pK_a values of 3-thioxo-1,2-dithiole-4- and -5-carboxylic acids and of 3-oxo-1,2-dithiole-4- and -5-carboxylic acids in aqueous solution at 298 K

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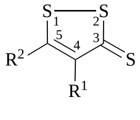
The pK_a values in aqueous solution of some 3-thioxo-1,2-dithiole-5-, 3-oxo-1,2-dithiole-5-, 3-thioxo-1,2-dithiole-4- and 3-oxo-1,2-dithiole-4-carboxylic acids have been determined both by UV–VIS spectrophotometry and by potentiometry at 298 K. The 3-thioxo-1,2-dithiole- and 3-oxo-1,2-dithiole-5-carboxylic acids exhibit very low pK_a values of the order of 1.20. The 1,2-dithiole-3-thione- and 1,2-dithiole-3-one-4-carboxylic acids exhibit pK_a values in the range 1.8–3.2. The pK_a values of 5-alkyl-4-carboxylic acids are 0.6 pH units lower than those of the corresponding unsubstituted dithiolone and dithiolethione acids. Thermodynamic ionization parameters determined by thermometric titrimetry show that: (i) for the 5-carboxylic acids, the strength is the result of an entropic effect; (ii) for the 4-carboxylic acids, the unexpected pK_a values are essentially of enthalpic origin.

Introduction

1,2-Dithiole-3-thiones **1** are promising compounds in the field of pharmacology. For instance, anetholtrithion ($R^1 = H$, $R^2 = p\text{-}CH_3OC_6H_4$) has been used in therapeutics for its choleretic properties for about 50 years.[1] Oltipraz (35972 R.P.) ($R^1 = CH_3$, R^2 = pyrazin-2-yl) is endowed with powerful schistosomicidal properties against *schistosoma Mansoni*, one of the agents of bilharziosis.[2] Promising chemopreventive properties have been shown by these two derivatives against some carcinoma (in particular the hepatic ones).[3,4] They must undoubtedly be related to the now well documented detoxifying properties of several dithiolethiones.[5] Dithiolethiones are also claimed to be powerful antioxidants.[6–8] Finally, it appears that oltipraz is an effective inhibitor of the HIV-1 replication by inactivation of reverse transcriptase.[9] From another point of view, the 1,2-dithiole nucleus seems to be endowed with structural features of interest in non-linear optics.[10]



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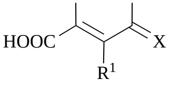
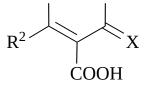
Despite numerous studies devoted to the knowledge of the physico-chemical properties of 1,2-dithiole-3-thiones[11,12] no pK_a values of 3-thioxo-1,2-dithiole-5-, 3-oxo-1,2-dithiole-5-, 3-thioxo-1,2-dithiole-4- and 3-oxo-1,2-dithiole-4-carboxylic acids (**2**, **2′**, **3** and **3′**) have been determined.

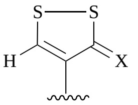




2a X = S; R^1 = H
2b X = S; R^1 = CH_3
2'a X = O; R^1 = H

3a X = S; R^2 = H
3b X = S; R^2 = CH_3
3c X = S; R^2 = C_2H_5
3'a X = O; R^2 = H
3'b X = O; R^2 = CH_3
3'c X = O; R^2 = C_2H_5

Such values would provide an interesting insight into the electronic effects of the 3-thioxo-1,2-dithiole-4-yl group **4** and 3-thioxo-1,2-dithiole-5-yl group **5** and the corresponding dithiolones:



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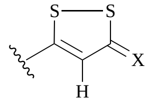


5 (X = S or X = O)

Together with the water/*n*-octanol partition coefficients values of these compounds,[13] they would also provide firm grounds for a rational design of powerful pharmacologically active derivatives.

This study is devoted to potentiometric and spectrophotometric determinations of pK_a values in water at 298 K of some dithiolethione and dithiolone carboxylic acids **2**, **2′**, **3**, **3′**.

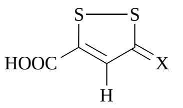
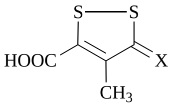
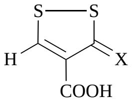
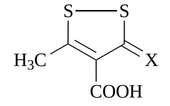
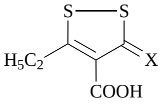
In order to explain these pK_a values, the ionization enthalpies and entropies in water of some derivatives of **2** and **3** were also determined at 298 K. This was done by thermometric titrimetry.

