SYNTHESIS OF PYRROLIDINOTHIENO- (OR [1]BENZOTHIENO)[3]AZEPINONES FROM THE CORRESPONDING AZEPINEDIONES OR *N*-(THIENYL OR [1]BENZOTHIENYL)ACETYLPROLINALS

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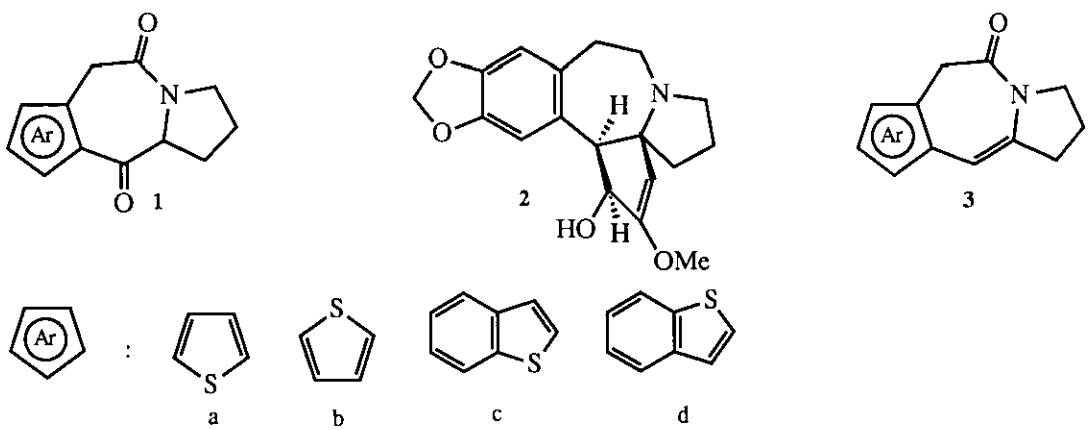
Abstract - Synthesis of pyrrolidinothieno (or [1]benzothieno)[3]azepines from the corresponding azepinediones or by direct cyclization of *N*- [thienyl(or[1]benzothienyl)]acetylprolinals.

In a previous paper we reported[1] the synthesis of pyrrolidinothieno (or [1]benzothieno)[3] azepinediones (**1**) whose structures have the pyrrolidinoazepine moiety subunit of the cephalotaxine alkaloid (**2**).

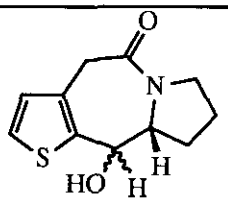
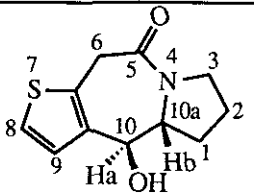
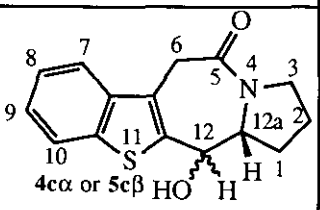
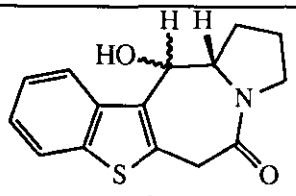
Scheme



A synthetic approach to analogues of **2** consists of using structure (**3**) as a key intermediate and we wish to report herein the synthesis of this type of compound. Our first attempt started from ketones (**1a-d**) (Scheme 1). We reported[1] the reduction of the carbonyl function of **1** in methylene group using triethylsilane in trifluoroacetic acid at room temperature. The reduction to alcohols (**4**) or / and (**5**) could be accomplished using sodium borohydride. Depending on the starting material a single alcohol was obtained (reduction of ketone (**1b**)) or a mixture of diastereomeric α-and β-alcohols. The results are reported in Table 1, and a marked difference between the two ring systems (thiophene or[1]benzothiophene) was observed. Actually, in the cases of **1a,b** the β-alcohol is the major product while in the cases of **1c,d**, the α-alcohol is the major product. Furthermore ketone (**1b**) gave a stereoselective reduction since the single

