Tetrahedron Vol. 43, No. 12, pp. 2709 to 2720, 1987
Printed in Great Britain.

0040-4020/87 $3.00 + .00

REGIOSELECTIVE ELECTROREDUCTION OF 6H-1,3-THIAZINES. COMPARISON WITH CHEMICAL REDUCTIONS
I - INVESTIGATION OF 2-PHENYL-6H-1,3-THIAZINES

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(*Received in Belgium* 28 *January* 1987)

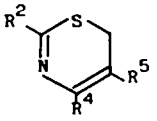
ABSTRACT

The electrochemical reduction of 2-phenyl-6H-1,3-thiazines carried out at a mercury cathode in acetate buffer + ethanol (1:1) has been studied :

- *In the case of compounds monoactivated at carbon 5 (R^5 = CHO or $COCH_3$) either hydrodimers (resulting from coupling at C-2), 3,6-dihydro-2H-1,3-thiazines (reduction of the imine bond) or tetrahydrothiazines can be obtained.*
- *Diactivated 6H-1,3-thiazines (R^4 = CO_2Et, R^5 = CHO or $COCH_3$) successively lead to 5,6-dihydro-4H-1,3-thiazines (reduction of the ethylenic bond) and tetrahydrothiazines.*
- *The reduction of a 6H-1,3-thiazine bearing only one withdrawing group at carbon 4 gives rise to a ring opening.*

At the same time, the action of various chemical reducing agents has been examined : the reduction of the imine bond is performed using $NaBH_3CN$ while $NaBH_4$ or $LiAlH_4$ leads to the reduction of the substituents on the heterocycle.

Many applications of hydrogenated derivatives of 6H-1,3-thiazines 1 have been reported : 2,3-dihydro compounds 2 have been used in cephalosporine synthesis[1] ; some 4,5-dihydro derivatives 3 exhibit herbicid properties[2] while tetrahydrothiazines 4 have been used in radioprotection[3] .



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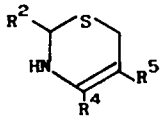

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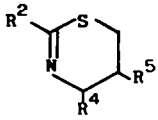

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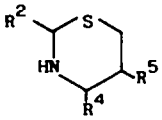

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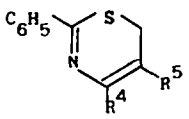
Generally, these compounds are not prepared by reduction of the corresponding thiazines. However we have recently observed[4] that regioselective reduction can be achieved by controlled potential electrolysis.

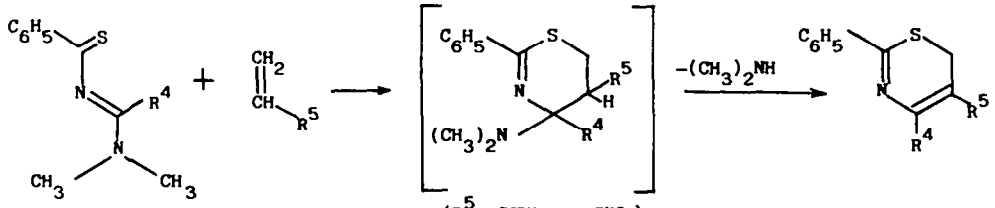
- The present paper is devoted to the study of 2-phenyl-6H-1,3-thiazines (compounds 1a to 1f), selected to investigate the influence of R^4 and R^5 substituents on the electroactivity



1a R^4 = H R^5 = CHO
1b R^4 = H R^5 = $COCH_3$
1c R^4 = CH_3 R^5 = $COCH_3$
1d R^4 = CO_2Et R^5 = CHO
1e R^4 = CO_2Et R^5 = $COCH_3$
1f R^4 = CO_2Et R^5 = 

of the heterocyclic structure. The results of electrolytic reductions will be compared to those obtained with various chemical reducing agents : aluminium amalgam, lithium aluminium hydride, borohydrides or triethylsilane.

The studied compounds have been prepared by cyclocondensation 4+2 between a N'-thioacylformamidine and methylvinylketone or acroleine :



(R^5 = $COCH_3$ or CHO)

As a logical extension of our work, investigation of 6H-1,3-thiazines bearing a heteroatomic group at C-2 will be reported in a future publication.

ELECTROCHEMICAL BEHAVIOUR OF 2-PHENYL-6H-1,3-THIAZINES

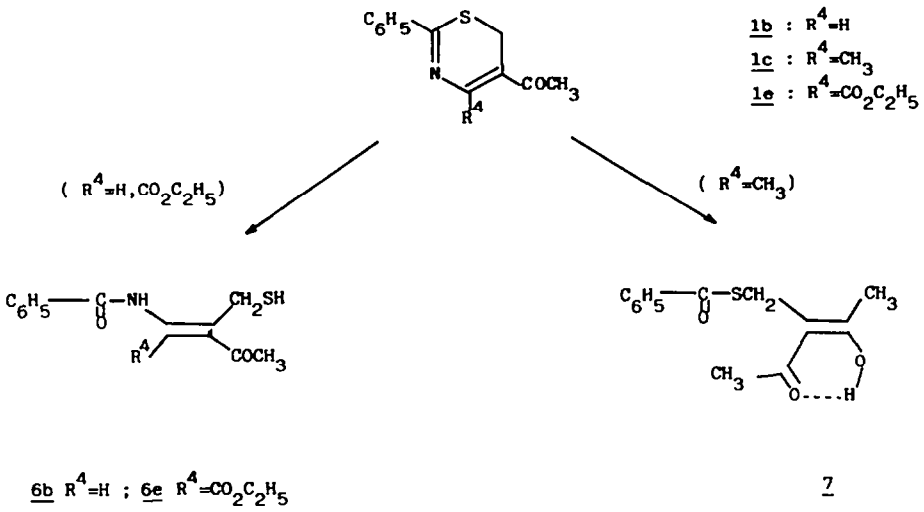
1 - PRELIMINARY STUDY : STABILITY OF THE SUBSTRATES IN PROTIC MEDIA

During the polarographic study in an acidic hydroalcoholic medium, we have observed a degradation of 2-phenyl-6H-1,3-thiazines :

- This instability is important in a mixture of 0.5 M sulphuric acid and ethanol (1:1 v/v) ; for compound 1f, it begins by a deprotection of the aldehyde group.
- In a mixture of 0.5 M acetate buffer and ethanol (1:1), this instability gets slower, specially when R^4 is a carbethoxy group (*), leading to a compound that gives a two-electron cathodic wave at -1.2 V vs.SCE and an anodic wave at -0.4 V vs. SCE.

