The Proton and Carbon Chemical Shift Assignments of 2-Substituted Thioxanthones

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The complete proton and carbon chemical shift assignments have been made for thioxanthone, 2-fluorothioxanthone, 2-chlorothioxanthone, 2-bromothioxanthone, 2-*N,N*-dimethylsulfonamidothioxanthone, 2-methylthioxanthone, 2-methoxythioxanthone and 2-acetylthioxanthone. Assignments were made with the aid of both COSY and CSCM two-dimensional nmr techniques. The C2 substituent alters chemical shifts in the unsubstituted heterocyclic ring.

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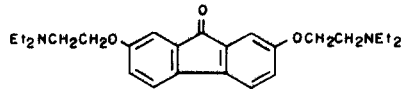
Introduction.

Heterocyclic molecules are a cornerstone in the synthesis of most pharmaceutical agents. One type of system critical to a wide range of drugs is the so-called "6,6,6" tricyclic heterocycle, heterocyclic analogs ("heterologs") of anthracene, 9,10-dihydroanthracene, and so forth. A similar system, the "6,7,6" system, also has been widely employed. These heterologs may have a heteroatom in the central ring and/or in the peripheral ring(s). The range of ills which are touched by drugs derived from such heterocycles include depression, anxiety, schizophrenia, allergic response, and parasitic infection. The interest in Tilorone, an orally effective interferon inducer, and related structrues [1], has served to fuel this activity. As the scope of the biological activity of such heterocycles becomes more apparent, and as more complex structures are prepared, it becomes increasingly important to be able to (a) readily identify reaction products involving these ring systems and (b) understand the effect of ring substituents upon the chemical, spectral and electronic properties of these heterocycles.



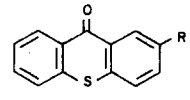
Tilorone

Thioxanthones substituted in the 2 position were selected for this study since 2-substituted heterocycles of this general type (*e.g.*, phenothiazine, thioxanthene) are found in important antipsychotic agents [2]. Most of these antipsychotic agents possess electron-withdrawing substituents *para* to the heterocyclic sulfur. Moreover, in Tilorone the aryl substituents are found *meta* to the carbonyl carbon, just as in 2-substituted thioxanthones. We find that systematic studies of the effect of such substituents upon the chemical and spectroscopic properties of these systems are lacking in the literature even though it is important to establish the effect(s) of the C2 substituent upon the unsubstituted aryl ring and the meso positions *and* to ascertain if such an effect is stronger at certain positions than at others.

Here, we report assignments of the proton and carbon-13 nmr chemical shifts of a number of 2-substituted thioxanthones ("6,6,6" tricyclic heterocycles) by the concerted application of various nmr techniques, including COSY and CSCM two-dimensional nmr spectroscopy.

Assignment Strategy.

Conventional proton and carbon-13 nmr spectra were acquired for thioxanthone (**1**), 2-fluorothioxanthone (**2**), 2-chlorothioxanthone (**3**), 2-bromothioxanthone (**4**), 2-*N,N*-dimethylsulfonamidothioxanthone (**5**), 2-methylthioxanthone (**6**), 2-methoxythioxanthone (**7**), and 2-acetylthioxanthone (**8**).



compound	R	compound	R
1	H	5	$S(O)_2N(CH_3)_2$
2	F	6	CH_3
3	Cl	7	OCH_3
4	Br	8	$C(O)CH_3$

Some chemical shift assignments can be made using one-dimensional spectra. However, at least four of the resonances in the proton spectra of all of these heterocycles were found in the region from 7.3 to 7.7 ppm. Since these resonances all are strongly coupled, they appear as complicated multiplets. The overlap of these multiplets prevents (a) assignment of chemical shift to any of the individual proton resonances in this region and (b) unequivocal confirmation of chemical shifts by proton homonuclear decoupling. (Selection of the correct decoupler frequency and the bandwidth to achieve the desired decoupling was very difficult, and led to irreproducible results.)

The proton-decoupled ^{13}C spectra generally were well dispersed. However, the ^{13}C spectra of **3** and **7** each contain two resonances at nearly the same chemical shift (~ 132 and 127 ppm, respectively), the spectra of **4** and **5** con-

tain two ^{13}C resonances only 0.1 ppm apart, and all but one of the ^{13}C spectra contain some resonances separated by less than 0.5 ppm. These small differences in chemical shift preclude unequivocal assignments of these resonances by chemical shift arguments or by calculations alone. Therefore, it is clear that more powerful experiments needed to be done to complete the chemical shift assignments.

To this end, 2D proton homonuclear J-correlated (COSY) spectra and two-dimensional proton-carbon chemical shift correlated (CSCM) spectra were obtained for the series **1-8**. The COSY experiment indicates which protons are coupled to any given proton [3]. This allows one to decide which proton signals belong to a given spin system, when more than one spin system is present [4]. This is a useful approach because **2-8** have two distinct spin systems: protons 1,3 and 4 on the substituted ring and protons 5-8 on the unsubstituted ring. Clearly, determining to which spin system a given proton belongs determines which ring it is on.

