^{13}C NMR Analysis of some 4-Hydroxy-2*H*-1,2-benzothiazine 1,1-Dioxides

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The ^{13}C nmr spectra of some 4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxides **I** have been recorded and analyzed. Spectroscopic assignments were made on the basis of chemical shift theory, APT and fully coupled ^{13}C nmr spectra. Spectral data support the enolic structure of these compounds.

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Introduction.

In previous work [1,2] we studied the synthesis and properties of 4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxides of general formula **I** as well as their ir and ^{1}H nmr spectra. Although in recent years some compounds of this family have acquired a great deal of importance for their strong antiinflammatory activity, no systematic ^{13}C nmr studies have been published. We report the ^{13}C nmr spectra of compounds **I** (Table 1) with particular attention to relationships between structure and spectroscopic behaviour.

Results and Discussion.

Chemical shift data are reported in Table 2. The ^{13}C nmr data are in accord with the proposed enolic structure [1,2]: i) No signal corresponding to a keto group was observed; ii) APT spectra showed two signals at *ca.* 155 and 105 ppm with the same phase as the quaternary carbons of the benzo ring (C-1 and C-6) (see below) which were assigned to C-7 and C-8 in agreement with literature data for enolic and ethylenic carbons [3,4]. In ^{1}H-coupled spectra (Figure 1), C-7 exhibited a long-range coupling (J *ca.* 3 Hz) which could be attributed to coupling from the hydroxyl proton.

The benzenoid carbons in decoupled spectra appear with chemical shifts between 138 and 121 ppm. The peaks at *ca.* 137 and 129 ppm with singlet fine structure [5] were identified by APT as the quaternary carbons. They were assigned to C-1 and C-6, respectively, based on substituent effects. The two pairs of remaining benzenoid carbons (C-3,4 and C-2,5) appeared in the fully coupled spectra

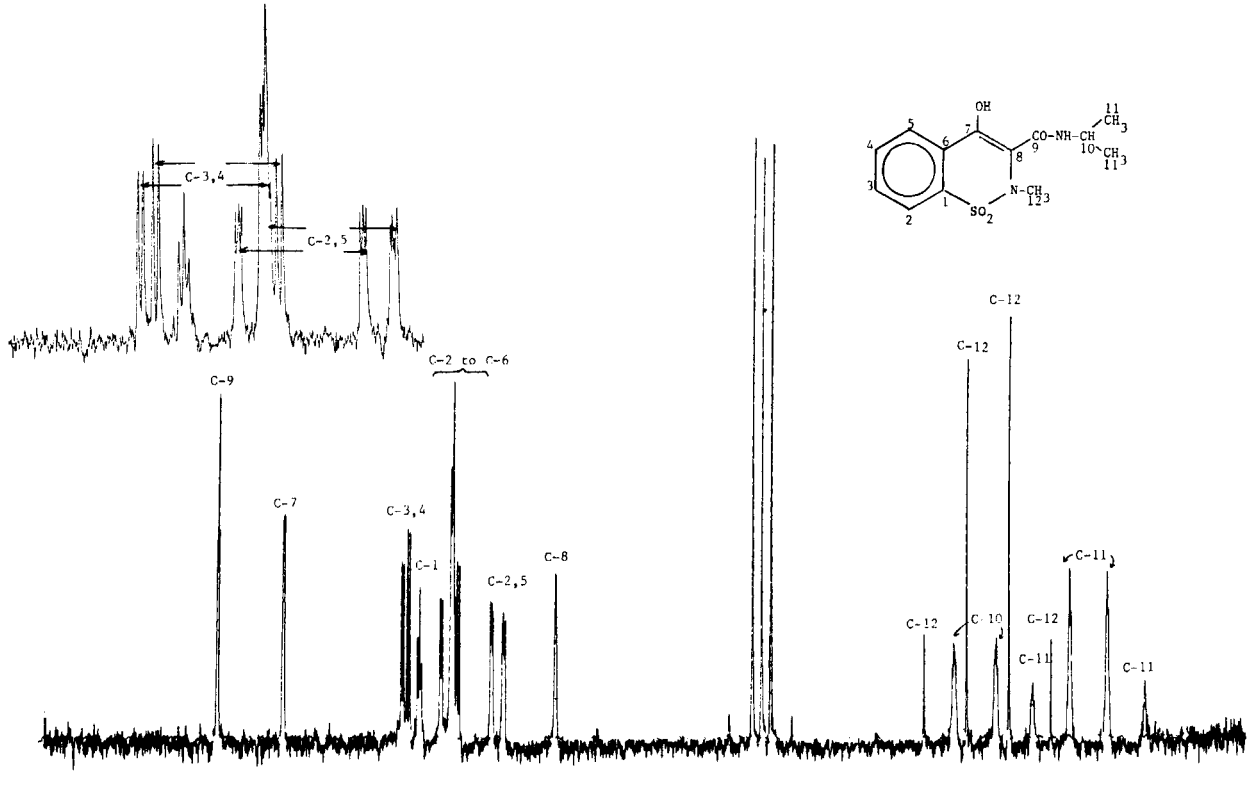
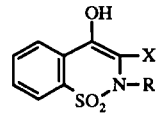
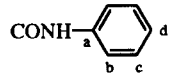
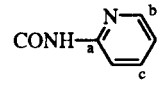
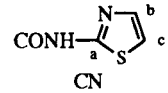


