Nuclear Magnetic Resonance Spectra of Heterocycles. Analysis of Carbon-13 Spectra of Thioxanthenones using Calculated Chemical Shifts, Substituent Constants, and PRDDO Molecular-orbital Calculations

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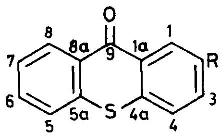
Changes in ^{13}C chemical shifts of a series of 2-substituted thioxanthenones indicate that the 2-substituent causes electronic changes in the unsubstituted ring. Analysis of the ^{13}C n.m.r. data using the dual-substituent parameter (d.s.p.) method and PRDDO molecular-orbital calculations shows that the 2-substituent alters, in a regular fashion, the electron density at C-6 and C-7, and at carbons adjacent to sulphur. The analysis also suggests that transmission of substituent effects from the 2-substituent to the unsubstituted ring takes place *via* a π-polarization mechanism operating through the heterocyclic sulphur.

Heterocyclic molecules are a cornerstone in the synthesis of many pharmaceutical agents.[1] One type of system critical to a wide range of drugs is the so-called '6,6,6' tricyclic heterocycle, heterocyclic analogues (heterologues) of 9,10-dihydroanthracene. These heterologues may have a heteroatom in the central ring and/or in the peripheral ring(s). The range of illnesses affected by drugs derived from such heterocycles include depression, anxiety, schizophrenia, allergic response, and parasitic infection.[2] 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 understand the effect of ring substituents upon the chemical, spectral, and electronic properties of these heterocycles.

Thioxanthenones substituted at C-2 (*i.e.*, *para* to sulphur) were selected for this study since 2-substituted heterocycles of this general type (*e.g.*, phenothiazine, thioxanthene) are found in important antipsychotic agents.[3] Most of these antipsychotic agents possess electron-withdrawing substituents *para* to the heterocyclic sulphur. 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 (*a*) whether the 2-substituent induces electronic changes in the unsubstituted aryl ring and the *meso* positions, and, if so, (*b*) how those substituent effects are transmitted.

Of particular interest is the suggestion that some '6,6,6' tricyclic heterocyclic drugs undergo oxidation *in vivo* at the 6 and 7 positions of the unsubstituted ring.[4] Since particular 2-substituents are required for biological activity in such heterocycles, we were interested in the possibility that both the biological activity and the *in vivo* reactivity of certain molecules is related to 2-substituent-induced perturbation of the electronic nature of the unsubstituted ring. Further, since many heterocyclic drugs contain a sulphur atom at one of the *meso* positions and a ring substituent *para* to it, we were interested to see if the transmission of electronic effects from the 2-substituent to the unsubstituted ring occurred through the sulphur, and if, in the case of thioxanthenone, the carbonyl group played an important part in that process. Finally, we were concerned about the applicability of Hammett substituent constants and the Taft dual-substituent parameter (d.s.p.) method[5] to the study of substituent effects in the thioxanthenone system.



Compd.	R	Compd.	R
(1)	H	(6)	Me
(2)	F	(7)	OMe
(3)	Cl	(8)	COMe
(4)	Br	(9)	NH_2
(5)	SO_2NMe_2	(10)	NO_2

In previous work, we reported[6] the ^1H and ^{13}C n.m.r. spectra of the following 2-substituted thioxanthenones: thioxanthen-9-one (**1**), 2-fluorothioxanthen-9-one (**2**), 2-chlorothioxanthen-9-one (**3**), 2-bromothioxanthen-9-one (**4**), 2-(*N*,*N*-dimethylsulphonamido)thioxanthen-9-one (**5**), 2-methylthioxanthen-9-one (**6**), 2-methoxythioxanthen-9-one (**7**), and 2-acetylthioxanthen-9-one (**8**). The substituent effects upon the n.m.r. spectra, of this series (**1**)–(**8**) plus 2-aminothioxanthen-9-one (**9**) and 2-nitrothioxanthen-9-one (**10**), will be investigated by analysing the ^{13}C n.mr. data in terms of calculated chemical shifts, correlations with linear free-energy parameters, and PRDDO[7] molecular-orbital (m.o.) calculations.