The CSCM experiment, which indicates which protons are coupled to any given carbon, was used for several reasons [5]. First, it separates protonated-^{13}C signals with similar chemical shifts into distinct responses. Second, overlapping proton signals are separated. Thus, chemical shifts of individual resonances are easily determined. Finally, CSCM spectroscopy facilitates proton chemical shift assignment if the assignments of the protonated-^{13}C resonances are known, or *vice-versa* [6]. The CSCM experiments were conducted under two sets of conditions. One of these detects correlations due to stronger, one-bond H-C couplings (in this manuscript referred to as CSCM). The other reports the weaker, long-range couplings between carbons and protons separated by more than one bond (termed LROCSCM, *i.e.*, Long-Range Optimized CSCM) [7].

In the systems discussed here, the combined use of COSY and CSCM spectra allowed assignment of protonated ^{13}C resonances to either the substituted ring (positions 1,3 or 4) or the unsubstituted ring (positions 5,6,7 and 8) after the proton chemical shifts were separated into spin systems as described above. The two-dimensional experiments could be used to distinguish between carbon signals with small chemical shift differences but located on different rings. Also, the "multiplicity" of the response in the contour plot of the CSCM experiment corresponded to the gross multiplicity of the proton signal that correlates with the response. This provided additional information about the location of C-H units, and could be used to aid in distinguishing between otherwise permutable ^{13}C chemical shift assignments. These assignments were consistent with the ^{13}C spin-lattice relaxation times obtained from an inversion recovery experiment (T_1IR) performed on **1**.

The assignment strategy can be summarized as follows: 1) Separate proton signals according to spin system, and therefore ring location, *via* COSY. 2) Make preliminary proton assignments using information from step 1 and from chemical shift and multiplicity arguments. 3) Separate protonated ^{13}C signals according to ring location using the CSCM experiment and information from step 1. 4) Assign protonated ^{13}C resonances using chemical shift arguments, information from previous steps, and CSCM multiplicity information. 5) Assign remaining proton chemical shifts using CSCM and the assigned protonated ^{13}C chemical shifts. 6) Assign quaternary carbon responses using chemical shift arguments and LROCSCM experiments.

Results and Discussion.

Thioxanthone (1).

If one were to follow the assignment strategy outlined above, the first step would be to separate the proton resonances of thioxanthone into separate spin systems. However, since thioxanthone possesses a plane of symmetry passing through the meso positions (C9, S) there is only one spin system. Therefore, there are only four proton and protonated carbon-13 resonances and the COSY experiment is superfluous for this compound.

The ^{13}C spectrum of **1** showed protonated ^{13}C resonances at 125.92, 126.23, 129.82, and 132.19 ppm, and quaternary ^{13}C resonances at 129.21, 137.22 and 179.87 ppm. Benzaldehyde contains a resonance at 129.5 ppm which has been assigned to C2/3 [8]. A comparison with the spectrum of benzaldehyde suggests that the resonance at 129.82 ppm should be assigned to positions C1,8 of **1**. This is substantiated by a CSCM experiment which correlates this ^{13}C resonance with the proton resonance at 8.60 ppm. This indirect assignment of H1,8 to 8.60 ppm is quite reasonable since the electron withdrawing/anisotropic effect of the adjacent carbonyl group is expected to shift these protons downfield relative to the remaining protons [9].

The next assignment is the resonance at 132.19 ppm to positions C3,6 of **1**, also by analogy to benzaldehyde. This assignment is arrived at by recognizing that there is only one protonated ^{13}C resonance in the ^{13}C spectrum of **1** at $\sim$ 132 ppm, and that the only ^{13}C resonance in either thiophenol [10] or benzaldehyde [8] in this same region is C4 of benzaldehyde at 134.2 ppm. The additive nature of ^{13}C chemical shifts suggests that the C3,6 resonance of **1** should occur between 134.2 ppm (C4 of benzaldehyde) and 129 ppm (C3,5 of thiophenol). Assignment of C3,6 of **1** to 132.19 ppm is consistent with this.

This leaves ^{13}C resonances in the spectrum of **1** at 125.92 and 126.23 ppm to be assigned to the remaining positions (C2,7 and C4,5). Analogies with simple model compounds fail at this point because there is only one resonance in either thiophenol or benzaldehyde assigned

to ~ 126 ppm -- C4 of thiophenol at 125.4 ppm. This indicates that C2,7 of **1** should fall between 125.4 and 129 ppm (C3 of benzaldehyde). However, that range is too wide to determine whether that position shoud be assigned to 125.92 or 126.23 ppm. Also, the behavior of the model compounds suggest that C4,5 of **1** should resonate at 129 ppm, an observation which complicates the situation further.

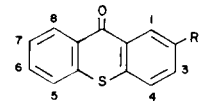
Examination of the contour plot of the CSCM spectrum of **1** showed that the correlation corresponding to the ^{13}C resonance at 125.92 ppm consisted of two separate intensities, *i.e.*, a "doublet". This indicates the proton resonance corresponding to this response must be primarily of doublet character, *i.e.*, possessing one large coupling that was resolvable in the contour plot of the CSCM spectrum. The vicinal proton couplings of 7-8 Hz present in these systems were resolvable in the contour plots of the CSCM spectra, while the much smaller, long-range proton-proton couplings were not. Thus the C-H correlations showed up as either "singlets", "doublets", or "triplets", depending on whether the proton resonance corresponding to that correlation had 0, 1, or 2 vicinal couplings. This permitted assignment of correlated C-H units according to what ring position provided for the correct multiplicity of the correlation. In the case of the response corresponding to 125.9 ppm, the "doublet" character required that it be located in the 4,5 position, since the proton resonance in that position would have only one large, vicinal coupling (to the proton 3,6). Similarly, the multiplicity of the correlation response corresponding to the ^{13}C resonance at 126.2 ppm is "triplet". This indicates that the corresponding proton resonance must have two vicinal couplings, which requires location of this C-H unit at positions 2,7. The proton resonance at 2,7 experiences vicinal couplings to protons at positions 1,8 and 3,6, providing for its "triplet" character in the contour plot of the CSCM spectrum. The multiplicities of the other responses coincided with their assignments: C1,8 at 129.8 ppm was a doublet, and C3,6 at 132.2 ppm was a triplet.