In order to explain this phenomena the behaviour of 5-acetyl-2-phenyl-6H-1,3-thiazines in sulphuric acid has been observed : 1b and 1e yield linear enamides 6b (55% yield) and 6e (75%) while 1c gives a linear thioester 7 (75%).

(*) We have controlled that the substrate evolution can be neglected during preparative electrolysis, specially when the experiments are carried out at 0°C.



6b R4=H ; 6e R4=CO2C2H5 7

Taking account of these results, the polarographic measurements and the preparative electrolysis have been carried out in acetate buffer only.

2 - POLAROGRAPHIC STUDY IN ACETATE BUFFER + ETHANOL (1:1)

The half-wave potentials, recorded in dilute solutions, are given in table I, showing three classes of 6H-1,3-thiazines :

TABLE I

Half-wave potentials recorded for 2-phenyl-6H-1,3 thiazines in a mixture of acetate buffer and ethanol (1:1).

Substrate concentration $C_s = 5.10^{-4}$ M

Drop period $\tau = 3s$.

6H-1,3 Thiazine	First wave (2e) $E_{1/2}$ (V.vs.SCE)	second wave (2e) $E_{1/2}$ (V.vs.SCE)
1a	- 0.67(*)	
1b	- 0.67(*)	
1c	- 0.72	
1d	- 0.48	- 1.05
1e	- 0.52	- 1.15
1f	- 0.79	

(*) Splitting in two monoelectronic waves for $C_s > 5.10^{-3}$ M.

- In the case of 1a, 1b and 1c, monoactivated at carbon 5, a two-electron wave ($E_{1/2}$ = - 0.7 V vs.SCE) is observed. For the two first compounds, it splits in two monoelectronic waves in more concentrated solutions ; separation between these two waves increases with the substrate concentration and the mercury drop period. Such a behaviour is characteristic of the duplication of the first reduction step[5].

- Polarograms of 1d and 1e, diactivated at C-4 and C-5 are peculiar since they present two cathodic waves, each one corresponding to a two-electron reduction.

- At last, for 1f, $E_{1/2}$ is about -0.8 V vs.SCE in dilute solution and becomes more cathodic as the substrate concentration increases or the drop period falls.

3 - VOLTAMMETRIC STUDY IN APROTIC MEDIUM

As will be seen further, the above classification corresponds to three kinds of different behaviour in preparative electrolysis. In order to get more informations about reduction mechanisms, we have performed a voltammetric study in aprotic medium, studying one compound of each class (thiazines 1a, 1e and 1f)[6]. Experiments were carried out at a hanging mercury drop in DMF.

6H-1,3-thiazine 1b (see figure 1)

The voltammogram of 1b shows a capacitive peak followed by a one-electron irreversible peak corresponding to the formation of an anion-radical. Then a two-electron reduction peak appears at a 0.55 V more cathodic potential.

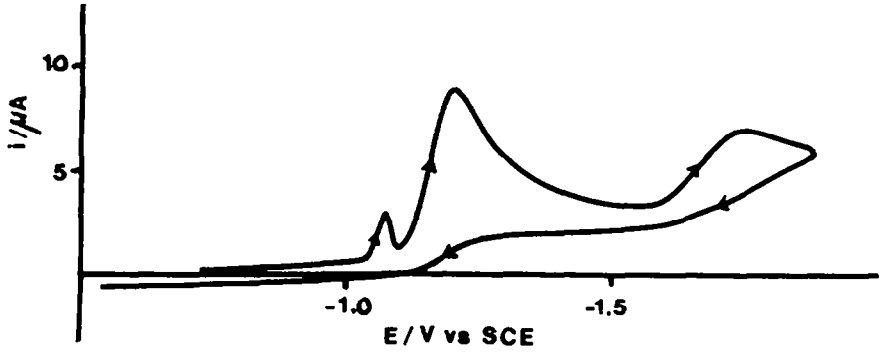


Fig.1: Cyclic voltammogram of 2.10^{-3}M thiazine 1b: Hg electrode; dry DMF + $Bu_4N^+ClO_4^-$; 25°C; Sweep rate= 0.050 V.s^{-1}.

The anion-radical resulting from the monoelectronic reduction of 6H-1,3-thiazine 1b is stable but disappears owing to a chemical dimerization that will be described later.

6H-1,3-thiazine 1e (see figure 2)

Again two cathodic peaks appear but the separation is now 0.30 V. The first monoelectronic peak is reversible : the anion-radical resulting from 1e does not dimerize quickly and consequently differs from the one formed by reduction of 1b.

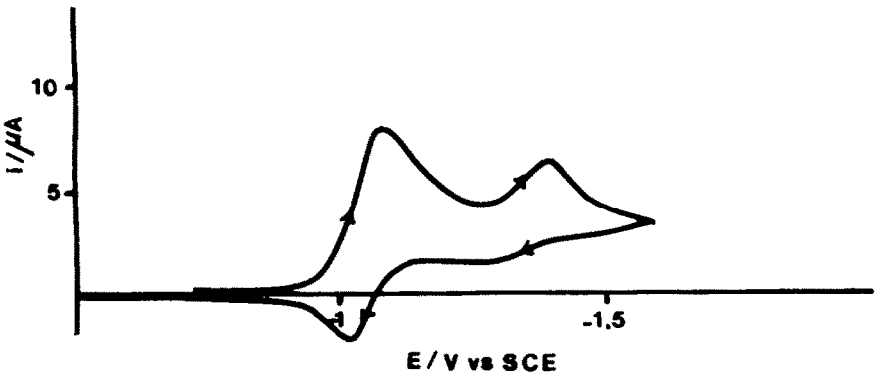


Fig.2: Cyclic voltammogram of 2.10^{-3}M thiazine 1e (conditions see fig.1).

6H-1,3-thiazine 1f (see figure 3)

A different cyclic voltammetric curve is obtained. By comparison with Figs. 1 and 2, we notice that the first irreversible peak corresponds to a two-electron process. It is followed by another irreversible reduction at very negative potentials.