Results and Discussion

The ^1H and ^{13}C chemical-shift assignments of (**1**)–(**10**) are given in Tables 1–3.

Carbon-13 *Chemical-shift Calculations*.—Carbon-13 chemical shifts were calculated using the substituent chemical-shift (s.c.s.) values given by Ewing.[8] Initially, calculations were carried out for (**1**) using 128.5 p.p.m. (benzene) as a starting point and adding to that the s.c.s. values for *S*-phenyl and CO–phenyl groups. The results of these calculations, and the actual assignments, are shown in Figure 1.

We have reported[6] that simple calculations of this type cannot be used, by themselves, to make ^{13}C assignments in thioxanthenones. For instance, both C-1 and C-4 have the same calculated chemical shift, *i.e.* 130.7 p.p.m. (Figure 1). However, there is only one observed, non-quaternary ^{13}C resonance (129.8 p.p.m.) that is close to this calculated value. Also, there are non-quaternary ^{13}C resonances observed at 125.9 and 126.2 p.p.m. Both these are close to the calculated chemical shift of C-2, *i.e.* 126.7 p.p.m. Therefore, the only non-quaternary ^{13}C

Table 1. Aryl-proton chemical shifts of 2-substituted thioxanthenones[a]

		δ/p.p.m.						
Compd.	R	1-H	3-H	4-H	5-H	6-H	7-H	8-H
(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)	COMe	9.10	8.18	7.62	7.58	7.66	7.53	8.60
(9)	NH_2	7.91	7.05	7.41	7.60	7.57	7.47	8.62
(10)	NO_2	9.44	8.42	7.74	7.63	7.71	7.58	8.64

[a] Measured at 200 MHz, 25 °C, in $CDCl_3$. Chemical shifts referenced to residual $CHCl_3$ set at 7.26 p.p.m. All chemical shifts accurate to ±0.05 p.p.m.

Table 2. ^{13}C Chemical shifts of protonated aryl carbons of 2-substituted thioxanthenones[a]

		δ/p.p.m.						
Compd.	R	C-1	C-3	C-4	C-5	C-6	C-7	C-8
(1)	H	129.82 (130.7)	132.19 (132.8)	125.92 (130.7)	125.92	132.19	126.23	129.82
(2)	F	115.29 (117.7)	120.97 (119.8)	127.93 (132.3)	125.93	132.42	126.44	129.85
(3)	Cl	129.33 (131.1)	132.51 (133.2)	127.42 (132.1)	126.02	132.54	126.57	129.94
(4)	Br	132.36 (133.9)	135.14 (136.0)	127.48 (132.3)	126.00	132.51	126.55	129.91
(5)	SO_2NMe_2	129.28 (129.3)[b]	129.98 (131.4)[b]	127.02 (131.5)[b]	126.08	132.97	127.12	129.93
(6)	Me	129.53 (131.4)	133.59 (133.5)	125.78 (130.6)	125.90	132.01	126.00	129.78
(7)	OMe	110.38 (116.3)	122.63 (118.4)	127.19 (131.7)	125.96	131.92	126.00	129.78
(8)	COMe	130.48 (130.8)	130.34 (132.9)	126.45 (130.6)	126.03	132.67	126.88	129.84
(9)	NH_2	113.44 (117.3)	121.30 (119.4)	127.03 (131.5)	125.97	131.81	125.75	129.83
(10)	NO_2	125.51 (125.8)	125.87 (127.9)	127.37 (131.6)	126.20	133.28	127.57	130.18

[a] Measured at 50.3 MHz, 25 °C, in $CDCl_3$. Chemical shifts referenced to the centre peak of $CDCl_3$ set at 77.00 p.p.m. All chemical shifts accurate to ±0.05 p.p.m. Calculated shifts shown in parentheses. [b] SO_2NMe_2 group is approximated by using additivities for an SO_2Me group.

