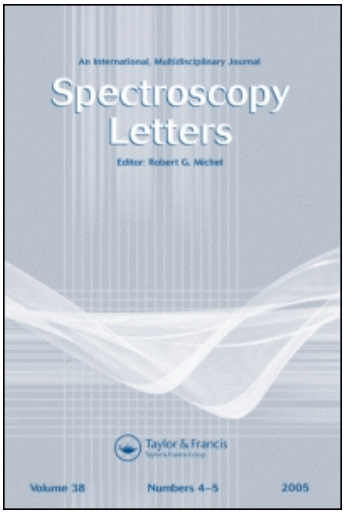


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SPECTROSCOPY LETTERS, 16(6), 431-439 (1983)

# A CARBON-13 NMR STUDY OF THE STRUCTURE OF 9-ACRIDANONE AND 9-THIOACRIDANONE IN NEUTRAL AND ACIDIC MEDIA

KEY WORDS: $^{13}C$ NMR, Tautomerism, Protonation

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## INTRODUCTION

The antimicrobial and antiparasitic properties of acridine derivatives are known for a long time[1]; more recently their anticancer activity has been reported[2]. Amongst the acridines, the derivatives of 9-acridanone 1 and of 9-thioacridanone 2 have interesting properties[3]. Since these compounds show a problem of tautomerism[4], it would be important to study their behaviour in order to understand the activity of acridanones and thioacri-



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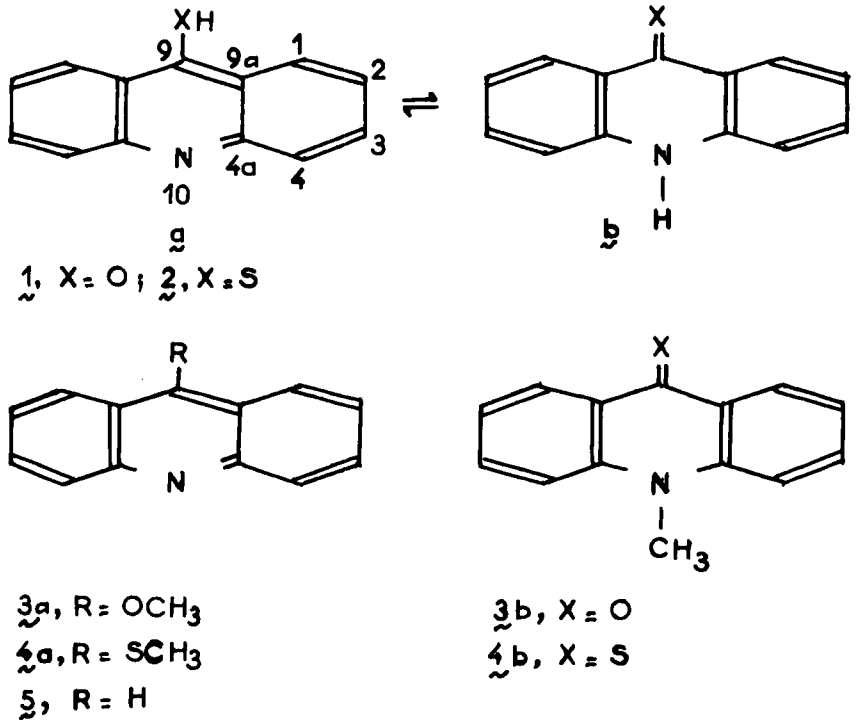


Figure 1

danones in media of different acidity. The present publication deals with the study, by means of $^{13}C$ NMR, of the structure of compounds 1 and 2 (Figure 1) in DMSO-$d_6$ and in trifluoroacetic acid. Five other derivatives, 3 to 5 (Figure 1), used as model compounds, were also studied in these conditions.

## EXPERIMENTAL

The $^{13}C$ NMR spectra were recorded at 20.0 MHz in the FT-mode on a Varian FT-80A spectrometer. Typical experimental conditions are: sweep width, 5000 Hz; pulse width, 8 $\mu$s(45°); acquisition time, 0.8 s; data points, 8192;

temperature, 28 ± 2°C. Because of the low solubility of the N-methyl 9-thioacridanone 4b in DMSO-$d_6$ its $^{13}C$ NMR spectrum has been recorded at 50.3 MHz on a Brucker WP 200SY spectrometer.