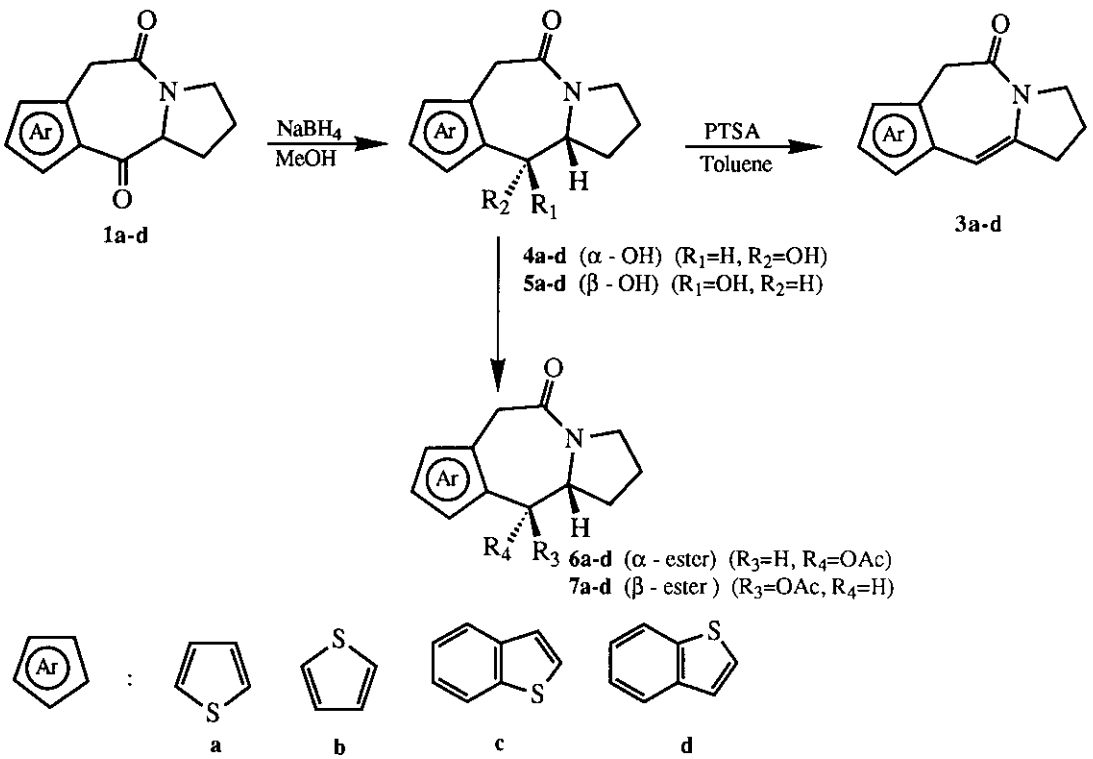
β-alcohol (**5b**) was isolated in good yield (85%).

Table 1:

Product	Yield	OH (α)	OH (β)	J_{Ha-Hb} *cis*	J_{Ha-Hb} *trans*	$J_{H6peq-Ha}$
 **4aα or 5aβ**	75%	46% –	– 54%	0 Hz –	– 10 Hz	2 Hz 2 Hz
 **5bβ**	85%	– –	– 100%	– –	– 8 Hz	– 2 Hz
 **4cα or 5cβ**	60%	85% –	– 15%	2 Hz –	– 8 Hz	2 Hz 2 Hz
 **4dα or 5dβ**	80%	70% –	– 30%	0 Hz –	– 10 Hz	2 Hz 2 Hz