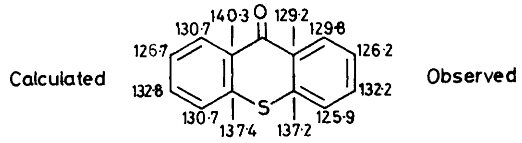
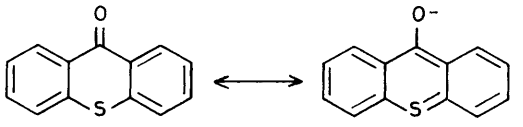


Figure 1. Calculated *vs.* observed ^{13}C chemical shifts of (**1**)



(**1a**) (**1b**)

Figure 2. Resonance structures of (**1**)

signal that could be assigned with any confidence from comparisons with calculated chemical shifts is C-3, which was calculated to resonate at 132.8 p.p.m. and was assigned to the peak at 132.2 p.p.m. Of the other signals, either of the resonances at 125.9 or 126.2 p.p.m. could have been assigned to C-2, and the resonance at 129.8 p.p.m. could have been either C-1 or C-4. Similar difficulties are encountered for the quaternary ^{13}C signals. The discrepancies between the calculated and observed shifts for C-1a and C-4a are such that either assignment of these quaternary carbon resonances (*i.e.* as assigned as shown in Figure 1 or transposed) would result in large errors for one or both positions. Therefore, there is a need for additional spectroscopic information in order to make unequivocal chemical-shift assignments.

Clearly, considering (**1**) as a substituted benzene does not lead to the correct prediction of chemical shifts for all carbons. In particular, there are large differences (Δδ) between the calculated and observed chemical shifts at positions C-1a and C-4. This observation indicates that there is some type of interaction between the two 'substitutents' (*S*-phenyl and CO-phenyl) on that benzene ring, which is consistent with the view that (**1b**) is a significant contributor to the electron distribution within (**1**),[9] as shown below in Figure 2.

Bromilow *et al.*[10] have discussed the non-additivity of ^{13}C substituent shifts for *meta* and *para* disubstituted benzenes and found that mutual (polar and resonance) substituent interactions were responsible for the failure of the calculations. The

Table 3. ^{13}C Chemical shifts of quaternary carbons of 2-substituted thioxanthenones[a]

		δ/p.p.m.					
Compd.	R	C-1a	C-4a	C-5a	C-8a	C-9	C-2
(**1**)	H	129.21	137.22	137.22	129.21	179.87	126.23
		(140.3)	(137.4)				(126.7)
(**2**)	F	130.78	132.50	137.11	128.24	179.06	161.24
		(141.9)	(133.0)				(161.5)
(**3**)	Cl	130.20	135.41	136.86	128.73	178.82	132.57
		(141.7)	(135.5)				(133.0)
(**4**)	Br	130.37	135.95	136.77	128.74	178.64	120.20
		(141.9)	(135.8)				(120.9)
(**5**)	SO_2NMe_2	129.16	142.03	136.10	128.78	178.71	133.91
		(141.1)[b]	(142.5)[b]				(139.0)[b]
(**6**)	Me	128.92	134.05	137.35	129.16	179.89	136.28
		(140.2)	(134.4)				(135.9)
(**7**)	OMe	130.15	129.08	137.43	128.51	179.55	158.30
		(141.3)	(129.7)				(158.1)
(**8**)	COMe	128.58	142.41	136.33	128.87	179.23	134.78
		(140.2)	(141.8)				(135.6)
(**9**)	NH_2	130.16	126.26	137.81	128.75	179.82	145.21
		(141.1)	(127.4)				(144.9)
(**10**)	NO_2	129.43	144.18	135.82	128.87	178.55	146.10
		(141.2)	(143.5)				(146.6)

[a] Measured at 50.3 MHz, 25 °C, in $CDCl_3$. Chemical shifts referenced to the centre peak of $CDCl_3$ set at 77.00 p.p.m. All chemical shifts accurate to ± 0.05 p.p.m. Calculated shifts in parentheses. [b] SO_2NMe_2 group approximated by using additivities for the SO_2Me group.

types of resonance interaction proposed between the sulphur atom and the carbonyl group in (**1b**) is consistent with this, and could reasonably be expected to result in non-additivity of substituent chemical shifts in (**1**). However, the specific differences between calculated and observed ^{13}C chemical shifts found for positions C-4 and C-1a are not easily rationalized. Further work is underway to elucidate the specific causes of these differences.