Figure 1. The ^{13}C nmr coupled spectrum of compound 12.

Table 1



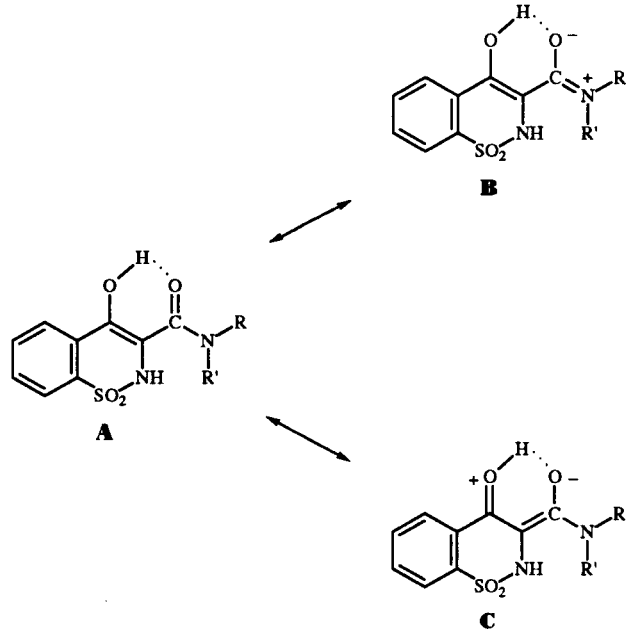
I

Compound	X	R
1	CO_2H	H
2	CO_2CH_3	H
3	$CO_2C_2H_5$	H
4	$CO_2CH(CH_3)_2$	H
5	$CO_2C(CH_3)_3$	H
6	$CONH_2$	H
7	$CONHCH_3$	H
8	$CONHCH(CH_3)_2$	H
9	$CON(C_2H_5)_2$	H
10		H
11		H
12	$CONHCH(CH_3)_2$	CH_3
13		CH_3
14	CN	H
15	CN	CH_3

(Figure 1) with doublet fine structure ($^1J_{CH}$ *ca.* 166 Hz). In practice, such carbons should exhibit multiplet hyperfine structure [5]. However, both pairs of ^{13}C nuclei showed substantially dissimilar long-range coupling. As Figure 1 clearly depicts the two doublet components of the two signals at *ca.* 132 ppm leading to distinct sharp doublets ($^2J_{CH}$ *ca.* 7 Hz). In contrast, those of signals at *ca.* 121 and 126 ppm, exhibited a pattern consisting of many lines. By analogy with the findings of Günther *et al.* for symmetrically *ortho* disubstituted benzenes [6,7] and of Whipple for Piroxicam [8] the 132 ppm signals were assigned to C-3,4 and the latter two to C-2,5.

The acid **1**, exhibited a carboxyl carbon resonance (171.4 ppm) at the same frequency of aromatic acid [9,10]. Formation of the esters produce a 2.6-4.4 ppm upfield shift. This shielding, which is not so large as that observed for benzoic esters [3,4], is similar to that reported for methyl *o*-hydroxybenzoate [9]. The chemical shift changes are also consistent with the proposed enolic structure, stabilized by intramolecular hydrogen bond. In the propyl and *t*-butyl esters (compounds **4** and **5**), the carbonyl carbons are slightly shielded relative to the other esters. On the basis of the γ effects, the upfield shift may be attributed to steric interactions, since one of the *i*-propyl (and two of the *t*-butyl) methyl groups must be gauche.