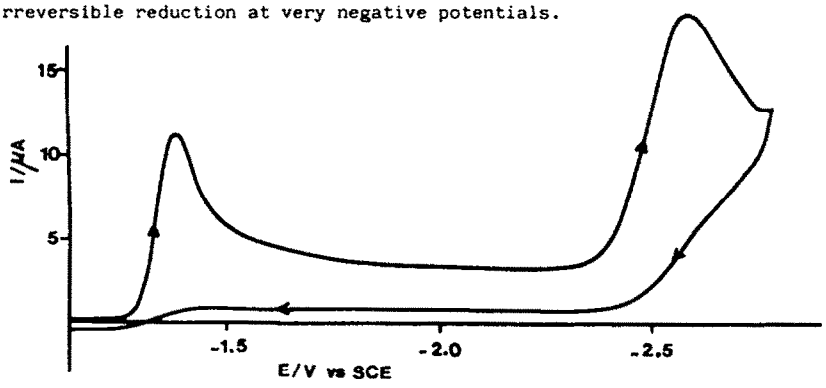


Fig.3 : Cyclic voltammogram of 2.10^{-3}M thiazine 1f (conditions see Fig.1).

The anion-radical is there unstable and leads to an intermediate, more easily reducible than the substrate, giving rise to a ring-opening reaction that will be detailed further.

REDUCTION OF 2-PHENYL-6H-1,3-THIAZINES

1 - 6H-1,3-THIAZINES MONOACTIVATED AT CARBON 5 (compounds 1a, 1b and 1c)

i) Electrochemical reductions

In the concentration range used in preparative electrolysis (5.10^{-2} M), compounds 1a and 1b show two well-separated monoelectronic waves.

- When carried out at the foot of the first wave (working potential E = -0.65 V vs.SCE for 1a and -0.80 V vs.SCE for 1b), reductions lead to hydrodimers 5a (70 % yield) and 5b (80 %), resulting from coupling at C-2 (see Scheme 1). A comparable behaviour has already been reported for thiazinium cations, whose reduction also afford dimers resulting from coupling at C-6 position[7].

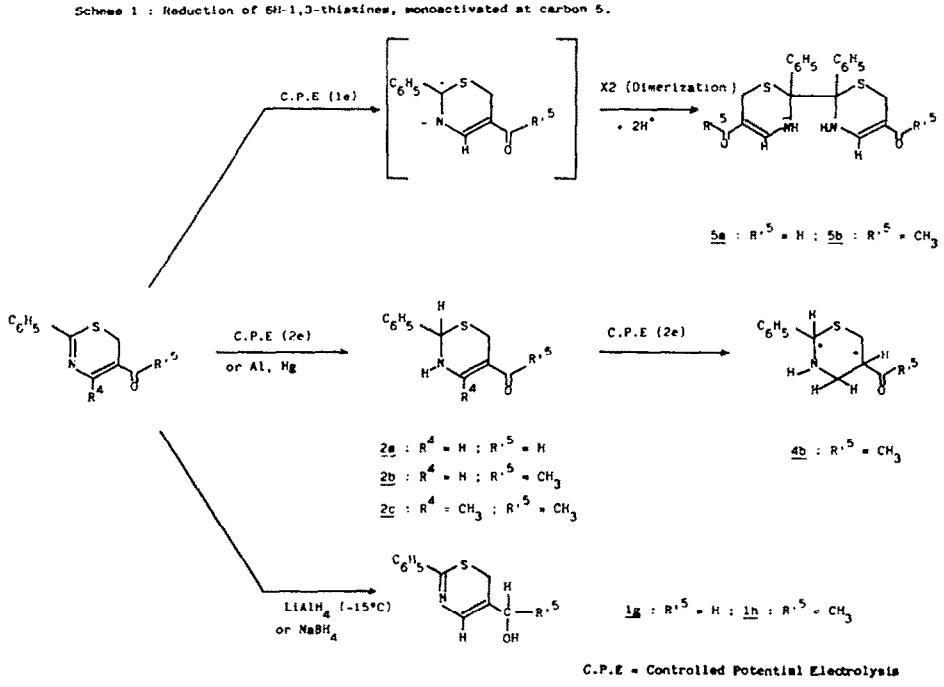
- When performed at the plateau of the two-electron wave (E = -1.15 V vs.SCE for 1a and -1.40 V vs.SCE for 1b), electrolysis yield the 2,3-dihydro compounds 2a (70 %) and 2b (75 %) resulting from hydrogenation of the imine bond[8].

Electroreduction of 1c is a two-electron process, leading to the dihydro-2,3 derivative 2c (60 %) (E = -1.15 V vs.SCE). Even at high concentration, no splitting of the wave can be observed, probably because the lifetime of the intermediate anion-radical is not long enough.

According to the informations resulting from voltammetry in DMF, the following mechanism can be suggested : monoelectronic reduction of these 6H-1,3-thiazines lead to an anion-radical which either dimerizes (lack of reversibility for the first reduction peak) or adds a proton and gives a radical whose reduction, followed by another protonation, furnishes the dihydro-2,3 compound.

Note : The dihydro compounds 2 are reducible in a more acidic medium : sulphuric acid 0.5 M + ethanol (1:1). Thus, electroreduction of 2b at -1.1 V vs.SCE is a two-electron process and a mixture of the tetrahydro diastereoisomers 4b (see Scheme 1) is obtained.

Scheme 1 : Reduction of 6H-1,3-thiazines, monoactivated at carbon 5.



ii) Chemical reductions

The dihydro compounds 2a and 2b can also be prepared by reaction of the corresponding 6H-1,3-thiazines with :

- borane in THF (20 % yield)
- sodium cyanoborohydride in ethanol with controlled acidic pH (2a:40 % ; 2b:70%)
- aluminium amalgam in methanol (2a:50 % ; 2b:90 %).

Selective reduction of the carbonyl group at C-5 that leads to the alcohols 1g and 1h can be performed using :
- sodium borohydride in THF (1g:85 % ; 1h:55 %)
- lithium aluminium hydride in ether at -15°C (1h:75 %).

Nevertheless if selective reduction of the imine bond or of the carbonyl group at C-5 is possible, we never have observed regioselective reduction of the ethylenic bond for this class of 6H-1,3-thiazines.