In DMSO-$d_6$ solutions, the chemical shifts were measured in the noise decoupled mode with respect to the central line of the solvent and referred to the TMS signal by the relationship[5]: $\delta_{TMS} = \delta_{DMSO\text{-}d_6} + 39.6$ ($\delta$ in ppm). In the case of trifluoroacetic acid solutions, field/frequency control was effected by means of the deuterium resonance of DMSO-$d_6$ placed in an internal capillary tube; chemical shifts were then determined with respect to TMS as an internal standard. The accuracy of the chemical shifts is better than 0.1 ppm.

The samples used in this study were either commercial products (1,5) or products prepared by conventional methods (2[6], 3a[7], 3b[8], 4a[9] and 4b[10]).

## RESULTS AND DISCUSSION

Physicochemical studies[14,15] conclude that the hydroxy tautomer 1a is not present at the equilibrium in the case of 9-acridanone 1, even in non polar solvents[16] (see also [4]). This result allows the determination of the effects produced by the N-methylation, by comparison of the chemical shifts of 9-acridanone derivatives 1b and 3b (Figure 2).

In turn, these SCS can be used to calculate the chemical shifts on the 9-thioacridanone tautomer 2b from the values of the N-methyl derivative 4b (Figure 3). Unfortunately, the absence of results concerning the S-methylation either in naphtalene and anthracene derivatives[17] prevent the calculation of the chemical shifts of the thiol tautomer 2a from the values of the S-methyl derivative 4a

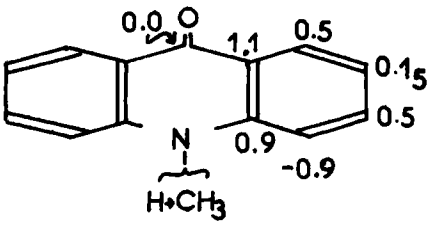


Figure 2. Substituent chemical shifts (SCS) produced by the N-methylation

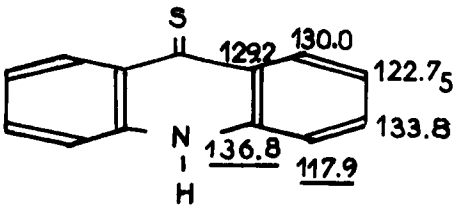


Figure 3. Calculated chemical shifts of the thione tautomer 2b

However, an estimation of the equilibrium constant 2a ⇄ 2b is possible from the $^{13}C$ NMR data of carbons C-4 and C-4a (underlined in Figure 3). The reason is that firstly, the chemical shifts of these carbons must be very similar in structures 2a and 4a, secondly, they must be very sensitive to the tautomeric change, being near the nitrogen atom N-10. Since the precision on the tautomeric constant is related to the value of the difference between the chemical shifts of the two forms in equilibrium[18], the preceding choice of carbon seems reasonable ($\Delta\delta$ about 12 ppm). A simple interpolation affords a value of 15 • 5% of tautomer 2a at the equilibrium. Literature results (UV and IR comparisons)[4,19] only conclude to the predominance of the thione form 2b.

Table 1. $^{13}C$ Chemical shifts[a]