Calculated ^{13}C chemical shifts for the substituted ring of compounds (**2**)–(**10**) were obtained by adding the 2-substituent s.c.s. values[8] to the calculated shifts of (**1**). The calculated ^{13}C chemical shifts for carbon atoms 1–4, 1a and 4a of compounds (**1**)–(**10**) are included in Tables 2 and 3, along with the differences ($\Delta\delta$) between the calculated and observed shifts.*

Correlations with Substituent Constants.—Since the ^{13}C chemical shift reflects the electronic environment of the carbon atom, ^{13}C n.m.r. spectroscopy is a useful tool for the investigation of substituent effects.[5,8,10,11] Here, changes in ^{13}C chemical shift of various positions of the thioxanthenone molecule were correlated with substituent parameters of the 2-substituent.

To ensure that the correlations found were reliable, a complete set[5] of 2-substituents was included, *and* spectra were obtained (*a*) at low concentration (*ca.* 1–6%), (*b*) at constant temperature, and (*c*) in the relatively non-interacting solvent $CDCl_3$. These precautions reduced the possibility of (*a*) accidental correlations due to either environmental effects or (*b*) insufficient variation in substituent electronic properties.

The first correlation investigated was $\Delta\delta_{C-7}$ *vs.* σ_P. This carbon is *para* to sulphur which, in turn, is *para* to the point of attachment of the 2-substituent. It seemed reasonable that transmission of electronic effects might involve the sulphur, and that σ_P might provide a good correlation. This was indeed the case, since the correlation coefficient (*r*) was found to be >0.99.

Since σ_P embodies a fixed ratio of field/inductive to resonance effects,[5,11] its utility is somewhat limited. The Taft d.s.p. treatment[5,10,11] [equation (1)] overcomes this limitation by correlating the substituent effect with both σ_I (inductive/field) and σ_R (resonance) substituent constants simultaneously, while allowing a variable ratio between the two. Thus, compared with single-parameter analyses, more widely varied systems can be studied, and additional information about the relative importance of inductive and resonance effects can be obtained from the ratio of the two susceptibility coefficients, ρ_R/ρ_I.[5,11] Also, the availability of four different σ_R scales extends the applicability of the d.s.p. method systems with varying electron demand upon the substituent.[5]

$$\text{s.c.s.} = \sigma_I\rho^i_I + \sigma_R\rho^i_R \qquad (1)$$

The d.s.p. method was applied to ^{13}C chemical shifts at positions 1a, 4a, 5a, 6, 7, and 9. The ^{13}C shifts at positions 5, 8, and 8a, and proton chemical shifts, were not analysed because very little change was found for these parameters throughout the series (**1**)–(**10**). For completeness, correlations were carried out using all four of the σ_R scales. The results of the correlations are summarized in Table 4.

The best correlation found was for C-4a with σ_I and $\sigma_R{}^{\circ}$, for which $f = 0.076$† and λ, the ratio of the two susceptibility coefficients ρ_R/ρ_I, = 3.75. The good fit for C-4a is expected since this atom is *para* to the 2-substituent. The λ value found is consistent with those in the literature for d.s.p. analyses involving the *para* positions of mono-substituted benzenes[5,8,10] and indicates that the transmission of electronic effects from the 2-substituent to C-4a is primarily by direct resonance interaction.

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* Even though two-dimensional ^{13}C–^1H correlated spectra were used to assign the chemical shifts of (**1**)–(**8**), the assignments of the quaternary carbon resonances of (**1**), (**5**), (**6**), (**7**), and (**8**) involved certain reasonable assumptions about the magnitudes of long-range ^{13}C–^1H couplings in these heterocycles. The constancy of the $\Delta\delta$ values for the quaternary carbons in the substituted aryl rings of compounds (**1**)–(**10**) suggests that these assumptions are valid.