2 - DIACTIVATED 6H-1,3 THIAZINES (compounds 1d and 1e)

i) Electrochemical reductions

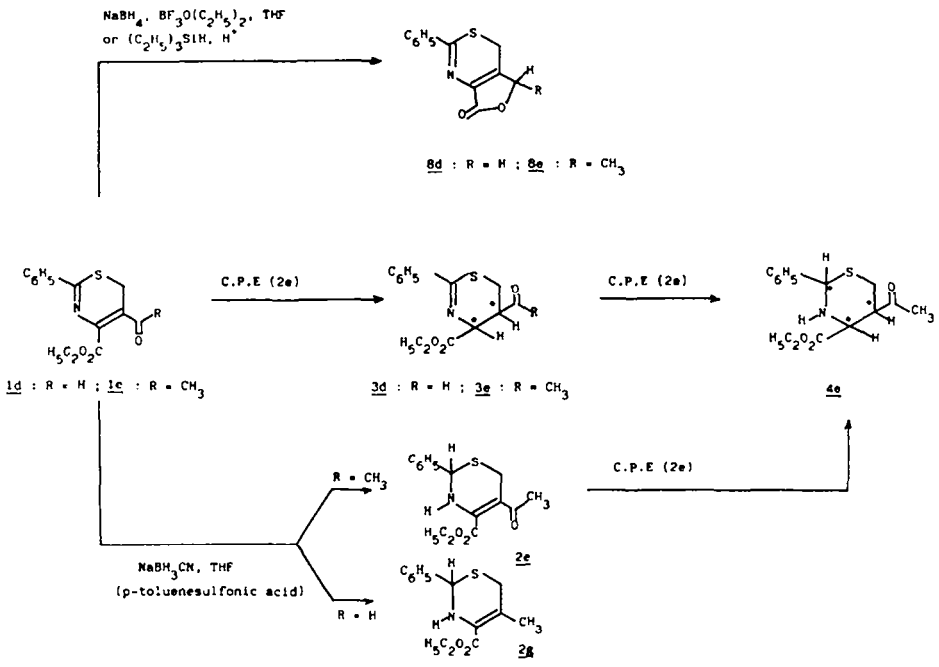
These thiazines give two well-separated polarographic waves. Electroreduction at the plateau of the first one (E = -0.80 V vs.SCE) is a two-electron process and electrolysis yields an isomeric mixture of the respective 5,6-dihydro-4H-1,3-thiazines (compounds 3d (75 % yield) and 3e (80 %) (cis:trans 3:1) see Scheme 2).

The second electron withdrawing substituent at C-4 decreases the electronic density of the ethylenic bond which is then more easily reducible than the imine bond. The stereochemistry of this electro-dihydrogenation is probably induced by the adsorption of the substrates (an adsorption peak is observed on polarograms in concentrated solutions) ; as a result, coperiplanar approach of protons is then favoured.

A preparative electrolysis carried out at -1.30 V vs.SCE (plateau of the second wave) affords the tetrahydro derivative 4e (75 %).

The electroactivity of the heterocycle is modified by the introduction of a carbethoxy group at C-4 ; moreover, the imine bond of 5,6-dihydro-4H-1,3-thiazines 3 is more difficult to reduce ($E_{\frac{1}{2}}$ = -1.1 V vs.SCE) than the one of 6H-1,3-thiazines 1.

Scheme 2 : Reduction of diactivated 6H-1,3-thiazines



ii) Chemical reductions

Different compounds can be obtained by chemical reductions :

- The carbonyl group of the substituent linked to C-5 is reduced by *in situ* generated borane in THF (reaction of sodium borohydride with BF_3 $O(C_2H_5)_2$)[9] or by triethylsilane in the presence of trifluoroacetic acid. The intermediate alcohols cyclise to lactones 8d (40 % yield) and 8e (50 %). It is worth noting that reaction of triethylsilane with α-βethylenic ketones generally leads to selective reduction of the ethylenic bond[10].

- The imine bond can be reduced by sodium cyanoborohydride in THF[11]. For 1e a selective reduction of this function is observed that yields 2e (75 %). For 1d a simultaneous reduction of the aldehyde group occurs and 4-carbethoxy-5-methyl-2-phenyl-3,6-dihydro-2H-1,3-thiazine 2g is obtained (50 %).

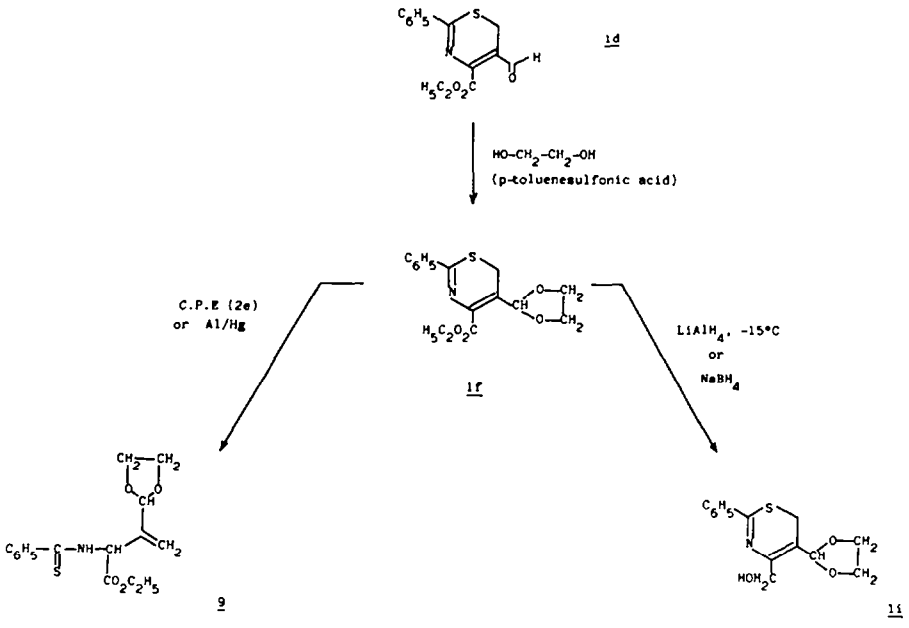
Concerning this class of 6H-1,3-thiazines, chemical and electrochemical reductions are complementary methods : they allow regioselective hydrogenations of the reducible bonds with preservation of the heterocyclic structure.

Note : The polarogram of derivative 2e shows a two-electron reduction wave ($E_{\frac{1}{2}}$ =-0.90 V vs.SCE) ; preparative electrolysis leads to the tetrahydro compound 4e (75 %); by comparison with the 6H-1,3-thiazine 1e, the ethylenic bond is more difficult to reduce in 3,6-dihydro-2H-1,3-thiazines.

