C. F. G. C. GERALDES
M. T. BARROS
M. I. SILVA
Chemistry Department
University of Coimbra
3000 Coimbra
PORTUGAL

C. D. MAYCOCK
Chemistry Department
Faculty of Sciences
University of Lisb
1200 Lisbon
PORTUGAL

STUDIES OF SOME β-KETODITHIOLANES AND β-KETODITHIANES BY PROTON AND ^{13}C NMR

Several β-keto-1,3-dithiolanes and one β-keto-1,3-dithiane were synthesized and characterized by proton and carbon-13 NMR spectroscopy. It was found that there is no general correlation beteween the preferred directions of enolization of the parent assymetric β-dicarbonyl compounds and the regioselectivity of protection of the carbonyl groups by formation of the 1,3-dithiolane (dithiane) rings. This indicates that steric effects due to the substituents next to the carbonyl groups are more important than electronic effects in determining the point of attack of the bulky nucleophilic dithiolate agent.

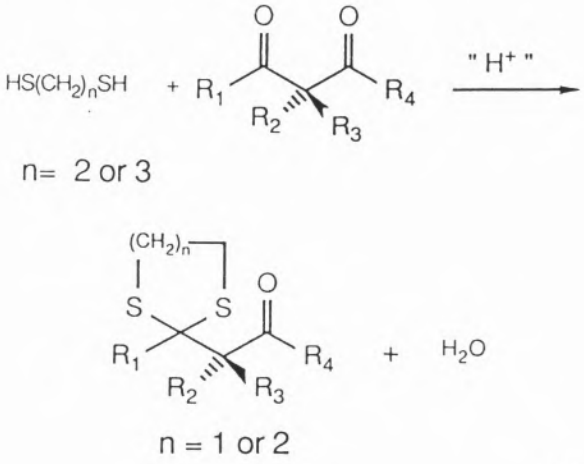
INTRODUCTION

The cyclic thioacetal compounds of the β-keto-1,3-dithiolane and β-keto-1,3-dithiane families are very interesting intermediates in organic synthesis, as they can originate effectively regioselective reactions at the free carbonyl function. The protected carbonyl group can later be regenerated using the appropriate hydrolytic methods [1, 2].

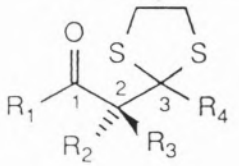
In this work, the β-ketodithiolane compounds **1-5**, **7** and **8**, as well as the β-ketodithiane compound **6** (see Fig. 1), were synthesized and characterized using proton and ^{13}C nuclear magnetic resonance (NMR) spectroscopy. The existence of a correlation between the preferential direction of enolization of assymmetric β-diketones and the preferred protection of one of their carbonyl groups by dithiols was also investigated. This was done by comparing the yields of regioisomers in the synthesis of β-ketodithiolanes and β-ketodithianes with the populations of species in the enol-enol tautomeric equilibrium present in solutions of the corresponding parent assymmetric β-diketones, which were previously obtained using proton, ^{13}C and ^{17}O NMR spectroscopy [3].

EXPERIMENTAL

The β-ketodithiolane compouds **1, 2, 3, 4, 5** and **7**, and the β-ketodithiane **6**, which are cyclic thioacetals, were synthesized from the corresponding β-diketones [4, 5] by reacting them with ethane-dithiol-1,2 (dithiolanes) or with propanedithiol-1,3 (dithiane **6**), as shown in the following equation:



1. $R_1 = CH_3$; $R_2 = R_3 = H$; $R_4 = CH_3$
   1-[2-methyl-2-(1,3-dithiolanyl)]-propanone



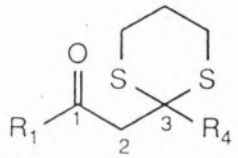
2. $R_1 = CF_3$; $R_2 = R_3 = H$; $R_4 = CH_3$
   1-[2-methyl-2-(1,3-dithiolanyl)]-3,3,3-trifluoro-propanone

3. $R_1 = C_6H_5$; $R_2 = R_3 = H$; $R_4 = CH_3$
   1-[2-methyl-2-(1,3-dithiolanyl)]-acetophenone

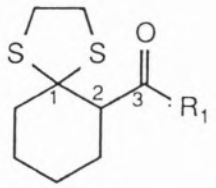
4. $R_1 = C_2H_5$; $R_2 = R_3 = H$; $R_4 = CH_3$
   1-[2-methyl-2-(1,3-dithiolanyl)]-2-butanone