| Compound | Solvent | C-1 | C-2 | C-3 | C-4 | C-9 | C-4a | C-9a | $CH_3$ |
|---|---|---|---|---|---|---|---|---|---|
| | DMSO-$d_6$[b] | 126.0 | 121.05 | 133.5 | 117.4 | 176.8 | 140.9 | 120.5 | |
| 1 | TFAA | 128.3 | 125.6 | 139.65 | 120.35 | 170.9 | 142.6 | 116.7 | |
| ~ | $\Delta$ | (2.3) | (4.55) | (6.15) | (2.95) | (-5.9) | (1.7) | (-3.8) | |
| | DMSO-$d_6$ | 129.9 | 122.6 | 132.8 | 120.2 | 192.9 | 138.0 | 129.5 | |
| 2 | TFAA | 127.6 | 130.4 | 140.0 | 121.8 | 165.8 | 139.1 | 125.2 | |
| ~ | $\Delta$ | (-2.3) | (7.8) | (7.2) | (1.6) | (-27.1) | (1.1) | (-4.3) | |
| | DMSO-$d_6$[c] | 122.4 | 125.5 | 130.6 | 129.4 | 161.25 | 149.95 | 119.6 | 64.3 |
| 3a | TFAA | 126.4 | 128.9 | 139.8 | 120.9 | 174.8 | 143.4 | 120.6 | 67.8 |
| ~ | $\Delta$ | (4.0) | (3.4) | (9.2) | (-8.5) | (13.55) | (-6.55) | (1.0) | (3.5) |
| | DMSO-$d_6$[b] | 126.5 | 121.2 | 134.0 | 116.5 | 176.8 | 141.8 | 121.6 | 33.7 |
| 3b | TFAA | 127.7 | 126.75 | 140.3 | 118.6 | 170.8 | 144.3 | 117.5 | 37.2 |
| ~ | $\Delta$ | (1.2) | (5.55) | (6.3) | (2.1) | (-6.0) | (2.5) | (-4.1) | (3.5) |
| | DMSO-$d_6$[d] | 127.2 | 126.4 | 130.5[e] | 130.1[e] | 146.15 | 148.3 | 127.7 | 20.1 |
| 4a | TFAA | 129.5 | 130.25 | 139.8 | 121.4 | 167.9 | 139.8 | 129.5 | 22.7 |
| ~ | $\Delta$ | (2.3) | (3.85) | (9.3) | (-8.7) | (21.75) | (-8.5) | (1.8) | (2.6) |
| | DMSO-$d_6$ | 130.5 | 122.9 | 134.3 | 117.0 | (f) | 137.7 | 130.3 | 35.1 |
| 4b | TFAA | 128.9 | 129.7 | 140.75 | 119.7 | 166.3 | 141.2 | 125.95 | 38.9 |
| ~ | $\Delta$ | (-1.6) | (6.8) | (6.45) | (2.7) | - | (3.5) | (-4.35) | (3.8) |
| | DMSO-$d_6$ | 128.5 | 125.8 | 130.5 | 128.9 | 136.1 | 148.5 | 126.1 | |
| 5 | TFAA | 131.2 | 129.85 | 139.9 | 120.4 | 150.6 | 140.7 | 127.35 | |
| ~ | $\Delta$ | (2.7) | (4.05) | (9.4) | (-8.5) | (14.5) | (-7.8) | (1.25) | |

[a] $\Delta = \delta_{TFAA} - \delta_{DMSO\text{-}d_6}$; [b] values of the reference 11; [c] values of the reference 12; [d] values of the reference 13; [e] the assigments of these signals may be inverted; [f] signal not observed even in the presence of a relaxation reagent [$Cr(acac)_3$].

Study of the structures in acidic medium

Protonation shifts are gathered in Table 1. These values should be corrected taking into account solvation effects[20] of the DMSO-$d_6$/trifluoroacetic acid pair. However, in a first approximation it could be assumed that these effects would be the same for a series of related compounds.

Analysis of Table 1 data ($\Delta$ values) shows a great similitude in protonation effects of oxygenated derivatives 1b and 3a. Likewise the comparison of the chemical shifts in trifluoroacetic acid proves that the protonation of 9-acridanones, 1b and 3b, and of 9-methoxyacridine 3a leads to a cation having the same electronic structure (Figure 4).

The similitude of protonation effects ($\Delta$ values, Table 1) of compounds 3a and 5 (acridine itself) strongly indicates that the positive charge is located in the acridine ring and not in the methoxy substituent, as in the canonical form represented in figure 4.

For sulfur derivatives a similar conclusion concerning the formation of a common cation can be drawn from the analysis of the chemical shifts in trifluoroacetic acid. However, considering the large effect on C-9 ($\Delta$ = 21.7$_5$ ppm) observed for the protonation of 9-thiometho-

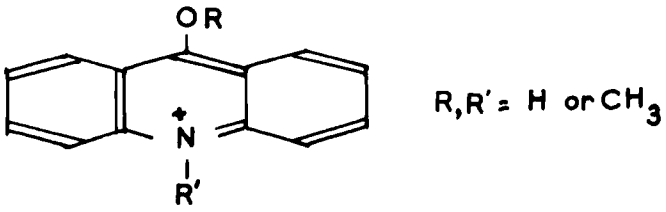


Figure 4. Structure of the cation obtained by protonation of 9-acridanones and 9-methoxyacridines

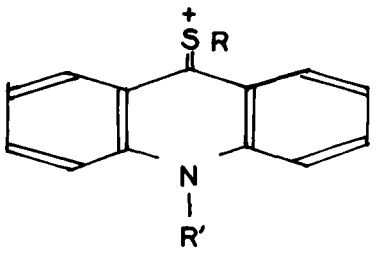


Figure 5. Structure of the cation obtained by protonation of 9-thioacridanones and 9-thiomethoxyacridines.

xyacridine 4a, a canonical form with the positive charge located on the sulfur atom must contributed largely to the resonance hybrid (Figure 5).

The Russian authors previously quoted[16] have concluded that the cation has a 9-mercaptoacridinium structure but a canonical form similar to that of figure 5 has been proposed[21] to explain some effects in 4-thiomethoxyquinoline.



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