These assignments were consistent with the spin-lattice (T_1) relaxation times of the ^{13}C nuclei of thioxanthone [11]. In solution, one expects the thioxanthone molecule to possess an axis of anisotropic reorientation that bisects the C2-C3 and C6-C7 bonds. This should result in the T_1 values for C2 and C3 being markedly different from those of C1 and C4 because of the difference between the angle of the C2(or 3)-H bond and the axis of reorientation (30°) and the C1(or 4)-H bond and that axis (90°) [12].

The T_1 values of the protonated ^{13}C resonances of thioxanthone, obtained using an inversion-recovery experiment, are: 3.4+/−0.2, 2.5+/−0.1, 2.5+/−0.1, and 3.6+/−0.2 seconds [13]. Inspection of the data shows two different ranges of values. Because of symmetry arguments, one set must be for positions 1,8 and 4,5 and the other must be for positions 2,7 and 3,6. Knowing the chemical shift assignment of C1/C8 at 129.82 assigns them a T_1 value of 3.4±0.2 seconds. The T_1 value for C4,5 was a similar 3.6±0.2 seconds. C3/C6 was assigned to 132.19 ppm and has a T_1 value of 2.5±0.1 seconds. The C2/C7 resonance at 126.23 ppm has the same T_1 of 2.5±0.1 seconds. These T_1 values are consistent with the proposed axis of reorientation, and could be used to make assignments in systems where CSCM multiplicity arguments could not be used.

Table 1

Proton Chemical Shifts of 2-Substituted Thioxanthones in Deuteriochloroform Aryl Protons [a]; Measured at 200 MHz and 25°



Compound	R	H1	H3	H4	H5	H6	H7	H8
1	H	8.60	7.59	7.55	7.55	7.59	7.46	8.60
2	F	8.27	7.35	7.54	7.52	7.59	7.47	8.58
3	Cl	8.54	7.53	7.50	7.54	7.61	7.48	8.57
4	Br	8.70	7.67	7.42	7.55	7.61	7.47	8.57
5	SO_2NMe_2	8.93	7.94	7.71	7.56	7.66	7.53	8.58
6	Me	8.40	7.39	7.42	7.52	7.57	7.44	8.60
7	OMe	8.05	7.23	7.47	7.54	7.58	7.45	8.61
8	C(O)Me	9.10	8.18	7.62	7.58	7.66	7.53	8.60

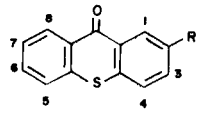
[a] Spectra referenced to residual deuteriochloroform set at 7.26 ppm. All chemical shifts reported to +/− 0.05 ppm.

The protonated ^{13}C chemical shift assignments, therefore, are: C1/C8: 129.82; C2/C7: 126.23; C3/C6: 132.19; C4/C5: 125.92 ppm. Based upon CSCM data, the proton chemical shifts are H1/H8: 8.60; H2/H7: 7.47; H3/H6: 7.60 and H4/H5: 7.56 ppm. These proton chemical shifts are in agreement with the earlier assignments of Sharpless and coworkers [14]. These assignments are summarized in Tables 1 and 2.

The quaternary carbon resonances of **1** naively could be assigned by analogy with thiophenol and benzaldehyde. This would assign C1a/C8a to the resonance at 137.22 ppm and C4a/C5a to the resonance at 129.21 ppm. However, in order to provide an unequivocal assignment, an LRO-CSCM experiment was conducted. In this procedure the delays Δ_1 and Δ_2 in the pulse sequence are varied in order to give responses due to longe-range carbon-hydrogen couplings [5,7]. These results were compared to the (traditional) CSCM experiment in order to distinguish between one-bond and longer range couplings. Using the LROCSCM experiment, it was observed that the resonance at 137.22 exhibited two three-bond couplings to H1 and to H3. This demands that, contrary to the conclusions reached by stu-

Table 2

Carbon-13 Chemical Shifts of 2-Substituted Thioxanthones in Deuteriochloroform Protonated Aryl Carbons [a], Measured at 50.3 MHz and 25°

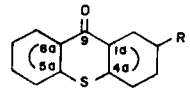


Compound	R	C1	C3	C4	C5	C6	C7	C8
1	H	129.82	132.19	125.92	125.92	132.19	126.23	129.82
2	F	115.29	120.97	127.93	125.93	132.42	126.44	129.85
3	Cl	129.33	132.51	127.42	126.02	132.54	126.57	129.94
4	Br	132.36	135.14	127.48	126.00	132.51	126.55	129.91
5	SO_2NMe_2	129.28	129.98	127.02	126.08	132.97	127.12	129.93
6	Me	129.53	133.59	125.78	125.90	132.01	126.00	129.78
7	OMe	110.38	122.63	127.19	125.96	131.92	126.00	129.78
8	C(O)Me	130.48	130.34	126.45	126.03	132.67	126.88	129.84

[a] Spectra referenced to the center peak of deuteriochloroform set at 77.00 ppm. All chemical shifts reported +/− 0.05 ppm.