Results and discussion

The agreement between potentiometric and spectrophotometric pK_a values (Table 1) is satisfactory, although the latter are systematically lower than the former. So far, we have no explanation for this phenomenon. We must remember, however, that the concentrations used in potentiometry ($\cong 8.10^{-4}$ mol^{-1}) are on the borderline of applicability of the method and that the solutions used in spectrophotometry contained 2% methanol. It is interesting to note that the concentrations determined together with pK_a values by the potentiometric method and the molar absorptivities determined together with pK_a values by the spectrophotometric method are consistent with the corresponding experimental values (see Experimental section).

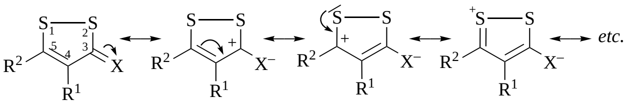
Generally, 3-thioxo-1,2-dithiole-4- and -5-carboxylic acids appears to be rather strong acids. This is especially the case for 5-carboxylic acids, the acidity of which is nearly identical to that of dichloroacetic acid (pK_a = 1.26).[14] The pK_a values found

Table 1 pK_a values[a] of 3-thioxo-1,2-dithiole-4- and -5-carboxylic acids **2**, **3** and of 1,2-dithiole-3-one-4- and -5-carboxylic acids **2′**, **3′**

Compound			pK_a	
			Potentiometry[b]	Spectrophotometry[c]
	X = S	**2a**	1.19 (1.04–1.42)	1.08 (1.00–1.14)
	X = O	**2′a**	1.18 (1.07–1.33)	1.08 (1.01–1.12)
	X = S	**2b**	1.6 (1.47–1.77)	1.26 (1.18–1.37)
	X = S	**3a**	2.81 (2.76–2.87)	2.77 (2.72–2.82)
	X = O	**3′a**	3.68 (3.61–3.76)	3.22 (3.06–3.46)
	X = S	**3b**	2.09 (2.07–2.11)	1.93 (1.87–1.98)
	X = O	**3′b**	3.04 (3.00–3.09)	2.69 (2.62–2.73)
	X = S	**3c**	2.03 (1.91–2.19)	1.89 (1.85–1.95)
	X = O	**3′c**	2.63 (2.48–2.85)	2.59 (1.49–2.67)

[a] The 95% confidence limits (given in parentheses) on the average value are given by $-\log (K_a \pm 2.447\ \sigma_{n-1}/n^{\frac{1}{2}})$ according to Student's table. [b] pK_a determined in water at 298 K. [c] pK_a determined in methanol–water 2 : 100 (v/v) at 298 K.

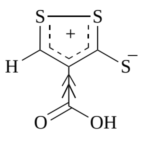
for 5-carboxylic acids are qualitatively in agreement with a very large number of physico-chemical results,[11,12] which can be rationalized by the considerable contribution of dithiolylium sulfide polar forms to the true structures of 1,2-dithiole-3-thione and 1,2-dithiole-3-one:[15]



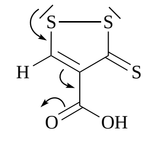
This is well evidenced by the values of the substituent constants of the group **5**: $\sigma_{p-} = 1.14$ (X = S) and $\sigma_{p-} = 0.86$ (X = O) found in a pioneering work by some of us.[16,17] The pK_a value 1.14 places the electroattractive effect of the 3-thioxo-1,2-dithiol-5-yl group on the same level as that of acetyl, formyl or even nitro groups. However, σ_{p-} values do not explain fully the very low pK_a values found (≅1.10). For example, the acids **2a**, **2′a** and **2b** are stronger than pyruvic acid (p$K_a \cong 2.40$).[14] They are also stronger than acrylic acids with a β attractive group such as *trans* β-nitroacrylic acid (p$K_a = 2.58$) and monoethyl fumaric acid and maleic acid (p$K_a = 3.40$ and 3.01 respectively).[14]

