecular H-bonds with the carbonyl group at C-2. On the contrary, if R′ is not a H-atom, the molecule should not form a H-bond. It is due to this reason that the lines of C-10 and C-11 in **IIa** are shifted upfield from their common values. Moreover, it is well established that if the carbonyl group becomes involved in H-bonding, the resonance of its carbon atom suffers a downfield shift [20]. On this basis C-2 may be distinguished from C-5 in **IIa** as the most downfield peak. But in all other compounds, the two carbon atoms resonate quite close to each other ($\Delta\delta < 0.6$ ppm) and thier chemical shifts may be considered to be interchangeable. Further it is to be noted that as the chain of the alkyl substituent on nitrogen atom is enlarged, the resonance peaks of the two carbonyl carbon atoms get closer to each other. The resonance peak of C-3 in all compounds occur around 72 ppm and the methyl carbon attached to C-3 resonates near 15.5 ppm which remains practically unaltered with substitution.

Methyl carbon of the substituents R′ in compounds **IIc–e** resonate at typical values between 11 to 14 ppm except in **IIb** where the methyl being directly attached to nitrogen atom resonates at 35 ppm. Also as expected from the inductive effect, the chemical shift value decreases with the increasing separation from the nitrogen atom [21]. Slightly higher δ-values for C′-1 in compounds **IIf** and **IIg** may be attributed to the π-electron system in the neighbourhood.

C-3 is an assymetric centre in *MBOAD*. As a consequence the proton NMR spectra of compounds **IIc–g** show diastereotopic effects in their substituent R′ [22]. However, this effect was not observed in the ^{13}C-spectra of any derivative reported here.

Experimental Part

After the synthesis the derivatives of *MBOAD* were isolated and purified using thin layer chromatography [14]. ^{13}C-spectra were recorded using J-modulation technique on a Bruker AM-400 instrument operating at 100.61 MHz. The chemical shifts correspond to 25 °C in *acetone-d_6* relative to *TMS*.

Acknowledgment

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References

[1] Bartsch H., Erker T. (1989) Liebigs Ann. Chem.: 177
[2] Kollenz G., Seidler P. (1984) Naturforsch. **39B**: 384
[3] Bonsignore L., Cabiddu S., Loy G., Secci M. (1982) J. Heterocyc. Chem. **19**: 124
[4] Iacobelli J., Uskokovic M., Werner W. (1965) J. Heterocyc. Chem. **2**: 323
[5] Uskokovic M., Iacobelli J., Toome V., Werner W. (1964) J. Org. Chem. **29**: 582
[6] Cattaneo A., Galimberti P., Melandri M. (1963) Boll. Cim. Farm. **102**: 541
[7] Uskokovic M., Werner W.: a) Fr. Pat. No. 1395918, April 16, 1965; cit. (1965) C.A. **63**: 14881d; b) Fr. Pat. No. 1394359, April 2, 1965; cit. (1965) C.A. **63**: 11592g; c) Belg. Pat. No. 630571, October 21, 1963; cit. (1964) C.A. **61**: 674h
[8] Schäfer H. (1961) Ger. Pat. No. 1085879, July 28, 1960 cit. C.A. **55**: 27383g
[9] Osman A. N., El-Enani M. M. (1981) (pub. 1983) Egypt. J. Pharm. Sci. **22**: 1; cit. (1984) C.A. **100**: 191516m
[10] Przytocka-Balik J., Bobranski B. (1978) Farmaco Ed. Sci. **33**: 360; cit. (1978) C.A. **39**: 109405z
[11] Brown R. E., Vasil St. G., Loev B., Mack R.: U.S. Pat. No. 4307091, December 22, 1981; cit. (1982) C.A. **96**: 110164w
[12] Uskokovic M., Werner W.: U.S. Pat. No. 3291824, December 13, 1966; cit. (1967) C.A. **66**: 76029z
[13] Also see Ref. cited in [3]
[14] Khan N., Babar Z., Razzaq A., Rama N. H. (in press) J. Chem. Soc. Pak.
[15] Breitmeir E., Vœlter W. (1990) ^{13}C-NMR Spectroscopy, 3rd revised edition. Verlag Chemie, Weinheim, p. 261
[16] Petridous-Fiser J., Papadopoulos E. P. (1982) J. Heterocyc. Chem. **19**: 123; also see Ref. [4] cited therein
[17] Shapiro M. J., Coppola G. M., Kahle A. D., Loosli H. R. (1980) J. Heterocyc. Chem. **17**: 1169
[18] Singh S. P., Parmar S. S., Farnum S. A. (1979) J. Heterocyc. Chem. **16**: 649
[19] Bhattacharyya J., Pakrashi S. C. (1980) Heterocycles **14**: 1469
[20] See for example: a) Maciel G. E., Ruben G. C. (1963) J. Am. Chem. Soc. **85**: 3903; b) Bergenthal D., Meister I., Rozsa Zs., Reish J. (1979) Phytochem. **18**: 161
[21] Ref. [15] p. 237
[22] Khan N., Ansari M. S. (to be published)

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