3 - 6H-1,3-THIAZINE MONOACTIVATED AT CARBON 4 (compound 1f)

Protection of the aldehyde group of compound 1d is performed with ethyleneglycol in the presence of small amounts of p-toluenesulfonic acid[12,13] and leads to 6H-1,3-thiazine 1f (70 % yield) bearing only one withdrawing substituent at C-4 (see Scheme 3).

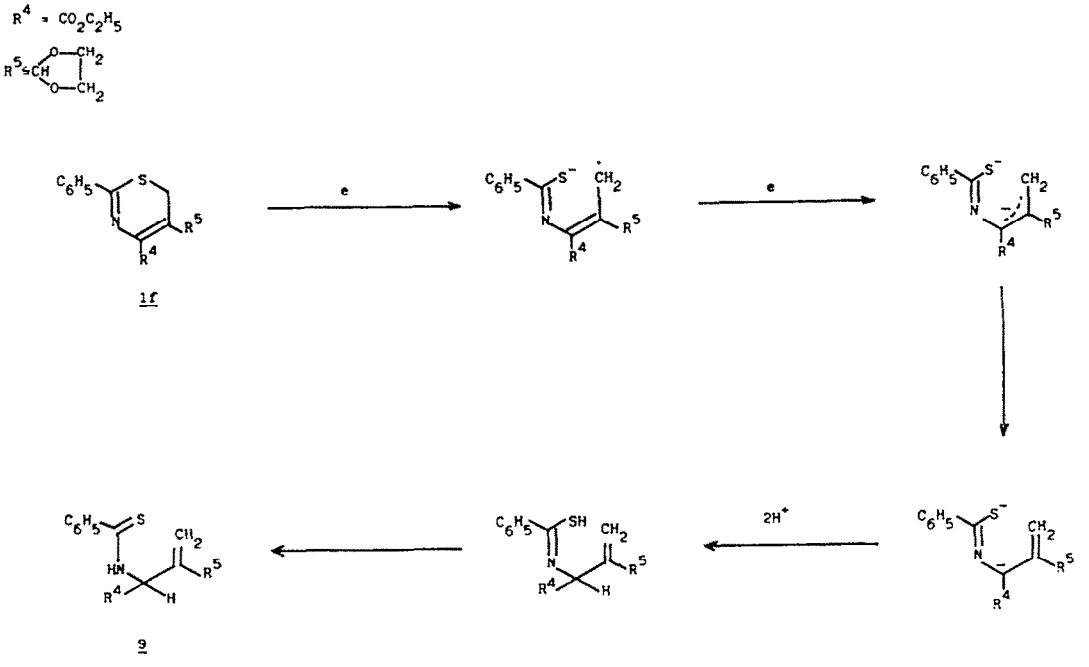
Scheme 3 : Reduction of a 2-phenyl-6H-1,3-thiazine monoactivated at carbon 4



i) Electrochemical reduction

The linear thioamide 9 (80 % yield) (see Scheme 3) is obtained when an electroreduction is carried out at the plateau of the two-electron wave (E =-1.25 V vs.SCE) ; in this case a ring opening occurs. It is worth remembering that the voltammetry in DMF of 1f gives a two-electron irreversible peak indicating instability of the anion-radical. The following mechanism may there be suggested : the first electronic transfer involves a cleavage of the S—C-6 bond (see Scheme 4) ; the resulting anion-radical is then immediately reduced. Such a cleavage of a carbon-heteroatom bond from the allyl position has already been noticed in the electroreduction of cephalosporine derivatives[14]. It is followed by a migration of the double bond, the negative charge of the carbanion being located α to the carbethoxy group.

Scheme 4 : Mechanism of electroreduction of 6H-1,3-thiazine 1f



ii) Chemical reductions

Deprotection of the aldehyde group is observed during chemical reductions in acidic medium and unreliable results are obtained.

An aluminium amalgam reduction, in methanolic solution, leads to the same result as the electrochemical path (60 % yield).

The regioselective reduction of the ester function into alcohol (compound 1i : see Scheme 3) is performed using sodium borohydride in THF or lithium aluminium hydride in ether 75 %(yield) ; as expected, the reduction is faster with $LiAlH_4$ and gives better yields.

CONCLUSION

The reductions of 2-phenyl 6H-1,3-thiazines in various conditions afford different results, the behaviour of the substrates being drastically dependent on the heterocyclic substitution.

Electrochemical reductions occur either at the imine bond or at the ethylenic bond but can also lead to a ring opening.

Chemical reductions are complementary with the former method as they allow selective reduction of the imine bond (sodium cyanoborohydride) or of the ring substituents (sodium borohydride or lithium aluminium hydride).

These first results prompt us to investigate other 6H-1,3thiazines bearing other substituents at C-2.

EXPERIMENTAL

ELECTROCHEMISTRY

i) Polarography

Polarograms were recorded with a three electrodes TIPOL TACUSSEL polarograph. The substrate concentration was 5.10^{-4} M in a mixture of aqueous acetate buffer (CH_3COOH 0.5 M and $NaCH_3CO_2$ 0.5 M) and ethanol (1:1).

ii) Voltammetry

Voltamperometric curves were registered with a UAP 4 TACUSSEL unit, coupled with an X-Y recorder. The working electrode was a hanging mercury drop and solutions were 2.10^{-3} M in DMF, containing tetraethylammonium as supporting electrolyte.

iii) Macroscale electrolysis

Preparative electrolysis were carried out at a mercury pool electrode in the cell described by **MOINET and PELTIER**[15]. A TACUSSEL PRT potentiostat was used and the amount of electricity was measured with a TACUSSEL IGS coulometer.

For a typical run, 10^{-2} to 10^{-3} mole of the substrate was dissolved in 150 cm^3 of catholyte (of same composition as in polarographic investigations). Electrolysis were then performed under a continuous nitrogen flow. An auxiliary polarographic device was used : polarograms were recorded during electrolysis in order to control advancement of the reduction or to detect evolution of the reduced compound.

After complete electrolysis, work-up of the catholyte was made as follows : decantation of mercury, removal of ethanol under reduced pressure, neutralization of the residual solution and extraction with dichloromethane. The organic layer was then dried on magnesium sulphate and the reduced compound collected after evaporation of the organic solvent.

2 - SPECTROSCOPY

^1H NMR spectra were obtained on a PERKIN ELMER R 24 B spectrometer (60 MHz) or a CAMECA spectrometer (250 MHz). ^{13}C NMR spectra were taken on a BRUKER spectrometer (90 MHz). IR spectra (as KBr pellets unless otherwise stated) were recorded with a UNICAM SP 1000 Spectrometer. Mass spectrometry studies were carried out with a VARIAN MAT 112 unit (70 eV).