5. $R_1 = COOC_2H_5$; $R_2 = R_3 = H$; $R_4 = CH_3$
   ethyl 2-oxo-3-[2-methyl-2-(1,3-dithiolanyl)]-propanoate

6. $R_1 = R_4 = CH_3$
   1-[2-methyl-2-(1,3-dithianyl)]-propanone



7. $R_1 = CH_3$
   6-acethyl-1,4-dithio-spiro-[4,5]-decane



8. $R_1 = R_4 = CH_3$
   1-1-di-[2-methyl-2-(1,3-dithiolanyl)]-methane

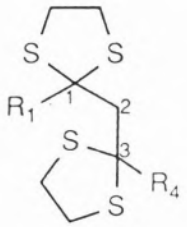


Figure 1

Chemical structures, IUPAC names and numbering scheme adopted for the carbon atoms of the backbone nuclei for NMR assignment purposes (this is not a IUPAC numbering scheme) of the β-ketodithiolanes and β-ketodithianes studied

Compound **8** was also synthesized through protection of both carbonyl carbons. The condensation reaction is carried out in solution of $ZnCl_2$/HCl in ether or in the presence of the diethyletherate adduct of boron trifluoride, $BF_3(C_2H_5)_2O$, both reactions taking place initially in the absence of water [6]. Table 3 summarizes the yields of synthesis as well as some physical data and results of microanalysis for the compounds which were synthetised for the first time in this work, as well as key references for the other compounds already described in the literature.

0.1 M solutions of these compounds were prepared in $CDCl_3$ (99.8% D), from Stohler Isotope Chemicals.

All NMR measurements were carried out at room temperature on a Varian XL-200 spectrometer equipped with Fourier transformation using the deuterium resonance of $CDCl_3$ as an internal lock. Proton spectra were obtained at 200.053 MHz and broadband proton decoupled ^{13}C spectra were obtained at 50.053 MHz. All the proton and ^{13}C chemical shifts were relative to TMS, which was used as an internal reference. The precision of the mea-

sured chemical shift values was ± 0.01 ppm for ^{1}H and ± 0.05 ppm for ^{13}C. Spectral assignments were carried out using comparisons with the literature values for similar compounds [4, 7], by performing homonuclear proton decoupling experiments or by recording proton-coupled or off-resonance proton-decoupled ^{13}C spectra.

RESULTS AND DISCUSSION

The β-ketodithiolane and β-ketodithiane compounds **1** to **8** were studied using proton and ^{13}C NMR spectroscopy. The corresponding chemical shift values are presented in Tables 1 and 2, respectively. In the cases of compounds **1, 3** and **6**, previously studied by proton NMR [4, 7], the proton chemical shifts obtained were in close agreement with literature values. The resonances of the bridge groups, $-SCH_2CH_2S-$ and $-SCH_2CH_2CH_2S-$, of the 1,3-dithiolanes and the 1,3-dithianes, respectively, are of importance in the diagnosis of these compounds. These resonances also depend on the conformation of the rings present in the compounds. The conformational properties of the five or six-membered rings of the dithiolanes and the dithianes, respectively, have been previously studied by proton NMR [5, 8-11]. The 1,3-dithiolane ring is very flexible and exists in a rapid equilibrium, in the NMR time scale, between C_2 half-chair (I) and C_1 envelope (II) conforma-

Table 1

Proton chemical shift values, (ppm), of β-ketodithiolanes and β-ketodithianes in $CDCl_3$ solutions

Compound	Central Part			R_1						R_4
	$CH_{(3)}$	SCH_2	CH_2	CH_3	CH_2	OCH_2	$CH_{(2',6')}$	$CH_{(3',5')}$	$CH_{(4')}$	CH_3
1	3.17	3.30	—	2.15	—	—	—	—	—	1.81
2	3.47	3.34	—	—	—	—	—	—	—	1.91
3	3.78	3.34	—	—	—	—	7.97	7.47	7.55	1.96
4	3.17	3.32	—	1.06	2.45	—	—	—	—	1.86
5	2.90	3.40	—	1.92	—	4.32	—	—	—	1.92
6	3.09	2.90	1.99	2.26	—	—	—	—	—	1.75
7	3.12 [a]	3.24	—	2.23	—	—	—	—	—	—
		3.21								
8	2.88	3.32	—	1.90	—	—	—	—	—	1.90

[a] Non-equivalent

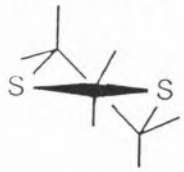
Table 2

^{13}C chemical shifts, δ(ppm), of β-ketodithiolanes and b-ketodithianes in $CDCl_3$ solutions