The thermodynamic results (Table 2) found for acid **2a** throw some light on the origin of the phenomenon. Reference to monochloroacetic acid is especially interesting because of the ionization enthalpy values of acid **2a** and of monochloroacetic acid ($\Delta H_i^\circ = -4682$ J mol^{-1}) which are about the same order of magnitude.[18,19] On the other hand, the ionization entropy value of **2a** is far less negative than that of monochloroacetic acid ($\Delta S_i^\circ = -70.7$ J K^{-1} mol^{-1}). Hence, it is an entropic effect that is at the origin of the strength of the acid **2a**. According to Bolton and Hepler,[19] who grounded their reasoning on the behavior of some phenols, their entropy values may be attributed to variations of 'charge density distributions between substituent and reaction centers'. The negative charge of the base is likely to be more delocalized in the dithiolethione-carboxylate than in the monochloroacetate ions and the two bases are not similarly aquated. Hence, the low pK_a values of 3-thioxo-1,2-dithiole-5-carboxylic acids may be explained by solute–solvent interactions. It is interesting to note that dithiolone acid **2′a** exhibits the same pK_a value as dithiolethione **2a**. This stresses the importance of solvation effects, since the σ_{p-} values of the groups **5** (X = S and X = O) are somewhat different.

Concerning the 3-thioxo-1,2-dithiole-4-carboxylic acids, as the established value[16,17] ($\sigma_{p-} = 0.07$) shows a weak electroattractive effect of the 3-thioxo-1,2-dithiole-4-yl group, the found value p$K_a = 2.80$ is normal. If one admits, indeed, that in 3-thioxo-1,2-dithiole-4-carboxylic acids, the 1,2-dithiole nucleus can be both electroattractive, by inductive effect, −I, owing to the partial positive charge of the nucleus, and electron-donating, by mesomeric effect, +R (hypotheses which are in agreement with the σ_{p-} value), the 1,2-dithiole nucleus can

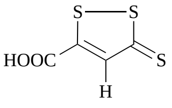
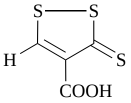
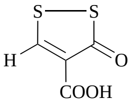
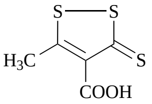
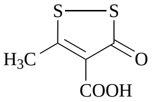


–I effect



+R effect

Table 2 Thermodynamic ionization parameters of 3-thioxo-1,2-dithiole-4- and -5-carboxylic acids **2**, **3** and 3-oxo-1,2-dithiole-4-carboxylic acids **3′** (water; $T = 298$ K)

Compound	pK_a	$\Delta G°$/J mol^{-1}	$\Delta H°$/J mol$^{-1\,a}$	$T\Delta S°$/J mol$^{-1\,a}$	$\Delta S°$/J mol^{-1} K$^{-1\,a}$
 **2a**	1.14	+6445	−5638 (−6137; −5141)	−12085 (−12 582; −11 586)	−40.5 (−42.2; −38.9)
 **3a**	2.79	+15924	−4063 (−4345; −3781)	−19987 (−20 269; −19 705)	−67.1 (−68.0; −66.1)
 **3′a**	3.39	+19349	−1413 (−1466; −1360)	−20 761 (−20 825; −20 709)	−69.7 (−69.9; −69.5)
 **3b**	2.00	+11415	−12653 (−13 136; −12 169)	−24 068 (−24 551; −23 584)	−80.8 (−82.4; −79.1)
 **3′b**	2.83	+16153	−6667 (−6928; −6406)	−22 820 (−23 081; −22 559)	−76.6 (−77.5; −75.7)

[a] The 95% confidence limits (given in parentheses) on the average value are given by $\Delta X \pm 2.447\ \sigma_{n-1} n^{\frac{1}{2}}$ according to Student's table.

then be compared to the methoxy group, which in some instances has the same effects. The pK_a value of the monomethyl carbonate (p$K_a = 2.92$)[20] does not differ markedly, indeed, from that of acid **3a**.

The 5-substituted acids **3b**, **3′b**, **3c** and **3′c** exhibit pK_a values which are systematically about 0.60 unit lower than those of the unsubstituted acids **3a** and **3′a**. At first glance, higher pK_a values for 5-alkyl substituted acids **3b**, **3′b**, **3c** and **3′c** were rather expected owing to the inductive effect. This is not the case and, moreover, the magnitude of the unexpected effect is surprising.