Table 3

Carbon-13 Chemical Shifts of 2-Substituted Thioxanthones in Deuteriochloroform Quaternary Carbons [a]. Measured at 50.3 MHz and 25°



Compound	R	C1a	C4a	C5a	C8a	C9	C2
1	H	129.21	137.22	137.22	129.21	179.87	126.23
2	F	130.78	132.50	137.11	128.24	179.06	161.24
3	Cl	130.20	135.41	136.86	128.73	178.82	132.57
4	Br	130.37	135.95	136.77	128.74	178.64	120.20
5	SO_2NMe_2	129.16	142.03	136.10	128.78	178.71	133.91
6	Me	128.92	134.05	137.35	129.16	179.89	136.28
7	OMe	130.15	129.08	137.43	128.51	179.55	158.30
8	C(O)Me	128.58	142.41	136.33	128.87	179.23	134.78

[a] Spectra referenced to the center peak of deuteriochloroform set at 77.00 ppm. All Chemical shifts reported +/− 0.05 ppm.

dies of model compounds, the resonance at 137.22 is due to C4a. The LROCSCM experiment also demonstrated a correlation between the carbon resonance at 129.21 and protons assigned to H2 and H4. This unequivocally assigns this resonance to C1a. The carbonyl carbon (C9) is assigned to the resonance at 179.87 ppm. These assignments are summarized in Table 3. All of the ^{13}C assignments of **1** support the earlier assignments of Still and coworkers [15].

2-Fluorothioxanthone (**2**).

In analyzing the spectra of **2**, carbon-fluorine couplings provided additional information helpful in assigning the quaternary carbon responses and in confirming assignments made *via* 2D experiments.

Inspection of the COSY spectrum of **2** allowed separation of the spin systems. Initial assignment of the resonance (a doublet of doublets) at 8.58 ppm to H8 was done

by analogy to **1**. The three-spin system consisted of resonances at 8.27, 7.35 and 7.54 ppm. The most downfield of these was assigned to H1. The COSY spectrum indicated that this resonance was coupled more strongly to the resonance at 7.35 ppm than to the one at 7.54 ppm. This observation, along with the observed splitting patterns, indicated that H3 resonated at 7.35 ppm. This is consistent with the chemical shift effect of the fluorine nucleus at position 2, which shifted H1 upfield by approximately 0.3 ppm compared to the position of H1 in **1**. This assignment of H3 involved a similar shift upfield compared to the corresponding resonance in **1**. This leaves H4 to be assigned to 7.54 ppm. The four-spin system consisted of H8 (8.58 ppm) and three overlapping signals in the region from 7.4 to 7.7 ppm. These could not be assigned using the COSY spectrum.

The CSCM experiment provided additional information. The carbon resonance that correlated with H8 was observed at 129.85 ppm, thereby assigning that signal to C8. This is consistent with the assignment of C1/C8 in thioxanthone (**1**). Next, the positions 1 and 3 were assigned *via* the contour plot to place C1 at 115.29 ppm and C3 at 120.97 ppm. These carbon resonances had carbon-fluorine (two bond) coupling constants of 23.0 ± 0.3 and 23.7 ± 0.3 Hz, respectively. Likewise, C4 was assigned to the resonance at 127.93 ppm, with an observed carbon-fluorine three-bond coupling of 7.3 ± 0.3 Hz. These carbon-fluorine couplings are consistent with values found elsewhere [16,17] and serve to confirm the chemical shift assignments made by CSCM.

The multiplicities of the contours were not well-defined and this prevented assignment of positions C5-C7 *via* CSCM (multiplicity) data. However, as noted throughout this manuscript, the chemical shifts of C5-C8 are rather constant in the series **1-8**. This was used to assign the chemical shifts of C5-C7 by analogy with **1**. These gave the following assignments: C5, 125.93; C6, 132.42; C7, 126.44 ppm. The CSCM spectrum yielded the following proton assignments: H5, 7.52; H6, 7.59; H7, 7.47 ppm.

Assignment of the quaternary carbon signals represents a greater challenge since neither the COSY nor the one-bond CSCM experiments provide any information about them. However, making these assignments can be aided by using the fluorine as a magnetically active marker. Thus, C1a and C4a should be coupled to fluorine while C5a and C8a should not. The magnitude of the coupling, in turn, could be used to distinguish C1a from C4a.

Two resonances, 130.78 and 132.50 ppm exhibited coupling to fluorine. The former had a coupling constant of 6.7 ± 0.3 Hz while the latter had a coupling of 3.3 ± 0.3 Hz. Consequently, the carbon with the larger (three bond) coupling is C1a while the one with the smaller (four bond) coupling is C4a. Two remaining carbons, 137.11 and 128.24 ppm, must belong to C5a and C8a. The resonance at 137.11 ppm is very close to C5a in **1** and is assigned to C5a in **2**. C8a was assigned to 128.24 ppm, consistent with the chemical shift of C8a in **1** (129.21 ppm).

The carbon at 161.04 ppm had the largest carbon-fluorine coupling (239.6 ± 0.3 Hz) and was assigned to C2. The remaining quaternary carbon, C9, occurred at 179.06 ppm and exhibited at 2.9 ± 0.3 Hz coupling to fluorine.

2-Chlorothioxanthone (**3**).