Scheme 1



In benzothiazine carboxamides, the amino group exerts little effect on the carbonyl shielding based on comparison of data for the acid **1** and the carboxamide **6**: the carbonyl carbons resonating at 171.48 and 171.80 ppm, respectively. No geminal C-N-H coupling was observed for compounds **6** and **13**. Carbonyl carbons of the remaining amides (compounds **7-12**) show multiplet hyperfine structure which could be attributed to long-range coupling interactions.

In *N,N*-diethylcarboxamide **9**, the partial double bond character of the amide CO-N bond [11], which arises from the contribution of a polar resonance structure **B** along with the normal covalent structure **A** (Scheme 1, R = R' = C_2H_5), would lead to the nonequivalence of the nitrogen substituents [12]. However, only one resonance for CH_3 and CH_2 were observed [13]. These observations can be explained if less double bond character is assumed in the amide bond, which is clearly attributable to competitive delocalization (cross conjugation) due to the contribution of an ionic resonance structure **C**. This observation further supports the proposed enolic structure and is in agreement with the ir spectra of these compounds [14].

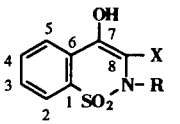
In the nitrile **14** and in its 2-methyl derivative **15**, the molecular geometry precludes the stabilization through intramolecular hydrogen bond. However, ^{13}C nmr spectra of these compounds clearly show the general enolic structure of benzothiazine esters and amides [20].

EXPERIMENTAL

All melting points are uncorrected and were taken on a Büchi capillary melting point apparatus. The ir spectra were recorded

Table 2

^{13}C Chemical Shifts Assignment (ppm) [a]



Compound	C-1	C-2 and C-5		C-3 and C-4		C-6	C-7	C-8	X	R
1	137.67 [b]	121.34 [b]	125.74 [b]	132.80 [b]	132.10 [b]	128.70 [b]	154.71 [b]	106.18 [b]	171.48 [b]	
2	137.71 [c] S [d] M	121.79 [c] D (165) [d] M	126.10 [e]	132.61 [e]	132.55 [e]	128.06 [e]	154.42 [c] S [d] D (3.0)	105.61 S	168.87 (CO) [c] S [d] M 53.0 (CH_3) [c] Q (142)	
3	137.38 [c] S [d] M	121.53 [c] D (167) [d] M	125.78 [c] D (166) [d] M	132.40 [e]	132.25 [e]	127.75 [e]	154.09 [c] S [d] D (3.3)	105.44 S	168.32 (CO) [c] S [d] M 62.05 (CH_2) [c] T (140) 13.97 (CH_3) [c] Q (126)	
4	136.54 [c] S [d] M	121.44 [c] D (166) [d] M	125.73 [e]	132.62 [c] D (166.4) [d] D (6.8)	131.48 [e]	128.64 [e]	153.13 [c] S [d] D (3.0)	105.33 S	167.04 (CO) [c] S [d] M 71.10 (CH) [c] D (139) 20.30 (CH_3) [c] Q (128)	
5	137.20 [c] S [d] M	121.02 [c] D (166.8) [d] M	126.80 [e]	132.60 [c] D (167) [d] D (6.3)	131.08 [e]	128.32 [e]	154.30 [c] S [d] D (3.2)	104.98 S	167.30 (CO) S 82.10 (CO-*C*) S 28.60 (CH_3) [c] Q (127)	
6	137.71 [c] S [d] M	122.12 [c] D (166.1) [d] M	125.81 [c] D (165.06) [d] M	132.04 [c] D (166.6) [d] D (7.3)	132.81 [c] D (166) [d] D (6.0)	128.84 [e]	155.32 [c] S [d] D (3.1)	105.77 S	171.8 (CO) S	
7	137.87 [e]	123.06 [c] D (166) [d] M	126.87 [c] D (167) [d] M	133.23 [e]	134.19 [e]	129.40 [e]	155.06 [c] S [d] D (3.0)	106.54 S	170.23 (CO) [c] S [d] M 27.01 (CH_3) [c] D (138)	
8	137.69 [c] S [d] M	122.34 [c] D (165.4) [d] M	126.09 [c] D (167.8) [d] M	132.25 [c] D (166.6) [d] D (7.0)	133.17 [e]	129.17 [e]	154.48 [c] S [d] D (3.5)	106.22 S	168.35 (CO) [c] S [d] M 41.33 (CH) [c] D (143) 22.89 (CH_3) [c] Q (126)	
9	136.53 [c] S [d] M	121.58 [c] D (166.0) [d] M	125.67 [c] D (167.2) [d] M	132.41 [c] D (166.4) [d] D (6.8)	131.15 [c] D (166) [d] D (6.4)	129.62 [e]	152.18 [c] S [d] D (3.0)	108.53 S	167.18 (CO) [c] S [d] M 42.12 (CH_2) [c] T (139) 13.47 (CH_3) [c] Q (127)	
10	137.84 or 137.41 [c] S [d] M	[f]	[f]	132.82 [e] [g]	132.23 [e] [g]	128.96 [e]	155.60 [c] S [d] D (2.9)	106.33 S	167.98 (CO) [c] S [d] M 137.84 or 137.41 (C-a) [c] S [d] M [f]	