† The goodness-of-fit (f) of the correlation is given by f = SD/RMS, where SD is the root mean square of the deviations of the calculated substituent effects from the observed ones, and RMS is the root mean square of the measured s.c.s. values. Generally, a correlation of good precision is one in which $f \leqslant 0.10$.[5,11a]

Table 4. Summary of d.s.p. calculations[a]

Carbon	σ_R	ρ_I	ρ_R	λ	f
1a	o	+0.925	−2.229	−2.409	0.365
	BA	+1.083	−1.410	−1.301	0.420
	−	+1.470	−1.680	−1.142	0.217
	+	+1.174	−0.706	−0.601	0.497
4a	o	+6.015	+22.53	+3.475	0.076
	BA	+5.796	+15.78	+2.723	0.145
	−	+1.013	+15.27	+13.85	0.311
	+	+5.319	+8.657	+1.628	0.285
5a	o	−1.788	−1.802	+1.008	0.147
	BA	−1.673	−1.181	+0.706	0.222
	−	−1.327	−1.238	+0.933	0.122
	+	−1.620	−0.625	+0.386	0.331
6	o	+1.341	+1.258	+0.938	0.099
	BA	+1.280	+0.839	+0.655	0.181
	−	+1.028	+0.829	+0.806	0.220
	+	+1.250	+0.453	+0.363	0.269
7	o	+1.580	+1.545	+0.978	0.087
	BA	+1.519	+1.029	+0.678	0.211
	−	+1.215	+1.061	+0.873	0.159
	+	+1.478	+0.550	+0.373	0.305
9	o	−2.241	−0.405	+0.181	0.187
	BA	−2.171	−0.272	+0.125	0.180
	−	−2.081	−0.199	+0.096	0.210
	+	−2.163	−0.148	+0.068	0.184

[a] Substituent constants taken from ref. 5(*a*) except that σ_I and $\sigma_R{}^{\circ}$ for (**5**) are from O. Exner, 'Correlation Analysis in Chemistry: Recent Advances,' ed. N. B. Chapman and J. Shorter, Plenum Press, New York, 1978, ch. 10. Correlations involving the other σ_R values did not include compound (**5**).

Since C-4a correlates well with substituent constants and also experiences large chemical-shift changes (*ca.* 18 p.p.m.) in this series of compounds, it is reasonable to expect that the electron density at the adjacent sulphur atom would change in a manner consistent with the changes at C-4a. It also seems reasonable that the sulphur atom could then induce changes in the unsubstituted aryl ring. This would result in changes in the unsubstituted ring that would correlate with the substituent constants, the substituent effects having been transmitted *via* the sulphur atom.

Related work [13,*] involving the sulphonium ylides of some of these compounds has shown that the methylide carbon chemical shift correlates with the 2-substituent. This supports the idea that the sulphur electron density varies with the moiety at C-2.

The other possible mode of transmission of electronic effects to the unsubstituted ring is *via* the carbonyl group. However, this seems unlikely since neither the C-1a or C-9 chemical shifts correlate with the substituent constants. These non-correlations are not surprising since C-1a and C-9 are *meta* to the 2-substituent.

Of particular interest in the present study are the results for the 6- and 7-positions. As shown in Table 4, both C-6 and C-7 correlate well with σ_I and $\sigma_R{}^{\circ}$, with values of $f = 0.099$ and 0.087, respectively. The good quality of these fits indicates that the 2-substituent does, indeed, control the chemical shifts of these positions of the unsubstituted ring. The λ values for both positions also are similar ($\lambda = 0.938$ for C-6 and 0.978 for C-7) which indicates that inductive and resonance mechanisms are equally important in transmitting substituent effects to C-6 and C-7. This fact, coupled with the fact that the ρ values for C-6 and C-7 are of the same sign, indicates that the transmission of substituent effects to C-6 and C-7 involves a π-polarization mechanism.[8,12,14] This view is consistent with the transmission of substituent effects through the sulphur atom.