The COSY spectrum of **3** exhibited two resonances at ~ 8.6 ppm, a doublet of doublets centered at 8.57 ppm (assigned to H8) and a doublet at 8.54 ppm (assigned to H1). The resonance at 8.54 ppm showed coupling to two other closely overlapping signals, one doublet of doublets centered at 7.53 ppm (assigned to H3) and a doublet at 7.50 ppm (assigned to H4). While this completed assignment of the three-spin system, intense overlap in the COSY spectrum prohibited analysis of the H5-7 signals.

The CSCM experiment correlated H1 with C1 at 129.33 ppm. The proton resonance assigned to H3 correlated with C3 at 132.51 ppm and the H4 resonance correlated with C4 at 127.42 ppm. The C8 resonance, which correlated with H8, was found at 129.94 ppm. Positions 5-7 were assigned by analogy to **1** and **2** thus placing C5 at 126.02 ppm, C6 at 132.54 ppm and C7 at 126.57 ppm. The multiplicities of the contour responses were all consistent with the assignments. The CSCM spectrum gave the following proton assignments for positions 5-7: H5, 7.54; H6, 7.61; H7, 7.48 ppm. The CSCM experiment provided an additional benefit since it separated C3 and C6. Initially, it appeared as if both resonated at 132.53 ppm.

The quaternary carbons were assigned as discussed previously. C8a was assigned to a signal at 128.73 ppm since this resonance was closest to C8a in **1** and **2**. Similarly, C5a was assigned to the resonance at 136.86 ppm since this parallels the assignment of C5a in **1** and **2**. C1a was assigned to 130.20 ppm and C4a to 135.41 ppm, consistent with the chemical shifts observed for **2** taking into account the differences in the halogens. The carbonyl carbon (C9) resonated at 178.92 ppm and C2 resonated at 132.57 ppm. As we shall discuss below, this resonance at 132.57 ppm changes dramatically when the C2 substituent becomes bromine while the other resonances remain almost constant. This serves to further support the assignment of C2.

2-Bromothioxanthone (**4**).

The COSY spectrum of **4** clearly separated its two proton spin systems. The four-spin system consisted of H8 (doublet of doublets) at 8.57 ppm and H5-7 between 7.45 and 7.65 ppm. The three-spin system consisted of a doublet at 8.70 ppm (H1), a doublet of doublets at 7.67 ppm (H3) and another doublet at 7.42 ppm (H4). The CSCM

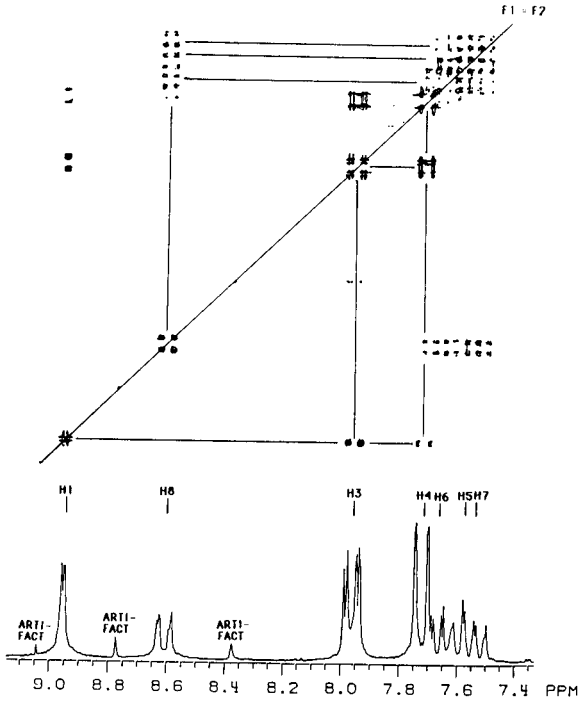


Figure 1. COSY spectrum of 2-*N*,*N*-dimethylsulfonamidothioxanthone (**5**). The F1 = F2 diagonal is labeled. The lines on the contour plot indicate the couplings within the two spin systems.

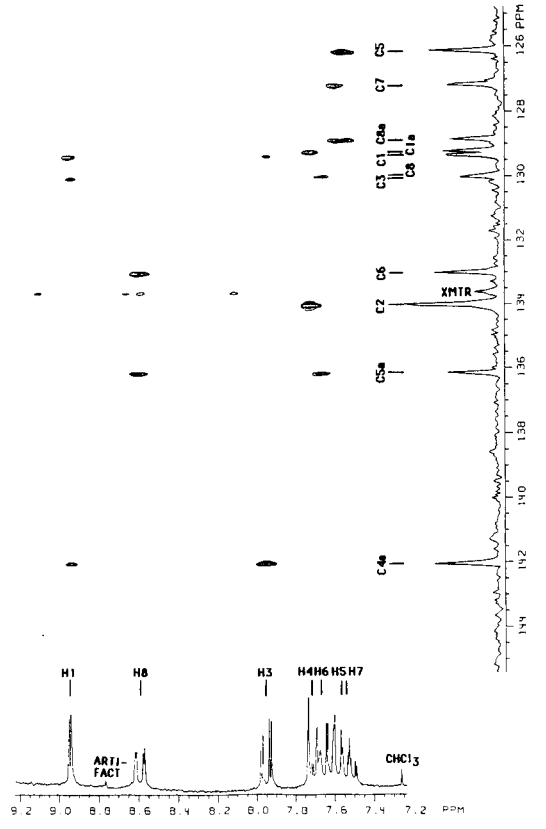


Figure 3. LROCSCM spectrum of 2-*N*,*N*-dimethylsulfamidothioxanthone (**5**). The experiment was optimized for C-H couplings of approximately 12 Hz.