Table 2 (Continued)

Compound	C-1	C-2 and C-5		C-3 and C-4		C-6	C-7	C-8	X			R	
11	134.9 [c] S [d] M	123.40 [c] D (162.3) [d] M	126.04 [e]	133.40 [c] D (166.0) [d] D (6.3)	132.10 [e]	128.70 [e]	158.0 [c] S [d] D (3.0)	111.20 S	167.0 (CO) [c] S [d] D (1.8)	149.9 (C-a) S			
									147.9 (C-b) [c] D (177)		138.2 (C-c) [c] D (152)		
12	133.99 [c] S [d] M	124.17 [e]	126.16 [c] D (165) [d] M	131.68 [c] D (165.7) [d] D (7.5)	132.72 [e]	128.62 [e]	156.47 [c] S [d] D (3.5)	111.26 S		167.21 [c] S [d] M			39.27 (N-CH_3) [c] Q (142)
									41.41 (CH) [c] D (143)	22.22 (C-CH_3) [c] Q (124.4)			
13	134.57 [c] S [d] M	123.51 [e]	126.34 [e]	132.35 [c] D (166.3) [d] D (6.7)	133.05 [c] D (166) [d] D (6.9)	129.22 [e]	156.26 [c] S [d] D (2.3)	114.08 S	168.63 (CO) S		165.0 (C-a) [h] [c] S [d] M		38.30 (N-CH_3) [c] Q (140.6)
									127.94 (C-b) [h] [c] D (192) [d] D (6.4)		112.64 (C-c) [h] [c] D (195) [d] D (10.2)		
14	137.01 [e] [g]	122.19 [c] D (165.0) [d] M	126.40 [g]	132.96 [g]	132.56 [g]	128.73 [e] [g]	154.39 [c] S [d] D (3.9)	92.90 S		115.0 (CN) S			
15	135.21 or 135.67 [e] [g]	124.28 [c] D (166) [d] M	127.75 [e] [g]	131.96 [e] [g]	134.06 [c] D (166) [d] D (6.2)	135.67 or 135.21 [e] [g]	165.04 [c] S [d] D (3.0)	84.45 S		122.46 (CN) S			41.21 (N-CH_3) [c] Q (134)

[a] Spectra of compounds **2-5** and **12** were performed in deuteriochloroform. Spectra of compounds **1,6-11** and **13-15** were performed in DMSO-d_6. [b] Signals could not be assigned through the analysis of the coupled spectrum due to the ease of decarboxylation of this compound (unpublished results). Assignments were made on the basis of the attached proton test and by comparison with the other benzothiazines. [c] Fine structure [5]. Coupling constants are expressed in Hz. [d] Hyperfine structure [5]. Coupling constants are expressed in Hz. [e] Multiplicity could not be determined because of peaks overlap. [f] The signals of the benzothiazine moiety interfere with those of C-b, C-c and C-d of the phenyl group. Three resonances at 126.01, 125.17 and 122.04 were detected. [g] Assignment of the signals was achieved by attached proton test and by analogy with other benzothiazines. [h] Assignments were made on the basis of coupled spectrum and by comparison with the ^{13}C nmr spectrum of 2-aminothiazol.

on a Beckman 180A spectrometer. Samples were run as potassium bromide pellets. The ^{13}C nmr spectra were recorded at 20 MHz on a Varian FT-80A spectrometer. The spectra were recorded at normal probe temperature (30°) using a decoupling power of 6W, pulse angles of 45°, a spectral width of 5000 Hz, an 8K data table, a 2s pulse repetition rate and *ca.* 0.7 Hz of line broadening due to exponential weighting of the free induction decay (FID). The ^1H nmr spectra were recorded on a Bruker AW-80 spectrometer. The presence of exchangeable protons was confirmed by use of deuterium oxide. Chemical shifts are quoted in ppm downfield from TMS. Signals are quoted as: S (singlet), D (doublet), T (triplet), Q (quartet), M (multiplet) and bs (broad signal).