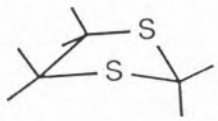
Compound	Central Part					R_1									R_4
	$C_{(1)}$	$C_{(2)}$	$C_{(3)}$	SCH_2	CH_2	CH_3	CH_2	CF_3	OCH_2	$C_{(1')}$	$C_{(2',6')}$	$C_{(3',5')}$	$C_{(4')}$	CO	CH_3
1	204.5	57.8	61.5	38.8	—	30.4	—	—	—	—	—	—	—	—	31.6
2	188.2	52.4	60.2	41.2	—	—	—	115.4	—	—	—	—	—	—	31.5
3	195.8	53.2	62.2	38.5	—	—	—	—	—	135.5	127.3	126.9	132.8	—	31.5
4	207.6	56.8	67.2	39.3	—	31.4	—	—	61.7	—	—	—	—	—	36.4
5	191.5	51.7	61.5	39.9	—	31.0	—	—	53.6	—	—	—	—	158.8	31.3
6	204.4	52.7	45.5	26.5	24.4	27.9	—	—	—	—	—	—	—	—	32.1
7	209.9	60.6	68.4	38.2	—	—	—	—	—	—	—	—	—	—	30.6
				3.21											
8	65.7	58.2	65.7	39.2	—	33.4	—	—	—	—	—	—	—	—	33.4

[a] Non-equivalent

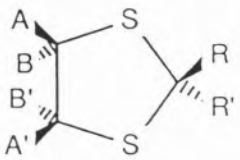
tions [8]. Its $C_{(4)}$ and $C_{(5)}$ protons form an AA'BB' spin system consisting of two pairs of diastereotopic nuclei (III). The $C_{(4)}$ and $C_{(5)}$ methylene protons of the 2,2-assymmetrically



I



II



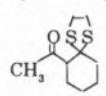
III

disubstituted 1,3-dithiolanes are, however, isochronous in all cases of flexible molecules except in compound **7**, which has a locked structure. Therefore, in the former cases, those methylene protons simplify to a singlet resonance, whereas in **7** they keep their AA'BB' complex pattern. The ^{13}C spectra also give a single resonances for the two cases, respectively. In the 1,3-dithiane **6**, the six-membered ring adopts a chair conformation [9] with the bulky substituent possibly occupying the equatorial position. A thorough study of the conformation of these cycles by NMR would require the measurement of vicinal coupling constants between the ring methylene protons, which would be possible either by direct observation at very low temperatures or indirectly at room temperature from the carbon-13 satellites of the singlet resonance [12].

The literature reports and the present results show that there is a certain degree of selectivity in the reaction of the carbonyl group in assymmetric β-dicarbonyl compounds when they are protected using the synthetic method described in the experimental section. Table 3 compares the isomer ratios of β-ketodithiolanes (dithianes) obtained from assymmetric β-dicarbonyl compounds (diketones and keto esters) and the equilibrium constant K for the enol-enol equilibrium present in $CDCl_3$ solution of those β-dicarbonyl compounds, obtained using ^{13}C NMR spectroscopy [3]. The preferential direction of enolization of the parent dicarbonyls, described by the value of K, was obtained by comparison of the ^{13}C chemical shifts of their two carbonyl compounds with model shift values for those nuclei in the two enol forms possible, using a method which has been described previously in the literature

Table 3

Comparison of the yields and isomer ratios obtained in the synthesis of the β-ketodithiolanes (dithianes) studied with the equilibrium constants K for the enol forms in the corresponding β-dicarbonyl compounds

Compound	R_1	R_4	Yield (%)	K	Isomer ratio	Characterization
1	CH_3	CH_3	95[a]	1.00	—	ref. 7
2	CF_3	CH_3	87	1.38 ± 0.05	19 : 1	b.q. 120°C/0.1mm; Found S, 27.81; calc. S, 27.85
3	C_6H5	CH_3	94	1.21 ± 0.09	19 : 1	ref. 7
4	C_2H_5	CH_3	82	[c]	4 : 1	b.q. 160°C/15mm; Found C, 50.79; H, 7.49; S, 33.95; Calc. C, 50.49; H, 7.41; S, 33.69
5	$COOC_2H_5$	CH_3	80	1.95 ± 0.10	19 : 1	ref. 5
6[b]	CH_3	CH_3	92	1.00	—	ref. 4
7			76	0.67 ± 0.04	9 : 1	b.q. 120°C/0.07mm; Found C, 55.70; H, 7.31; S, 29.63; Calc. C, 55.51; H, 7.45; S, 29.64
IV	CH_3	OC_2H_3	89	>>1	—	ref. 7