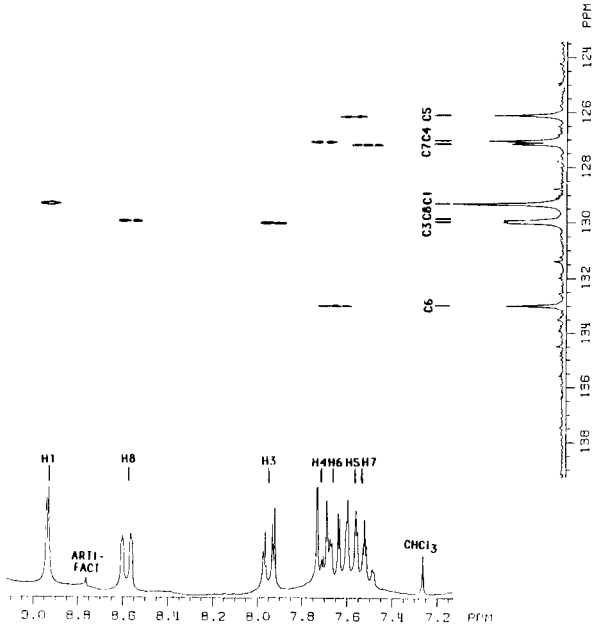


Figure 2. CSCM spectrum of 2-*N*,*N*-dimethylsulfonamidothioxanthone (**5**). The experiment was optimized for one bond C-H couplings.

spectrum correlated H8 with C8 at 129.91 ppm, H1 with C1 at 132.36 ppm, H3 with C3 at 135.14 ppm and H4 with C4 at 127.48 ppm. By analogy with other members in the series (see above) C5-7 were assigned as follows: C5, 126.00 ppm; C6, 132.51 ppm; C7, 126.55 ppm. The corresponding proton assignments from the CSCM spectrum were: H5, 7.55 pm; H6, 7.61 ppm and H7, 7.47 ppm. Again, all multiplicities of the contour plot responses supported these assignments.

The chemical shifts of carbons 5a and 8a are, throughout this entire series, rather constant. Additionally, the location of C5a is sufficiently unique that other resonances rarely occur near it. As a result it is possible to assign C5a and C8a to 136.77 and 128.74 ppm, respectively. The two remaining quaternary carbon signals were assigned so as to place C1a at 130.37 ppm and C4a at 135.95 ppm. These values are consistent with those observed for **2** and **3**. The carbonyl resonance was observed at 178.64 ppm. The remaining carbon resonance, at 120.20 ppm, was assigned to C2. This was consistent with the anticipated changes in chemical shift as one varies the halogen through the series **2**, **3** and **4**.

2-*N,N*-Dimethylsulfonamidothioxanthone (**5**).

The COSY spectra of members of this series are very much alike. The same is true of CSCM and LROCSCM spectra. The 2D spectra of **5** have been selected for presentation since they are representative. Moreover, the *N,N*-dimethylsulfonamido fragment is found in one of the more important thioxanthene-based anti-psychotic agents, thiothixene. Thus, Figures 2-4 represent the COSY, CSCM and LROCSCM of **5**, respectively.

The COSY spectrum of **5** showed two distinct spin systems. The 4-spin system consisted of H8 (doublet of doublets) at 8.58 ppm coupled to thre other proton signals between 7.5 and 7.7 ppm. The three-spin system consisted of H1 (doublet at 8.93 ppm), H3 (doublet of doublets at 7.94 ppm) and H4 (doublet at 7.71 ppm).

The CSCM spectrum then gave the following carbon assignments: C1, 129.28 ppm; C3, 129.98 ppm; C4, 127.02 ppm; C8, 129.93 ppm. C5-C7 were assigned by analogy with other members of this series, placing C5 at 126.08 ppm, C6 at 132.97 ppm and C7 at 127.12 ppm. The corresponding proton signals were found at 7.56, 7.66 and 7.53 ppm, respectively. Again, all multiplicities were consistent with these assignments.

Using an LROCSCM experiment, it was observed that the resonance at 136.10 ppm correlated with both H8 and H6 and was, therefore, assigned to C5a. Further, the resonance at 128.78 ppm correlated with H5 and H7 and was assigned to C8a. Similarly, the resonance at 142.03 ppm showed correlations with H1 and H3, and was assigned to C4a. The resonances at 129.16 and 133.91 ppm both correlated with H4. C1a was assigned to 129.16 ppm, consistent with the location of C1a in the rest of the series **1-8**. C2 was therefore assigned to 133.91 ppm. C9 resonates at 178.71 ppm. The carbons of the *N,N*-dimethyl group appeared at 37.91 ppm while their protons appeared at 2.76 ppm.

2-Methylthioxanthone (**6**).

The proton spectrum of **6** showed a broad singlet at 8.40 ppm. Based upon chemical shift, it was assigned to H1. This shape is unusual for H1; it appears as a doublet in all other members of the series **1-8**. Double-resonance experiments showed that this difference in shape was due to a coupling of ~1 Hz to the protons of the 2-methyl group. This coupling broadened the H1 resonance enough to obscure the H1-H3 coupling of 1.6 Hz (a normal value for this series [18]) that was observed in the proton spectrum which was acquired while the 2-methyl group was irradiated. This observation serves to verify the assignment of H1.