Literature procedures were followed in the preparation of compounds **1-5** [1], **6-8**, **10**, **11** [2] and **13** [21].

3-Oxo-1,2-benzoisothiazoline-2-(*N*,*N*-diethyl)acetamide 1,1-Dioxide.

A mixture of 0.12 mole of benzoisothiazolin-3-one 1,1-dioxide sodium salt, 0.08 mole of *N*,*N*-diethyl-2-chloroacetamide and 15 ml of *N*,*N*-dimethylformamide was heated at 120° for 6 hours. The reaction mixture was poured into ice-water and the resulting solid was filtered, washed with water, dried and recrystallized from ethanol (70% yield), mp 127°; ir: ν 1750 (C=O), 1690 (C=O), 1345 (SO_2) and 1185 cm^{-1} (SO_2); ^1H nmr (deuteriochloroform): δ 8.10-7.60 (M, 4, aromatics), 4.45 (S, 2, CH_2-CO), 3.60-3.20 (M, 4, N-CH_2-C), 1.30 (T, 3, CH_3) and 1.15 (T, 3, CH_3).

Anal. Calcd. for $C_{13}H_{16}N_2O_4S$: C, 52.70; H, 5.40; N, 9.46; S, 10.81. Found: C, 52.80; H, 5.53; N, 9.38; S, 10.70.

4-Hydroxy-*N*,*N*-diethyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-Dioxide (**9**).

A solution of sodium isopropoxide prepared from 0.23 g of sodium (0.01 g-atom) in 5 ml of absolute 2-propanol was refluxed in an oil bath (140°) and 0.740 g (0.0025 mole) of 3-oxo-1,2-benzoisothiazoline-2-(*N*,*N*-diethyl)acetamide 1,1-dioxide was added all at once as the powder. After 20 minutes the orange slurry was poured into ice-concentrated hydrochloric acid. The solid was filtered off, washed with water, dried and recrystallized from ethanol-water (65% yield), mp 125°; ir: ν 3400-2600 (OH), 3180 (NH), 1630 (C=O), 1600 (C=C), 1580 (C=C), 1320 (SO_2) and 1180 cm^{-1} (SO_2); ^1H nmr (deuteriochloroform): δ 14.30 (s, 1, OH), 8.00-7.50 (M, 4, aromatics), 6.30 (bs, 1, SO_2NH), 3.55 (Q, 4, CH_2) and 1.25 (T, 6, CH_3).

Anal. Calcd. for $C_{13}H_{16}N_2O_4S$: C, 52.70; H, 5.40; N, 9.46; S, 10.81. Found: C, 52.48; H, 5.65; N, 9.58; S, 10.98.

3-Oxo-1,2-benzoisothiazoline-2-acetonitrile 1,1-Dioxide.

The synthesis was carried out in the same manner as for 3-oxo-1,2-benzoisothiazoline-2-(*N*,*N*-diethyl)acetamide 1,1-dioxide, but using chloroacetonitrile (0.08 mole) (80% yield), mp 140° (ethanol); ir: ν 2900 (CH), 2230 (CN), 1740 (C=O), 1330 (SO_2) and 1180 cm^{-1} (SO_2); ^1H nmr (deuteriochloroform): δ 8.40-7.90 (M, 4, aromatics) and 4.30 (S, 2, CH_2).

Anal. Calcd. for $C_9H_6N_2O_3S$: C, 48.64; H, 2.70; N, 12.71; S, 14.41. Found: C, 48.48; H, 2.97; N, 12.59; S, 14.30.

3-Cyano-4-hydroxy-2*H*-1,2-benzothiazine 1,1-Dioxide (**14**).