A comparison of the ionization entropies of the unsubstituted acid **3a** and of the substituted acid **3b** and likewise for acids **3′a** and **3′b** shows that they are of the same order of magnitude (Table 2). This is not the case for the ionization enthalpies. It appears that the lower pK_a values of 5-alkyl-substituted derivatives, compared with those of the unsubstituted ones, result from an enthalpic effect. According to Bolton and Hepler,[19] these results seem to rule out a solute–solvent interaction and indicate rather an internal polar effect. The explanation which may be given is that in 5-alkylsubstituted derivatives, a conjugation between the dithiole nucleus and the carboxylic group is not possible, because of the steric effect of the 5-alkylsubstituent, although such conjugation would be possible in the 5-unsubstituted derivatives. As a result, enthalpy variations accompanying ionization are higher for the 5-alkyl-substituted derivatives. This explanation is nearly the same as that given by Laidler and co-workers[21] to explain the pK_a values of *ortho*-substituted benzoic acids. However, the magnitude of this last effect, called the '*ortho* effect'[22] is markedly weaker than that found in this work.

These results provide a physico-chemical basis for the already known fact that the reactivity of 4-substituted dithiolethiones (and dithiolones) is different from that of 5-substituted dithiolethiones (and dithiolones). They also provide a better knowledge of the electronic effects of the groups 3-thioxo-1,2-dithiol-4-yl **4** and 3-thioxo-1,2-dithiol-5-yl **5**.

Experimental

Materials

All commercially available chemicals were of analytical grade. The water used throughout this work was deionized on a set of ion exchanging columns (Bioblock Scientific, Illkirch, France) to $\rho > 2$ MΩ cm^{-1}.

Instrumentation

For analysis the following instruments were used: FTIR spectra with a Perkin-Elmer FTIR 16PC instrument, mass spectra with a VARIAN MAT 311 spectrometer, ^{1}H and ^{13}C NMR spectra with a Bruker AM 360 spectrometer.

Thermometric titrations were performed with the apparatus already described,[23] and the absorption was measured using a UV–VIS spectrophotometer (Uvikon Model 930) with 1 cm silica cells.

Potentiometric pK_a determinations

These were performed by titration of the carboxylic acids by sodium hydroxide in water at 298 K. pK_a values were extracted from the pH data by using a non-linear least-squares procedure.[24,25] pH values were measured with a Tacussel LPH 430T

Table 3 ^{1}H NMR data of 4-ethoxycarbonyldithiolones and the corresponding acids **3′** (δ; 300 MHz; CDCl$_3$)

Compound	(1H, s, 5-H)	(3H, s, 5-CH$_3$)	(3H, t, 5-CH$_2\mathit{CH}_3$)	(2H, q, 5-CH_2CH$_3$)	(3H, t, 4-CO$_2$CH$_2\mathit{CH}_3$)	(2H, q, 4-CO$_2\mathit{CH}_2$CH$_3$)	(1H, s, 4-COOH)
4-Ethoxycarbonyldithiolone	9.2	—	—	—	1.4	4.3	—
3′a	9.5	—	—	—	—	—	—
4-Ethoxycarbonyl-5-methyldithiolone	—	2.7	—	—	1.4	4.4	—
3′b	—	3	—	—	—	—	11.7
4-Ethoxycarbonyl-5-ethyldithiolone	—	—	1.4	3	1.4	4.4	—
3′c	—	—	1.4	3.5	—	—	11.4

Table 4 ^{13}C NMR data of 4-ethoxycarbonyldithiolones and the corresponding acids **3′** (δ; 75 MHz; CDCl$_3$)

Compound	C$_3$	C$_5$	5-CH$_3$	5-CH$_2$-CH$_3$	5-CH$_2$-CH$_3$	C$_4$	4-CO$_2$-CH$_2\mathit{C}$H$_3$	4-CO$_2$-CH$_2$CH$_3$	4-CO$_2$-CH$_2$CH$_3$	4-COOH
Ethoxycarbonyldithiolone	189.1	164.1	—	—	—	124.7	14.2	61.7	160.3	—
3′a	196	165.3	—	—	—	125.4	—	—	—	159.2
Ethoxycarbonylmethyldithiolone	190.2	177	21.4	—	—	122.3	14.2	61.6	162.1	—
3′b	198.1	184.2	22.6	—	—	119.6	—	—	—	160.2
4-Ethoxycarbonyl-5-ethyldithiolone	190.7	182.8		13.8	28.3	122.2	14.2	61.7	162.3	—
3′c	198.7	191.4		13.2	29.6	118.6	—	—	—	160

pH meter that was calibrated daily with six NBS buffers (commercial buffers manufactured according to the NIST recommendations). An Ingold Model 9811 (pH 0–14) glass electrode was used.