This conclusion also is supported by the d.s.p. results for C-5a. A correlation with σ_I and $\sigma_R{}^{-}$ was found ($f = 0.112$), and again the λ value (0.933) indicates that inductive and resonance effects contribute equally to the substituent effect. The substituent effect at C-5a is opposite to that at C-6 and C-7; C-5a shifts upfield when C-6 and C-7 go downfield and *vice-versa* (this same phenomenon was found for the ylide carbon chemical shift in a related series of ylides[13]). This 'inverted' substituent effect at C-5a is consistent with the π-polarization mechanism; as π-electron density is lowered at C-6 and C-7 and they become deshielded, it increases at the C-5a position and shields C-5a.

In summary, the d.s.p. analysis shows that the 2-substituent does affect the unsubstituted aryl ring in the thioxanthenones studied. The analysis also indicates that a π-polarization mechanism involving transmission of substituent effects through the sulphur atom is operating. This conclusion is consistent with the results of d.s.p. analysis of substituent effects in *para*-substituted benzophenones.[14] However, in that system, only a carbonyl group exists to transmit substituent effects from one aryl ring to the other. This suggests that in 2-substituted thioxanthenones, the carbonyl group does not transmit substituent effects because of its location *meta* to the 2-substituent.

One other interesting point should be mentioned. Ehrenson, *et al.*[5a] predict that, for d.s.p. correlations involving *para*-fluorophenyl ^{19}F n.m.r. chemical shifts in diphenyl sulphides and benzophenones, $\sigma_{R^{BA}}$ should provide the best fit of the n.m.r. data. This prediction was supported by Shapiro's work involving the ^{13}C n.m.r. of benzophenones.[14] However, we find that, in general, $\sigma_R{}^{\circ}$ provides the best correlations of ^{13}C chemical shifts in thioxanthenones. This suggests that thioxanthenone behaves somewhat differently than it's two 'component molecules' in terms of substituent effects. Since the carbonyl group does not appear to be involved in the transmission of substituent effects, it might have been reasonable to predict that thioxanthenones would behave like diphenyl sulphides. It is likely that the resonance interaction between the sulphur atom and the carbonyl group [(**1a**, **b**) Figure 1] renders this prediction incorrect.

Molecular-orbital calculations.—In order to investigate further the substituent effects in these systems, correlations of ^{13}C chemical shifts of carbons 4a, 5a, 6, and 7 with their electron densities (and related parameters), calculated using the PRDDO[7] approximation, were carried out. Some correlations between calculated parameters will also be presented.

While chemical shifts are not determined by electron density (q) alone,[8,11c,15,16] substituent-induced changes of ^{13}C chemical shifts in a series of closely related compounds often do correlate with calculated electron densities.[8,10,11c,15] This is because, for ^{13}C, the chemical shift (*i.e.* the shielding, S[†]) change at nucleus A is usually dominated by the paramagnetic shielding term, $S_{para}(A)$.[8,10,15–17] The equation for this term is given (in an abbreviated form) as equation (2).[18] In this equation, ΔE is the mean value of the electronic excitation energy, r the radius of the carbon 2p atomic orbital, ΣQ_{AB} the charge-density and bond-order matrix term reflecting charge distribution in the ground state of the molecule (which is summed over all atoms), and k, a collection of constants.

$$S_{para}(A) = -k(\Delta E^{-1})(r^{-3})_{2p}\, \Sigma\, Q_{AB} \qquad (2)$$

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[*] We are currently investigating the ^{33}S n.m.r. spectra of these compounds.

[†] We use the symbol S instead of the conventional σ to avoid confusion with other quantities represented by σ.

Table 5. Summary of correlations involving PRDDO parameters[a]