Also anomalous in the proton spectrum of **6** is the appearance of H3 and H4. Upon initial inspection, they appear to be a broadened triplet centered at around 7.4 ppm. Additionally, the COSY spectrum of **6** shows the H1 resonance to be coupled only to this single set of peaks, rather than to a doublet and to a doublet of doublets as in the rest of the series. Analysis of double-resonance spectra acquired with irradiation of the 2-methyl group led to the conclusion that H3 and H4 produce a strongly-AB quartet, *i.e.*, one whose outer lines are quite weak. The 1.6 Hz H1-H3 coupling was found to be splitting the upfield half of the AB quartet. This requires that the upfield signals arise from H3. With this information, it was possible to identify the resonances of H3 and H4 as 7.39 and 7.41 ppm, respectively. [19] The H8 resonance was again a doublet of doublets at 8.60 ppm, while H5-H7 could not be assigned from the COSY spectrum.

It is interesting to note that the appropriate sub-spectrum making up the COSY data matrix, when plotted by itself, shows the coupling of H1 to the upfield portion of the AB quartet alone. This allows direct verification of the chemical shift and signal intensities of H3. The appearance of H3 and H4 is easily understood after finding that the H3-H4 coupling is 8.2 Hz while the chemical shift difference between the two resonances is only 9.2 Hz.

The CSCM spectrum showed C1 to be at 129.53 and C8 to be at 129.78 ppm. Resonances at 133.59 and 125.78 ppm were assigned to C3 and C4 respectively. These correlated with proton signals at 7.39 and 7.42 ppm, as one would have expected from the discussion above. The CSCM spectrum exhibited no anomalies; the contours for C1, C2, and C4 had the proper multiplicities and were no different in appearance from other CSCM spectra from this series. This implies that the H3-H4 coupling is like that present in the other members of this series, in agreement with the findings from the one- and two-dimensional proton spectra.

Similar to other members in this series, C5-C7 were assigned to 125.90, 132.01 and 126.00 ppm, respectively. The corresponding protons were assigned from the CSCM spectrum to 7.52, 7.57 and 7.44 ppm. All the contour multiplicities were consistent with these assignments.

Assignment of the quaternary carbon resonances required acquisition of an LROCSCM spectrum that included the methyl group (proton and ^{13}C) resonances. There were three quaternary carbon resonances in the region 134-137 ppm. The LROCSCM spectrum showed coupling of the resonance at 136.28 ppm to the methyl group protons, thereby assigning it to C2. The other possible sources for that signal, C4a or C5a, would not have a large enough coupling to the methyl group protons to be detected by this experiment. The LROCSCM spectrum indicated that the resonance at 137.35 ppm was from position C5a, and that the resonance at 134.05 ppm was from position C4a. These three signals would have been permutable without the information from the LROCSCM spectrum. Si-

milarly, the LROCSCM spectrum allowed assignment of C8a to 129.16 ppm by virtue of that resonance's correlations with H5 and H7. In turn, this allowed assignment of C1a to 128.92 ppm. C9 was assigned to 179.89 ppm. The methyl group carbon resonance was at 21.16 ppm and the proton resonance was at 2.46 ppm.

2-Methoxythioxanthone (**7**).

The COSY spectrum of **7** showed the three-spin system to contain a doublet at 8.05 ppm, a doublet of doublets at 7.23 ppm and a doublet at 7.47 ppm. These were assigned to H1, H3 and H4, respectively. While H8 was found at 8.61 ppm, the remainder of the four-spin system could not be assigned from the COSY spectrum.

The CSCM experiment was used to assign C1, C3 and C4 to 110.38, 122.63 and 127.19 ppm, respectively. C8 was assigned to 129.78 ppm. Again, analogy with other members of the series suggested assignment of C5 to 125.96, C6 to 131.92 and C7 to 126.00 ppm. Because the carbon and proton signals of positions 5 and 7 are quite close, the contours corresponding to these positions overlap extensively. Analysis of the results of several independent CSCM experiments made it clear that the signal at 126.00 ppm was a triplet while the one at 125.96 ppm was a doublet, thereby rendering assignment of C5 and C7 unequivocal. The corresponding proton assignments are: H5, 7.54 ppm; H6, 7.58 ppm; H, 7.45 ppm.

The quaternary carbon resonances of **7** required an LROCSCM spectrum to facilitate assignment. Using similar methods as described above, the following assignments were made: C1a, 130.15; C4a, 129.08; C5a, 137.43; C8a, 128.51 ppm. The LROCSCM spectrum allowed assignment of the otherwise permutable C4a and C8a responses. All assignments are consistent with the rest of the series **1-8**. C2 was assigned to 158.30 ppm, and C9 was assigned to 179.55 ppm. The O-Me group had ^{13}C and ^{1}H signals at 55.63 and 3.92 ppm.

2-Acetylthioxanthone (**8**).

The COSY spectrum of **8** showed the three-spin system to contain H1 (doublet, 9.10 ppm), H3 (doubet of doublets, 8.18 ppm) and H4 (doublet at 7.62 ppm), H8 appeared as a doublet of doublets at 8.60 ppm; as usual, the remainder of the four-spin system was intractable.