The retained pH values for the fitting process were in the buffer range of the acid. (See refs. 24 and 25 for more details.) Owing to the poor solubility of acids in water, working solutions were filtered before study to eliminate undissolved compounds. Hence the concentrations of carboxylic acids were unknown. As a result, fitting the calculated titration curve to the experimental one required taking into account both pK_a values and concentrations as unknown parameters. To obtain meaningful statistical parameters, six titration curves were recorded for each compound. No allowance for the ionic strengths of solutions were made.

Spectrophotometric UV–VIS pK_a determinations

In order to ascertain potentiometric pK_a values, determinations were also performed by the spectrophotometric UV–VIS method. Two analytical wavelengths were chosen: 265 and 405 nm for dithiolethiones and 230 and 320 nm for dithiolones. The buffer solutions were the Britton and Robinson ones for pH > 2. For pH < 2, Bascombe and Bell's acidity functions were chosen. As before a non-linear least squares procedure was used. The molar absorptivity ε of the acid form was systematically considered as unknown. This allowed us to overcome the problem of too low pK_a values with the consequence that the acid form cannot exist alone in working solution with usual buffers. Alternatively, such a strategy allowed a comparison of the molar absorptivity determined through the fitting process with the experimental ones when they were available. Consistence of both the groups of results provided an indirect proof of accuracy of the experiments and of the calculations.

The solutions were prepared by dissolving weighed amounts of carboxylic acids in a minimum of methanol and then by diluting the methanolic solution in the buffer. The percentage of methanol in the working solutions never exceeded 2% (v/v).

Calorimetric measurements by thermometric titrimetry

The determination of the enthalpy ionizations in water of carboxylic acids **2a**, **3a**, **3′a**, **3b**, **3′b** was performed by thermometric titrimetry. This method with which we are acquainted[26,27] proved to be sufficiently sensitive and accurate to determine ionization enthalpies in water of carboxylic acids, despite their weak ionization enthalpies[28,29] (concerning the compounds of interest here, it is worth noting that the application of the Van't Hoff isochore procedure gave unreliable results). The reaction studied in the calorimeter was that of protonation of the sodium salts of acids (10^{-2} mol l^{-1}) by hydrochloric acid (1 mol l^{-1}).

To overcome the problem of precipitation of the acid during titration, which gives rise to a strong parasitic thermal effect, the initial slope method was used to extract the protonation heat from the whole thermal effect.[30,31]

Experiments were performed at 298 K. Gibbs energies of ionization were calculated using the well-known relation $\Delta G° = -RT\ln K_a$ and entropies of ionization by $\Delta H = \Delta G + T\Delta S$. According to Jordan,[32] such experimental conditions warranted the very convenient relation $\Delta H \approx \Delta H°$. As a result, the ionization thermodynamic parameters obtained were the standard ones. In this work, the thermometric procedure was validated by the determination of the thermodynamic ionization parameters of monochloroacetic acid in water, the values of which were known and proved to be close to that of acids **2**, **2′**, **3** and **3′** [Found: $\Delta H_i° = -4652$ J mol^{-1} (-4763; -4541) (lit.,[18,19] -4682 J mol^{-1})].

^{1}H and ^{13}C NMR data of 4-ethoxycarbonyldithiolones and of their corresponding acids **3′** are given in Tables 3 and 4.

Syntheses

3-Thioxo-3*H*-1,2-dithiole-5-carboxylic acid 2a. This preparation has been described by Klingsberg[33] and Faust and Mayer.[34] We preferred to use a different procedure.[5] The action of aqueous sodium sulfide on 5-ethoxycarbonyl-1,2-dithiole-3-thione gave **2a** (72%). 5-Ethoxycarbonyldithiolethione was prepared by sulfuration of diethyl oxaloacetate with P$_4$S$_{10}$ in refluxing xylene, according to the procedure of preparation of 4-phenyl-5-ethoxycarbonyldithiolethione described by Trebaul.[35]