Carbon	X	Y	Slope	*r*
4a	π-Population	$\Delta\delta$	-228 p.p.m./π e$^-$ [b]	0.97
	σ-Population	$\Delta\delta$	$+455$ p.p.m./σ e$^-$ [b]	0.96
	Mulliken charge	$\Delta\delta$	$+382$	>0.99
	Mulliken charge (*S*)[c]	$\Delta\delta$	$+890$	0.91
	π-Population	Mulliken charge	-0.594	>0.99
5a	π-Population	$\Delta\delta$	-161 p.p.m./π e$^-$ [b]	0.97
	σ-Population	$\Delta\delta$	$+233$ p.p.m./σ e$^-$ [b]	0.97
	Mulliken charge	$\Delta\delta$	$+389$	0.98
	Mulliken charge (*S*)[c]	$\Delta\delta$	$+95.5$	0.94
	π-Population	Mulliken charge	-0.417	>0.99
6	π-Population	$\Delta\delta$	-354 p.p.m./π e$^-$ [b]	0.90
	Mulliken charge	$\Delta\delta$	$+346$	0.88
	Mulliken charge (*S*)[c]	$\Delta\delta$	$+73.8$	0.96
	π-Population	Mulliken charge	-0.890	0.89
7	π-Population	$\Delta\delta$	-178 p.p.m./π e$^-$ [b]	0.98
	Mulliken charge	$\Delta\delta$	$+247$	0.94
	Mulliken charge (*S*)[c]	$\Delta\delta$	$+88.4$	0.96
	π-Population	Mulliken charge	-0.662	0.96

[a] $\Delta\delta$ refers to the ^{13}C chemical shift change. [b] Shift-to-charge ratio (s.c.r.). [c] (*S*) indicates that this value is for the sulphur atom.

The relationship of S_{para} to electron density resides in the $r-3$ term, which has been shown to depend on electron density;[16,18] *r* increases as electron density increases and *vice-versa*. Changes in the ΔE and ΣQ_{AB} terms are usually considered to be insignificant when considering a series of compounds which differ in substituent only.[8,16] Therefore, S_{para}, and, as a result the total shielding, *S*, will increase (algebraically) as the electron density increases and *vice-versa*.

Correlations between ^{13}C chemical-shift changes and changes in both total (Δq_t) and π(Δq_π) calculated electron densities exist in the literature.[8,11c] In general, Δq_π correlates with *para* carbon shifts in substituted benzenes better than does Δq_t.[8,11c] In this work, the correlations of interest involved carbon atoms at several different locations in the thioxanthenone molecule, only one of which (C-4a) was *para* to the substituent. Therefore, both π- and σ-orbital populations (electron densities), and factors related to total electron densities, were used for correlations.

Correlations are presented in Table 5. For all carbons of interest (4a, 5a, 6, 7), fair to good correlations ($0.90 \leqslant r \leqslant 0.98$) exist between (*a*) π-orbital populations and changes in ^{13}C chemical shift (*b*) Mulliken charges and changes in ^{13}C chemical shift,* and (*c*) the Mulliken charges of the sulphur and the ^{13}C chemical-shift changes. The slopes of correlations (*a*), (*b*), and (*c*) are given, and all are consistent with the common idea that increasing electron density causes upfield ^{13}C shifts (*i.e.* to a numerically smaller chemical shift) and *vice-versa*. It follows from the other correlations that the π-orbital populations should correlate with the Mulliken charges ($r \geqslant 0.89$). For carbons 4a and 5a, the σ-orbital populations also correlate with the ^{13}C chemical-shift changes. However, the slopes of these correlations are of the opposite sign and are 1.5 to 2.0 times larger than those of correlations (*a*); *i.e.* the σ populations change less than do the π populations and in the opposite direction. Similar phenomena have been reported.[10,11c] The good correlations between the π-orbital populations and ^{13}C shifts for C-4a and C-5a illustrate the strong influence of π-electron density upon aromatic chemical shifts.

These correlations involving ^{13}C shifts† support the idea that the 2-substituent affects the electron densities at the carbons of interest, resulting in the chemical-shift changes seen. The correlations with the sulphur-atom Mulliken charge are consistent with the view that sulphur transmits electronic effects from the 2-substituent to the unsubstituted ring. The results of these calculations, along with the previous work,[9c] show that the PRDDO method is useful for the study of complex heterocyclic systems of interest as potential neuroleptic agents.

The slopes of certain correlations give the shift-to-charge ratio (s.c.r.). The s.c.r. values (where applicable) are noted in Table 5. That the s.c.r. values are consistent with those reported in the literature[8,10,11c,16b] supports the validity of the present analysis.