Given the proton assignments, the CSCM spectrum located C1 at 130.48 ppm, C3 at 130.34 ppm, C4 at 126.45 ppm and C8 at 129.84 ppm. The remaining protonated carbon-13 resonances were assigned as before, placing C5 at 126.03 ppm (doublet), C6 at 132.67 ppm (tripet) and C7 at 126.88 ppm (doublet). The corresponding proton signals resonated at 7.58, 7.66 and 7.53 pmm, respectively.

An LROCSCM spectrum served to make quaternary carbon-13 assignments. The signal at 128.87 ppm correlated with H5 and H7, thereby assigning it to C8a. The resonance at 136.33 ppm correlated with H6 and H8, requiring that it be assigned to C5a. C4a was assigned to the resonance at 142.41 ppm, which correlated with H1 and H3. The signal at 128.58 ppm correlated with H4, and was assigned to C1a. This assignment is consistent with the location of C1a in the rest of the series **1-8**. This leaves the signal at 134.78 ppm, which also correlated with H4, to be C2. C9 resonates at 179.23 ppm, and the carbonyl resonance of the acetyl moiety occurred at 196.72 ppm. The methyl group has its carbon resonance at 26.50 ppm and its proton resonance at 2.74 ppm.

The results of these studies are summarized in Tables 1-3.

EXPERIMENTAL

The syntheses of compounds **1-8** have been reported previously [20] and thioxanthone and 2-chlorothioxanthone are available commercially [21]. All of the compounds were shown to be homogeneous by tlc [22].

The nmr spectra used in this work were acquired using a Nicolet NT-200 spectrometer operating at 200.068 MHz for proton and 50.31 MHz for carbon-13 observation. The system is equipped with a Nicolet 1280 data processor and a NIC model 293A' programmable pulser. All spectra were taken on saturated (at 25°) solutions of **1-8** in deuteriochloroform. Chemical shifts are reported relative to TMS, using either the residual protiochloroform signal set to 7.26 ppm as internal reference for proton spectra, or the center peak of the $CDCl_3$ signal set to 77.00 ppm as internal reference for ^{13}C spectra. Probe temperature was maintained at 25° throughout the acquisition of all spectra.

Conventional proton spectra of **1-8** were acquired twice. Initial acquisition used spectral widths of 2000-2400 Hz digitized with 8K (4K real) data points. Then, spectra of the aromatic regions alone were acquired using spectral widths of 400-500 Hz digitized with 2K (1K real) data points. Typically, 16-64 scans were taken, and double exponential multiplication with an apodization factor of 0.5 was applied to the FID's prior to Fourier transformation if necessary.

Conventional ^{13}C spectra also were acquired twice. The first runs used spectral widths of 12000 Hz digitized with 16K (8K real) data points. These FID's were conditioned using exponential multiplication with an apodization factor of 1.0 Hz prior to Fourier transformation. Typically, 64-256 scans were taken. The second runs consisted of spectra of the aromatic regions which typically were acquired using 700-1500 Hz spectral widths digitized with 4K or 2K (2K or 1K real) data points. Signal conditioning usually consisted of exponential multiplication with apodization factors of 0.5-1.0 Hz, sometimes followed by double exponential multiplication with an apodization factor of 0.5. From 36 to 64 scans were taken. All ^{13}C spectra were acquired using broadband proton decoupling.

The ^{13}C relaxation time data were obtained using a saturated sample of **1** in deuteriochloroform at 25°. Because interest only was in relative relaxation rates, not absolute ones, samples were not degassed prior to use. The standard 180°-*tau*-90°-acquire inversion recovery pulse sequence was employed [13]. Spectra were acquired for sixteen different *tau* values between 0.30 and 50.00 sec. The spectral width was 700 Hz digitized with 4K (2K real) data points. One hundred scans were taken for each spectrum. Data were processed using exponential multiplication (apodization factor 0.4 Hz) of the raw FID's and automatic constant scaling of the transformed spectra. The spectra were analyzed with the three parameter fitting routine [23] within the Nicolet software.

COSY spectra of the aromatic regions were acquired using the standard 90°-t_1-90°-acquire pulse sequence. This employs phase cycling of the 90° pulse and receiver phase to give the equivalent of quadrature detection in both dimensions [24]. 512 blocks of 1K data points each were acquired and subjected to double Fourier transform. Sixteen scans were taken for each block. In both dimensions, the raw FID's and interfero-

grams were conditioned prior to transformation using either double exponential multiplication, or exponential multiplication followed by sinusoidal multiplication, all with apodization factors of 0.5. Data were displayed as a contour plot using the absolute value mode.

The pulse sequence used for CSCM spectra is that given by Bax [25a]. In the CSCM experiment the delays [25b] were Δ_1 = 3.3 msec and Δ_2 = 2.0 msec, and in the LROCSCM experiment Δ_1 = 41.7 msec and Δ_2 = 25.0 msec. Phase cycling was again employed to achieve quadrature detection in both dimensions, and the coherence transfer echo was detected [25c]. Carbon-13 spectral widths were 700-1500 Hz, and proton widths were 400-500 Hz, except for the LROCSCM spectrum of **6**, which used a carbon-13 spectral width of 6850 Hz and a proton spectral width of 950 Hz. Typically, 70-128 blocks of 1K or 2K data points were acquired. These FID's were processed using exponential and double exponential multiplication (apodization factors 0.5 to 5.0) prior to the first Fourier transformation. The interferograms usually were zero-filled to 256 data points prior to signal conditioning (as before) and second Fourier transformation. The data were displayed as contour plots in the absolute value mode.

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