3-Oxo-3*H*-1,2-dithiole-5-carboxylic acid 2′a. This preparation has been described by Faust and Mayer.[36] We preferred to use the action of benzonitrile oxide on the dithiolethione **2a** (65%).[37]

4-Methyl-3-thioxo-3*H*-1,2-dithiole-5-carboxylic acid 2b. This compound was obtained by sulfuration with P$_4$S$_{10}$ of diethyl 2-methyloxaloacetate followed by treatment with aqueous sodium sulfide (46%).[38]

3-Thioxo-3*H*-1,2-dithiole-4-carboxylic acid 3a. We followed the procedure of Egner *et al.*,[5] except for the sulfuration agent, which was P$_4$S$_{10}$ in refluxing xylene, starting from diethyl 2-formylmalonate (53%).

3-Oxo-3*H*-1,2-dithiole-4-carboxylic acid 3′a. This compound was obtained by the action of benzonitrile oxide on the corresponding dithiolethione ester followed by hydrolysis with a mixture of sulfuric and acetic acids at 100 °C. Thus *4-

ethoxycarbonyl-1,2-*dithiole*-3-*one*. [(80%), white crystals, mp 40 °C (acetone); ν_{max}/cm^{-1} 1724 (C=O ester), 1664 (C=O)] gave *3′**a** (69%), white crystals, mp 160 °C (toluene); ν_{max}/cm^{-1} 3250–2900 (OH), 1728 (C=O acid), 1612 (C=O); *m*/*z* (EI): 161.9442 (calc. for $C_4H_2O_3S_2$: 161.9446) (Calc.: C, 29.64; H, 1.24; S, 39.49. Found: C, 30.22; H, 1.31; S, 39.72%).

5-Methyl-3-thioxo-3*H*-1,2-dithiole-4-carboxylic acid 3b. This compound was prepared according to the method of Trebaul and Teste.[39]

5-Methyl-3-oxo-3*H*-1,2-dithiole-4-carboxylic acid 3′b. This compound was prepared using the same method as for 3′**a**. Thus *4-*ethoxycarbonyl*-5-*methyl*-1,2-*dithiole*-3-*one*. [(80%), yellow oil; ν_{max}/cm^{-1} 1732 and 1708 (C=O ester), 1666 (C=O)] gave *3′**b**. (80%), white crystals, mp 112 °C (toluene); ν_{max}/cm^{-1} 3100–2900 (OH), 1728 (C=O acid), 1598 (C=O); *m*/*z* (EI): 175.9617 (calc. for $C_5H_4O_3S_2$: 175.9601) (Calc.: C, 34.10; H, 2.29; O, 27.27. Found: C, 34.21; H, 2.33; O, 26.99%).

5-Ethyl-3-thioxo-3*H*-1,2-dithiole-4-carboxylic acid 3c. This compound was prepared according to the method of Trebaul and Teste.[39]

5-Ethyl-3-oxo-3*H*-1,2-dithiole-4-carboxylic acid 3′c. This compound was prepared by the same procedure as 3′**a** and 3′**b**. Thus *4-*ethoxycarbonyl*-5-*ethyl*-1,2-*dithiole*-3-*one*. [(75%), yellow oil; ν_{max}/cm^{-1} 1730 and 1710 (C=O ester), 1666 (C=O)] gave *3′**c**. (80%), white crystals, mp 98 °C (toluene); ν_{max}/cm^{-1} 3100–2800 (OH), 1736 (C=O acid), 1586 (C=O) (Calc.: C, 37.90; H, 3.18; O, 25.26. Found: C, 37.87; H, 3.23; O, 24.82%).