The synthesis was performed in the same manner as for compound **9**, but using a solution of 0.46 g (0.02 g-atom) of sodium in 6 ml of absolute ethanol and 1.11 g (0.005 mole) of 3-oxo-1,2-benzoisothiazoline-2-acetonitrile 1,1-dioxide. After heating for 45 minutes the mixture was poured into ice-hydrochloric acid from which **14** slowly crystallized. The compound was purified by dissolving the crude product in dilute sodium hydroxide and filtered to eliminate insoluble impurities. The solution was extracted with methylene chloride (2 ml). The aqueous alkaline layer yielded, upon acidification with 10% hydrochloric acid (ice bath) a solid which was filtered, washed with water and dried affording pure **14** (40% yield), mp 171° dec; ir: 3400-3200 (OH), 3170 (NH), 2240 (CN), 1600 (C=C), 1325 (SO_2) and 1180 cm^{-1} (SO_2); ^1H nmr (acetone-d_6): δ 8.40 (bs, 2, exchangeable, NH and OH) and 8.20-7.60 (M, 4, aromatics).

Anal. Calcd. for $C_9H_6N_2O_3S$: C, 48.64; H, 2.70; N, 12.71; S, 14.41. Found: C, 48.63; H, 2.82; N, 12.56; S, 14.33.

4-Hydroxy-2-methyl-*N*-isopropyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-Dioxide (**12**).

Compound **8** (0.001 mole) was added to a solution of 0.24 ml of methyl iodide, 4 ml of ethanol and 1.2 ml of 1*N* sodium hydroxide. After 24 hours at room temperature the reaction mixture was concentrated to half of its volume, and treated with 5 ml of ice water. The resulting solid was filtered, dried and recrystallized from methanol, affording **12** (60% yield), mp 183°; ir: ν 3500-2500 (OH), 3340 (NH), 1620 (C=O), 1600 (C=C), 1340 (SO_2) and 1180 cm^{-1} (SO_2); ^1H nmr (deuteriochloroform): δ 13.65 (S, 1, exchangeable, OH), 8.05-7.40 (M, 4, aromatics), 6.60 (D, 1, exchangeable, NH), 4.15 (M, 1, CH), 2.80 (S, 3, N-CH_3) and 1.20 (D, 6, CH_3).

Anal. Calcd. for $C_{13}H_{16}N_2O_4S$: C, 52.70; H, 5.40; N, 9.46; S, 10.81. Found: C, 52.58; H, 5.60; N, 9.40; S, 10.66.

3-Cyano-4-hydroxy-2-methyl-2*H*-1,2-benzothiazine 1,1-Dioxide (**15**).

This compound was prepared as was described for compound **12**. The crude product showed two spots by tlc. In order to obtain pure **15**, the solid was extracted with chloroform (2 x 2 ml). The chloroform-insoluble residue was identified as pure **15** (40% yield), mp 95°; ir: ν 3350-3200 (OH), 2230 (CN), 1600 (C=C), 1320 (SO_2) and 1175 cm^{-1} (SO_2); ^1H nmr (DMSO-d_6): δ 8.40-7.50 (M, 5, 1 H exchangeable, aromatics + OH) and 2.95 (S, 3, CH_3).

Anal. Calcd. for $C_{10}H_8N_2O_3S$: C, 50.84; H, 3.39; N, 11.86; S, 13.55. Found: C, 50.98; H, 3.20; N, 11.42; S, 13.70.

Acknowledgements.

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coupled spectra of symmetrically *ortho*-disubstituted benzenes [6], differs substantially for carbons in the α and β-positions to the substituted carbons thus providing a "fingerpoint" to establish the assignment. Such difference is attributable to the two sets of coupling constants determining the spectra of α and β-carbons.

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[13] In agreement with this, the ^{1}H nmr spectrum of compound **9** exhibits only two signal sets for CH_3 and CH_2. However, the precursor 3-oxo-1,2-benzoisothiazoline-2-(*N*,*N*-diethyl)acetamide 1,1-dioxide shows separate signal sets for the two ethyl groups.

[14] The ir spectra of these compounds exhibit broad weak OH absorption band extending from 3500 to 2500 cm^{-1}. These absorptions, in accordance with Rasmussen [15] are attributable to the fact that all such compounds were of the conjugate chelate type (**A** ↔ **C**). Similar absorptions were observed in several conjugate systems [16-19].

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[20] Again the ir and ^{1}H nmr data are fully consistent with the enolic structure and the absence of an intramolecular hydrogen bond. The ir spectra show complete absence of carbonyl absorption and the presence of a broad OH absorption band at 3400-3200 cm^{-1} which suggests the presence of intermolecular hydrogen bonds in polymeric association. The ^{1}H nmr spectra show the OH signal in a shielded position with respect to that of esters and amides [1,2] which appeared at δ 10-15.

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