3 - SUBSTRATES SYNTHESIS

Melting points given in the following were obtained on a REICHERT apparatus. Chromatographies were carried out on silica gel columns (95 x 2.5 cm, Kieselgel 60 MERCK, 230-240 mesh ASTM). The preparation procedure for 6H-1,3-thiazines 1a, 1b, 1c, 1d, 1e and 1g has been already reported[8,16].

Compound 1f

6H-1,3-thiazine 1d (4 mmol) and ethyleneglycol (12 mmol) were refluxed together in benzene (50 cm^3) containing small amounts of p-toluene sulfonic acid during 6 hrs. The water resulting from reaction was removed with a Dean and Stark separator. The mixture was then washed with a $NaHCO_3$ saturated solution and the aqueous layer extracted with ethyl acetate. The resulting organic layers were dried before solvent removal under reduced pressure. Purification of the residual oils by chromatography (elution with 40 % ethyl acetate/hexane) gave 1f, m.p. 77°C. Calculated for $C_{16}H_{17}NO_4S$ (found) : C 60.17 (59.49) ; H 5.37 (5.32) ; S 10.04 (10.01). IR : 1735 cm^{-1} . ^1H NMR ($CDCl_3$) δ 5.4 (1H, s, O-CH-O), 4.35 (2H, q, J = 7 Hz, ester), 4.0 (4H, s, acetal), 3.5 (2H, s, C-6), 1.40 (3H, t, J = 7 Hz, ester). Higher mass recorded in MS : m/z = 319 ($M^{+\cdot}$).

Compound 1h

6H-1,3-thiazine 1b (2 mmol) in dry Et_2O (20 cm^3) was added dropwise to a stirred suspension of $LiAlH_4$ (4 mmol) in dry Et_2O (30 cm^3), cooled at -15°C under nitrogen. After 1 hr the reaction mixture was poured into a 10 % water/ether mixture. Extraction was carried out with CH_2Cl_2 and the organic layer was washed with water and dried over $MgSO_4$. Solvent removal under reduced pressure led to an oil which after chromatography (elution with 50 % ethyl acetate/hexane) gave 2h. ^1H NMR ($CDCl_3$) δ 7.0 (1H, s, vinylic CH), 4.4 (1H, q, J = 6 Hz), 3.4 (2H, s, C-6), 1.3 (3H, d, J = 6 Hz, CH_3). Higher mass recorded in MS : m/z = 219 ($M^{+\cdot}$).

Compound 1i

The above procedure was applied, starting with 6H-1,3-thiazine 1f. Chromatographic purification (elution with 45 % ethyl acetate/hexane) led to 1i. Crystallization from ethanol gave white crystals : m.p. 106-108°C. Calculated for $C_{14}H_{15}NO_3S$ (found) : C 60.63 (60.07), H 5.45 (5.19), N 5.05 (5.05). IR : 3430 cm^{-1} . ^1H NMR ($CDCl_3$) δ 5.7 (1H, s, O-CH-O), 4.5 (2H, s, CH_2 alcohol), 4.0 (4H, s, acetal), 3.45 (2H, s, C-6), 3.05 (1H, s, OH).

4 - OBTENTION AND CHARACTERIZATION OF THE REDUCTION COMPOUNDS[17]

i) Reduction of the imine bond

5-Formyl-2-phenyl-3,6-dihydro-2H-1,3-thiazine (2a) and 5-acetyl-2-phenyl-3,6-dihydro- 2H-1,3-thiazine (2b)

Electroreduction of 6H-1,3-thiazines 1a and 1b was performed, at 0°C, at -1.15 V vs.SCE for 1a and -1.40 V vs.SCE for 1b. The corresponding 2,3-dihydrothiazines were obtained and crystallized (ethanol) straight after extraction.

These compounds have already been prepared by reduction of the starting thiazines with either sodium cyanoborohydride or triethylsilane[2]. They can as well be obtained using the following procedure : (BF_3, THF) or (BH_3, $S(CH_3)_2$) (4 mmol) is added to a stirred solution of thiazine 1a or 1b (3 mmol) in dry THF at 0°C, under nitrogen. After 24 hrs, acetic acid (1 cm^3) is added to the reaction mixture and solvent is removed under reduced pressure.

5-Acetyl-4-methyl-2-phenyl-3,6-dihydro-2H-1,3-thiazine (2c)

To a freshly prepared aluminium amalgam (8 mmol) (an Al foil is stirred in an aqueous 5 % mercuric chloride solution until gaz evolution is observed ; the solution is decanted and the foil washed with water and ethanol and immediately used) was added, at room temperature, a solution of thiazine 1c (2 mmol) in methanol (20 cm^3) containing 0.5 cm^3 of water. Under stirring, a mild exothermic reaction occured and the Al foil dissolved within 2 hrs. The mixture was then filtered and the solid residue washed with methanol. Solvent removal gave a brown oil which was crystallized from ethanol as white crystals of 2c, m.p. : 153-154°C.

Electroreduction of 1c at -1.15 V vs.SCE and 0°C also led to 2c. IR : 3280, 1660 cm^{-1}. ^1H NMR (DMSO) δ 7.8 (1H, d, J = 4 Hz, NH), 5.6 (1H, d, J = 4 Hz, C-2), 3.3-3.8 (2H, AB quartet, J = 15 Hz, C-6), 2.2-2.4 (6H, 2s, methyl and methyl of acetyl). Higher mass recorded in MS : m/z = 233 ($M^{+\cdot}$).