References

1 B. N. Halpern and O. Gaudin, *Arch. Int. Pharmacodyn. Ther.*, 1950, **83**, 49.
2 H. Bella, A. G. Rahim, M. D. Mustapha, M. A. Ahmed, S. Wasfi and J. L. Bennett, *Am. J. Trop. Med. Hyg.*, 1982, **31**, 775.
3 R. G. Mekta and R. C. Moon, *Anticancer Res.*, 1991, **11**, 593.
4 S. S. Ansher, P. Dolan and E. Bueding, *Hepatology*, 1983, **3**, 932.
5 P. A. Egner, T. W. Kensler, T. Prestera, P. Talalay, A. H. Libby, H. Joyner and T. J. Curphey, *Carcinogenesis*, 1994, **15**, 177.
6 M. Mori, T. Sugawara, S. Yuaxa and K. Kawai, *Eur. Patent*, 94 113 804.2, 1995.
7 A. Tomoyuki, M. Naruyoshi, K. Akihito and S. Kazuya, *17th International Symposium on Organo-Sulfur Compounds*, Tsuhuba, Japan, 1996.
8 J. L. Burgot, C. Martin, H. O. Bertrand, J. M. Warnet and M. O. Christen, *International Symposium on Natural Antioxidants*, Peking, China, 1995.
9 H. J. Prochaska, Y. Yek, P. Baron and B. Polsky, *Proc. Natl. Acad. Sci.*, 1993, **90**, 3953.
10 A. Botrel, B. Illien, P. Rajczy, I. Ledoux and J. Zyss, *Theor. Chim. Acta*, 1993, **87**, 175.
11 C. Th. Pedersen, in *Advances in Heterocyclic Chemistry*, Academic Press, New York, 1982, **31**, 63.
12 C. Th. Pedersen, *Sulfur Reports*, 1995, **16**, 173.
13 M. Bona, P. Boudeville and J. L. Burgot, *J. Pharm. Sci.*, 1995, **84**, 1107.
14 E. P. Serjeant and B. Dempsey, in *IUPAC – Ionization Constants of Organic Acids in Aqueous Solution*, Pergamon Press, Oxford, 1979.
15 N. Lozac'h and J. Vialle, in *The Chemistry of Organic Sulfur Compounds*, Pergamon Press, Oxford, 1966, **2**, 257.
16 M. Saidi, Ph.D. Thesis, University of Rennes I, Rennes, 1988.
17 J. L. Burgot, A. Darchen and M. Saidi, *Comm. Section Ouest de la Société Française de Chimie*, 1988.
18 J. J. Christensen, R. M. Izatt and L. D. Hansen, *J. Am. Chem. Soc.*, 1967, **89**, 213.
19 P. D. Bolton and L. G. Hepler, *Quart. Rev.*, 1971, **25**, 521.
20 J. P. Guthrie, *Can. J. Chem.*, 1978, **56**, 2342.
21 T. W. Zawidzki, H. M. Papee and K. J. Laidler, *Trans. Faraday Soc.*, 1959, 1743.
22 J. Steigman and D. Sussman, *J. Am. Chem. Soc.*, 1967, **89**, 6406.
23 J. L. Burgot, *Talanta*, 1978, **25**, 339.
24 O. Zekri, P. Boudeville, P. Genay, B. Perly, P. Braquet, P. Jouenne and J. L. Burgot, *Anal. Chem.*, 1996, **68**, 2598.
25 B. Legouin and J. L. Burgot, *The Analyst*, 1996, **121**, 43.
26 M. A. Bernard and J. L. Burgot, *Anal. Chem.*, 1979, **51**, 2122.
27 G. Burgot and J. L. Burgot, *Chem. Pharm. Bull.*, 1994, **42**, 1553.
28 J. Jordan and W. H. Dumbough, *Anal. Chem.*, 1959, **31**, 210.
29 L. Avedikian, *Bull. Soc. Chim. Fr.*, 1966, 2570.
30 H. J. Keily and N. D. Hume, *Anal. Chem.*, 1956, **28**, 1294.
31 F. Becker, J. Barthel, N. G. Schmahl, G. Lange and H. M. Luschow, *Z. Phys. Chem.* (New series), 1963, **37**, 33.
32 J. Jordan, in *Treatise on Analytical Chemistry*, part I, vol. 8, ed. I. M. Kolthoff and P. J. Elving, Interscience, New York, 1968, p. 5175.
33 E. Klingsberg, *Chem. Ind.* (*London*), 1960, 1568.
34 J. Faust and R. Mayer, *Z. Chem.*, 1967, 275.
35 C. Trebaul, *Bull. Soc. Chim. Fr.*, 1973, 721.
36 R. Mayer and J. Faust, *Chem. Ber.*, 1963, **96**, 2702.
37 F. Boberg and J. Knoop, *Liebigs Ann. Chem.*, 1967, **708**, 148.
38 M. Abazid, Ph.D. Thesis, University of Rennes I, 1990.
39 C. Trebaul and J. Teste, *Bull. Soc. Chim. Fr.*, 1969, 2456.

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