Experimental

2-Aminothioxanthen-9-one (**9**) *and 2-Nitrothioxanthen-9-one* (**10**).—These compounds were prepared according to literature methods,[19] except that for (**10**) sublimation (155 °C, 0.025 mmHg) was used for final purification in addition to the reported procedures.[19b]

N.M.R. Spectra.—N.m.r. spectra were obtained using a Nicolet NT-200 spectrometer operating at *ca.* 200.07 MHz for ^{1}H and *ca.* 50.03 MHz for ^{13}C observation. The ^{1}H and ^{13}C chemical-shift assignments of (**9**) and (**10**) were obtained using the same techniques as those employed in making the assignments of compounds (**1**)–(**8**),[6] as well as comparisons with the assignments of (**1**)–(**8**).

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* For C-6, the *r* value for the Mulliken charge correlation is 0.88. The slope of the correlation (which is consistent with the other Mulliken charge correlations) indicates that this correlation does not deviate grossly from the other correlations of this type, *i.e.* C-6 behaves in a manner consistent with the other carbons in question. Therefore, this correlation is included in Table 5. The fact that C-6 has the smallest range of chemical shifts among the carbons in question may be responsible for this *r* value being slightly lower than for the other carbons.

† Correlations involving core (1s) eigenvalues were also investigated. Since the calculated core (1s) eigenvalues should reflect the electron density about the nucleus (R. J. Buenker and S. D. Peyerimhoff, *Chem. Phys. Lett.*, 1969, 3, 37), the eigenvalues and Mulliken charges would be expected to behave in a similar fashion. In general, fair to good correlations were found for the eigenvalues with both chemical shift changes and Mulliken charges. However, the slopes of the correlations for C-5a were the opposite of those for the other carbons. The reason for the inconsistent behaviour of the C-5a eigenvalues is unknown.

Correlations.—Single-parameter correlations and plots were made using Cricket Graph (version 1.1)* operating on a Macintosh computer (1 MB RAM). The d.s.p. calculations were done, in the main, using the mutliple-linear-regression routine in Cricket Statworks (version 1.2), also using the Macintosh computer.

MO Calculations.—The PRDDO[7] calculations were performed as reported previously,[9c] using a minimum basis set that included d orbitals on the sulphur atom. Standard exponents for s and p orbitals were used.[20] A d-orbital exponent of 1.85 was employed. The basic structural parameters of the thioxanthenone framework were obtained from the crystal structure of (**3**).[21] This framework was then idealized to C_s symmetry for all structures calculated. The chloro (**3**), bromo (**4**), and the *N*,*N*-dimethylsulphonamido (**5**) derivatives were not included. The current program is not able to do calculations on molecules with bromine, and the other substituents require d orbitals on both the substituent atoms [Cl in (**4**) and S in (**5**)] and the heterocyclic sulphur for proper evaluation of substituent effects. Only one set of d orbitals is allowed in the basis set at present.

In order to check whether or not the assumption of an unchanging, planar thioxanthenone framework is valid, geometry optimizations were carried out for thioxanthen-9-one (**1**) and 2-nitrothioxanthen-9-one (**10**). It was found that very little change in the geometry of the molecules or the calculated charges and populations occurred in the optimized structures.† Therefore, all the results reported are those obtained using the planar (non-idealized) structures.

The calculations were done on an IBM 4381-P03 computer except for the geometry optimizations, which were done using a Cray XMP/24 computer.

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† The following parameters were allowed to vary: (*a*) bond lengths in the central ring, (*b*) carbonyl bond length, (*c*) angle between aryl planes ('dihedral angle'), and (*d*) location of sulphur and C-9 above and below the intersection of the aryl planes. The geometry of the nitro group, and its relationship with the aryl ring, was allowed to vary in (**10**). The variations found for relevant parameters were: (*a*) bond lengths, 1.5% (avg.), 3.3% (max.); (*b*) bond angles, 1.0% (avg.), 2.8% (max.); (*c*) 'dihedral angle' < 1%; (*d*) Mulliken charges, 6.1% (avg.), 11.1% (max.); (*e*) π populations, 0.3% (avg.), 0.8% (max.); (*f*) eigenvalues, 0.04% (avg.), 0.3% (max.). The relatively large variation of the Mulliken charges is due to the small (numerical) values for that parameter.