[a] The secondary product obtained is the compound with both carbonyl groups protected; [b] β-Ketodithiane compound; [c] Not studied

[13] for compound 3. The values of K obtained for the compounds studied in reference 3, and listed in Table 3, correspond to an application of that method to the compounds listed. A more complete description of that method and the results obtained will be published soon [3]. The constant K is defined in such a way that a value of $K > 1$ means that the carbonyl group closest to the R_1 substituent is preferentially enolized. This comparison shows that there is not a a general correlation between the carbonyl group which enolizes preferentially and the group which is preferentially protected. In fact, while in the linear β-diketones and in the β-ketoester corresponding to IV, the group which is preferentially protected is the one which enolizes to a lesser extent, in the rigid β-diketone corresponding to **7** the preferentially protected group is also the most enolized one. The results obtained therefore indicate that the substituent groups of the β-dicarbonyl compounds affect the point of nucleophilic attack by the bulky dithiolane dianion mainly through stereochemical effects.

CONCLUSION

The synthesis of various β-keto-1,3-dithiolane compounds and of one dithiane analog allowed their characterization by NMR spectroscopy. The five and six-membered rings are quite flexible, generally simplifying the expected spectra.

It was found that preferred directions of enolization of assymmetric β-dicarbonyl compounds do not generally correlate with preferred protection of carbonyl groups in those compounds by formation of 1,3-dithiolane (dithiane) rings, indicating that stereochemical, rather than electronic effects, determine the attack of the bulky dithiolate nucleophile.

ACKNOWLEDGMENTS

This work was supported by INIC and by JNICT, Portugal.

(Received, 6th February, 1987, in revised version 21st January 1988)

REFERENCES

[1] D. SEEBACH, N. R. JONES and E. J. COREY, *J. Org. Chem.*, **33**, 300 (1968).
[2] B. T. GROBEL and D. SEEBACH, *Synthesis*, 357 (1977).
[3] C. F. G. C. GERALDES, M. T. BARROS, C. D. MAYCOCK and M. I. SILVA, J. *Mol. Struct.*, to be published.
[4] I. STAHL, B. SCHRAMM, R. MANSKE and J. GOSSELCK, *Liebigs Ann. Chem.*, 1158 (1982).
[5] I. STAHL, R. MANSKE and J. GOSSELCK, *Chem. Ber.*, **223**, 800 (1980).
[6] P. J. BARRY and B. M. CRAIG, *Can. J. Chem.*, **33**, 716 (1955).
[7] L. A. FEDOROV, M. S. ZHUKOV, N. Y. KORSAKOVA, Y. M. DEDKOV and A. N. ERMATOV, *Izv. Akad. Nauk. SSSR, Ser. Kheim*, 1763 (1984).
[8] L. A. STERNSON, D. A. COVIELLO and R. S. EGAN, *J. Am. Chem. Soc.*, **93**, 6529 (1971).
[9] E. L. ELIEL and R. O. HUTCHINS, *J. Am. Chem. Soc.*, **91**, 2703 (1969).
[10] J. GELAN and M. ANTEUNIS, *Bull. Soc. Chim. Belg.*, **78**, 599 (1969).
[11] E. L. ELIEL, V. S. RAO and F. G. RIDDELL, *J. Am. Chem. Soc.*, **98**, 3583 (1976).
[12] N. SHEPPARD and J. J. TURNER, *Proc. Roy. Soc., Ser. A*, **252**, 566 (1959).
[13] A. A. KOLT'SOV, YU. A. IGNAT'EV, V. V. KOPEIKIN and E. F. PANARIN, *Zh. Org. Khim.*, **12**, 1982 (1976).

RESUMO

Estudos RMN de β-ceto-1,3-ditiolanos e β-ceto-1,3-ditianos

Sintetizaram-se vários β-ceto-1,3-ditiolanos e um β-ceto-1,3-ditiano, tendo sido caracterizados por RMN de protão e de 13C. Verificou-se não haver qualquer correlação geral entre a direcção preferencial de enolização dos compostos β-dicarbonílicos assimétricos parentes e a regioselectividade da protecção dos grupos carbonílicos devido à formação dos anéis 1,3-ditiolano (ditiano). Este facto indica que os efeitos estereoquímicos dos substituintes próximos dos grupos carbonilo são mais importantes do que os efeitos electrónicos no que respeita à definição do ponto de ataque do agente nucleofílico volumoso que é o ditiolato.