5-Acetyl-4-carbethoxy-2-phenyl-3,6-dihydro-2H-1,3-thiazine (2e)

Sodium cyanoborohydride (4 mmol) and bromocresol green as pH indicator were added to a stirred solution of 6H-1,3-thiazine 1e in dry THF (30 cm³). The acidity was kept constant by dropwise addition of a p-toluenesulfonic solution (1 g in 20 cm³ THF) to maintain the solution yellow coloured. The solvent was removed under reduced pressure, the residue washed with water and extracted with ethyl acetate. After drying the organic layer ($MgSO_4$), the solvent was removed and the residual purified by chromatography (elution with 30 % ethyl acetate/hexane) to give 2e. Recrystallization from ether gave white crystals, m.p. 116-117°C. Calculated for $C_{15}H_{17}NO_3S$ (found) : C 61.83 (61.55), H 5.88 (5.64), S 11.00 (10.99), N 4.81 (4.90). IR : 3330, 1735, 1660 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.10 (1H, d, J = 4 Hz, NH), 5.4 (1H, d, J = 4 Hz, C-2), 4.3 (2H, q, J = 7 Hz, ester), 3.2-3.7 (2H, AB quartet, J = 16 Hz, C-6), 2.1 (3H, s, methyl ketone), 1.3 (3H, t, J = 7 Hz, ester). ^{13}C NMR ($CDCl_3$) δ 195.0 (ketone), 144.4 (vinylic), 106.4 (vinylic), 58.4 (C-2), 26.1 (C-6). Higher mass recorded in MS : m/z = 291 ($M^{+\cdot}$).

4-Carbethoxy-5-methyl-2-phenyl-3,6-dihydro-2H-1,3-thiazine (2g)

The above procedure was applied starting with 6H-1,3-thiazine 1d. Purification by chromatography (elution with 10 % ethyl acetate/hexane) gave 2g as a colourless oil. IR (thin film) : 3300, 1720 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.35 (1H, d, J = 4 Hz, C-2), 4.35 (3H, m, CH_2 ester and NH), 3.25-3.70 (2H, AB quartet, J = 17.5 Hz, C-6), 2.2 (3H, s, methyl), 1.3 (3H, t, J = 7 Hz, ester). Higher mass recorded : m/z = 263 ($M^{+\cdot}$).

ii) Reduction of the ethylenic bond

The following 5,6-dihydro-4H-1,3-thiazines were obtained by electrolysis of 6H-1,3thiazines 1d and 1e at -0.8 V vs.SCE.

4-Carbethoxy 5-formyl 2-phenyl 5,6-dihydro 4H-1,3 thiazine (3d)

Colourless oil after chromatographic purification (elution with 30 % ethyl acetate/hexane). ^1H NMR ($CDCl_3$) δ 9.8 (1H, s, CHO), 5.0 (1H, d, J = 7 Hz, C-4), 4.35 (2H, q, J = 7 Hz, ester), 3.0-3.45 (3H, m, C-6 and C-5), 1.35 (3H, t, J = 7 Hz, ester). Higher mass recorded : m/z = 277 ($M^{+\cdot}$).

5-Acetyl 4-carbethoxy 2-phenyl 5,6-dihydro 4H-1,3-thiazine (3e)

White crystals, m.p. 46-47°C. Calculated for $C_{15}H_{17}NO_3S$ (found) : C 61.83 (61.72), H 5.88 (5.78), S 11.00 (10.87). ^1H NMR ($CDCl_3$) δ 5.2 (1H, d, J = 3 Hz, C-4 trans), 4.9 (1H, d, J = 9 Hz, C-4 cis), 4.35 (2H, q, J = 7 Hz, ester), 3.0-3.45 (3H, m, C-6 and C-5), 2.4 (3H, s, methyl ketone), 1.35 (3H, t, J = 7 Hz, ester). Higher mass recorded : m/z = 291 ($M^{+\cdot}$).

iii) Tetrahydro compounds

5-Acetyl-2-phenyl-3,4,5,6-tetrahydro-2H-1,3-thiazine (4b)

Electroreduction of 2b was carried out at -1.3 V vs.SCE. 4b was purified by chromatography eluting with 50 % ethyl acetate/hexane. Crystallization from ether gave white crystals, m.p. 89-91°C. Calculated for $C_{12}H_{15}NOS$ (found) : C 65.12 (64.42), H 6.83 (6.91), N 6.33 (6.25), S 14.49 (14.14).

IR : 3290, 1705 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.15 (1H, s, C-2), 3.5-3.9 (4H, m, C-4, C-5 and C-6), 2.25 (3H, s, methyl ketone), 1.6 (1H, br. s, NH). ^{13}C NMR ($CDCl_3$) δ 207.3 (ketone), 63.5 (C-2), 47.2 (C-4), 41.3 (C-5), 29.1 (C-6). Higher mass recorded : m/z = 221 ($M^{+\cdot}$).

5-Acetyl-4-carbethoxy-2-phenyl-3,4,5,6-tetrahydro-2H-1,3-thiazine (4e)

Electroreduction of 1e was carried out at -1.3 V vs.SCE. 4e was purified by chromatography, eluting with 30 % ethyl acetate/hexane. Crystallization from ether gave white crystals, m.p. 135-136°C. Calculated for $C_{15}H_{19}NO_3S$ (found) : C 61.41 (61.09), H 6.53 (6.46), N 4.77 (4.80).

IR : 3320, 1735, 1710 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.15 (1H, s, C-2), 3.9 (1H, d, J = 10.5 Hz, C-4), 2.95-3.00 (3H, m, C-5 and C-6), 2.25 (3H, s, methyl ketone), 2.1 (1H, br.s, NH). ^{13}C NMR ($CDCl_3$) δ 208.9 (ketone), 62.1 and 65.2 (C-2 and C-4), 50.3 (C-5), 31.6 (C-6). Higher mass recorded : m/z = 293 ($M^{+\cdot}$).

iiii) Other reduction compounds

hydrodimers (5a and 5b)

Electroreduction of 6H-1,3-thiazines 1a and 1b was performed at 0°C and E = -0.65 V vs SCE (1a) or E = -0.80 V vs.SCE (1b). Hydrodimers completely precipitate in the electrolysis cell as white solids isolated by filtration 5a and 5b.

Compound 5a : m.p. 212-214°C. IR : 3280, 1590 cm^{-1}. ^1H NMR (CF_3COOD) δ 8.30 (1H, s, CHO), 8.60 (1H, s, NH), 2.90-3.90 (2H, AB quartet, J = 16 Hz, C-6). Higher mass recorded : m/z = 408 ($M^{+\cdot}$).

Compound 5b : m.p. 218-220°C. IR : 3300, 1590 cm^{-1}. ^1H NMR (CF_3COOD) δ 8.80 (1H, s, NH), 2.85-3.95 (2H, AB quartet, J = 16 Hz, C-6), 2.55 (3H, s, methyl ketone). Higher mass recorded : m/z = 436 ($M^{+\cdot}$).

Lactones (8d and 8e)

6H-1,3-thiazine 1d or 1e (4 mmol) was stirred in dry THF (20 cm^3) at -20°C, under nitrogen. BF_3 etherate (4.1 mmol) and next a suspension of $NaBH_4$ (4.1 mmol) in THF (20 cm^3) was added. The resulting mixture was stirred at 0°C for 1 hr, then at room temperature for 3 hrs. The solution was poured on to a mixture of water (20 cm^3) and acetic acid (10 cm^3). The aqueous layer was extracted with CH_2Cl_2 and the organic layer washed with water and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue chromatographied (elution with 60 % ethyl acetate/hexane) to yield 8d and 8e as white crystals (ethyl acetate).

Compound 8d : m.p. 184-186°C. Calculated for $C_{12}H_{9}NO_2S$ (found) : C 62.32 (62.06), H 3.92 (3.75), N 6.06 (6.10). IR : 1765 cm^{-1}. ^1H NMR (DMSO) δ 5.1 (2H, s, lactone), 4.25 (2H, s, C-6). Higher mass recorded : m/z = 231 ($M^{+\cdot}$). Compound 8e : m.p. 149-150°C. Calculated for $C_{13}H_{11}NO_2S$ (found) : C 63.65 (63.68), H 4.52 (4.47), N 5.71 (5.54), S 13.07 (13.23). IR : 1770 cm^{-1}. ^1H NMR (DMSO) δ 5.3 (1H, q, J = 6.5 Hz, lactone), 4.25 (2H, s, C-6), 1.3 (3H, d, J = 6.5 Hz, methyl). ^{13}C NMR (DMSO) 168.3 and 164.1 (C-2 and ketone), 139.7 (vinylic), 133.6 (vinylic), 76.5 (CH lactone), 22.9 (C-6), 17.6 (CH_3). Higher mass recorded : m/z = 245 ($M^{+\cdot}$).

Linear thioamide (9)

This compound was prepared on treatment of 6H-1,3-thiazine 1f with aluminium amalgam in the same way as previously described (preparation of 2c). After chromatographic purification of the crude reaction mixture (elution with 40 % ethyl acetate/hexane), 9 was obtained , m.p. 79-81°C. Electroreduction of 1f at -1.25 V vs.SCE also led to compound 9. Calculated for $C_{16}H_{19}NO_4S$ (found) : C 59.79 (60.06), H 5.96 (5.99), N 4.36 (4.32). IR : 3280, 1755 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.80 (1H, d, J = 8 Hz, NH), 6.10 (1H, d, J = 8 Hz, allylic CH), 5.70 (2H, s, vinylic CH_2), 5.40 (1H, s, acetal), 4.30 (2H, q, J = 7 Hz, ester), 4.0 (4H, s, CH_2 acetal), 1.30 (3H, t, J = 7 Hz, ester). ^{13}C NMR ($CDCl_3$) δ 198.3 (thioketone), 141.4 (vinylic), 124.0 (vinylic CH_2), 104.6 (CH acetal), 60.6 (CH). Higher mass recorded : m/z = 321 ($M^{+\cdot}$).

5 - EVOLUTION OF 6H-1,3-THIAZINE IN DILUTE SULPHURIC ACID

2-Acetyl-1-benzamido-3-mercaptopropene (6b)

6H-1,3-thiazine 1b (5 mmol) was stirred in a mixture of ethanol and aqueous sulphuric acid 0.5 N (1:1 v/v, 60 cm^3) at 50°C during 3 hrs. The solvent was removed under reduced pressure and the residue extracted with CH_2Cl_2. The organic layers were washed with water, dried ($MgSO_4$) and the solvent was removed. The resulting oil was chromatographied (elution with 50 % ethyl acetate/hexane) to yield 6b as white crystals (ether) : m.p. 102-103°C. Calculated for $C_{12}H_{13}NO_2S$ (found) : C 61.25 (61.29), H 5.57 (5.59), N 5.95 (5.94). IR : 1690, 1660 cm^{-1}. ^1H NMR ($CDCl_3$) δ 12.7 (1H, d, J = 9 Hz, NH), 7.9 (1H, d, J = 9 Hz, vinylic CH), 3.55 (2H, d, J = 7 Hz, CH_2S), 2.4 (3H, s, methyl ketone), 1.8 (1H, t, J = 7 Hz, SH). ^{13}C NMR ($CDCl_3$) δ 202.1 (ketone), 165.0 (amide), 136.8 (vinylic CH), 116.0 (vinylic C), 26.6 (allylic CH_2). Higher mass recorded : m/z = 235 ($M^{+\cdot}$).

2-Acetyl-1-benzamido-1-carbethoxy-3-mercaptopropene (6e)

The same procedure was applied starting with 6H-1,3-thiazine 1e. The enamide 6e was obtained as white crystals (ether) : m.p. 69-70°C. Calculated for $C_{15}H_{17}NO_4S$ (found) : C 58.62 (58.60), H 5.58 (5.50), N 4.56 (4.37). IR : 1650, 1680, 1720 cm^{-1}. ^1H NMR ($CDCl_3$) δ 13.3 (1H, s, NH), 4.55 (2H, q, J = 7 Hz, ester), 3.50 ($2H_3$ d, J = 7 Hz, allylic CH_2), 2.55 (3H, s, methyl ketone), 2.05 (1H, d, J = 7 Hz, SH), 1.45 (3H, t, J = 7 Hz, ester). ^{13}C NMR ($CDCl_3$) δ 203.2 (ketone), 164.5 and 163.5 (amide and ester), 141.0 and 114.6 (vinylic C), 23.4 (allylic CH_2). Higher mass recorded : m/z = 307 ($M^{+\cdot}$).

5-(2-Acetyl-3-hydroxy-2-butenyle)-thiobenzoate (7)

Same procedure starting with 1c. Purification by chromatography (elution with 30 % ethyl acetate/hexane) and crystallization from ethyl acetate gave 7 as white crystals : m.p. 69-70°C. Calculated for $C_{13}H_{16}NO_3S$ (found) : C 62.37 (62.35), H 5.64 (5.70), O 19.19 (19.24), S 12.81 (12.97). ^1H NMR ($CDCl_3$) δ 16.55 (1H, s, OH), 3.95 (2H, s, allylic CH_2), 2.10 (6H, br. s, allylic methyl and methyl ketone). Higher mass recorded : m/z = 250 ($M^{+\cdot}$).

ACKNOWLEDGEMENT

The authors are grateful to Electricité de France (Club Electrochimie Organique) for partial support of this work .

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