Stereochemical assignments are based on spectroscopic considerations. For example, the ^1H NMR spectrum of α-alcohol (**4a**) reveals a doublet for the pseudoaxial proton H_{6pax} (δ = 3.60 ppm, $J_{H6pax-H6peq}$ = 16 Hz) and a doublet of a doublet for the pseudoequatorial proton H_{6peq} (δ = 3.76 ppm, $J_{H6peq-H6pax}$ = 16 Hz and $J_{H6peq-H10}$ = 2 Hz). The proton H_{10a} is a triplet (δ = 4.26 ppm, J_{H10-H1} = 6 Hz), no coupling is observed with the proton H_{10} which occupies a *cis* position. The proton H_{10} is a doublet of a doublet (δ = 4.71 ppm, $J_{H6peq-H10}$ = 2 Hz and J_{H10-OH} = 10 Hz). These observations allow to assign an α configuration to this alcohol. In the same manner, the ^1H NMR spectrum of **5a** exhibits a doublet of a doublet for H_{6peq} (δ = 3.88 ppm , J_{gem} = 16 Hz and $J_{H6peq-H10}$ = 2 Hz), a doublet of a triplet for H_{10} (δ = 4.53 ppm , $J_{H10-H6peq}$ = 2Hz, J_{H10-OH} = 10 Hz, $J_{H10-H10a}$ = 10 Hz). The coupling constant of 10 Hz between H_{10} and H_{10a} is characteristic of a *trans* coupling and allow to assign a β configuration to alcohol (**5a**).

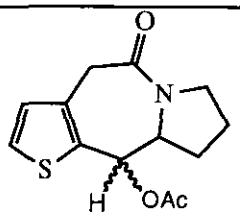
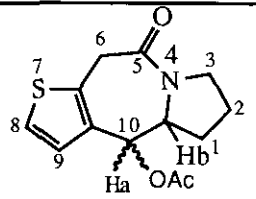
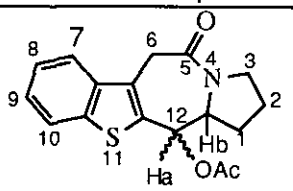
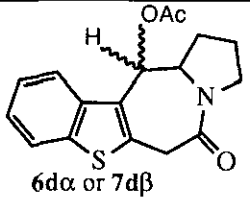
Scheme 1



In the [1]benzothiophene series similar remarks could be made and the spectroscopic data were reported in the Experimental supported the structures of the α-(**4c,d**) and β-(**5c,d**) alcohols. Examination of molecular models exhibits two different carbonyl spatial environments and explained these results. The stereoselective attack of the hydride reagent in the case of **1b** is due to the free space observed in this molecular model compared to the three other ketones (**1a,c,d**) in which the sulfur atom or the benzene ring enhanced the approach of the reducing reagent. A similar observation had been reported for the reduction of a 6-membered cyclic ketone during the synthesis of cryptopleurine.[2]

Recently, we reported isomerization of hydroxy groups in pyridazine series,[3] when they were treated with a basic (sodium ethoxide) or an acidic (*p*-toluenesulfonic acid) reagent, notably during the esterification. Thus, we decided to investigate that reaction. Esterification of alcohols (**4**) and (**5**) was performed using acetic anhydride in the presence of pyridine[4] and the results are summarized in Table 2. It is interesting to note that the single alcohol (**5b**) gave a mixture of esters (**6b+7b**) (α = 47%, β = 53%) and the mixture of alcohols (**4a+5a**) (α = 46%, β = 54%) the corresponding mixture of esters (**6a+7a**). In contrast to these results, in the [1]benzothiophene series we observed a partial or a total isomerization leading to the α-ester as the major or the single product. Stereochemical assignments are again based on spectroscopic considerations. The *cis* or *trans* relationship between H_{10} and H_{10a} in the thiophene series (**6a,b** and **7a,b**) is supported by the absence of a coupling constant for **6a,b** (*cis* isomers) and a coupling constant of 10 Hz for **7a,b** (*trans* isomers). Similar observations could be made for **6c,d** and **7c,d**.

Table 2:

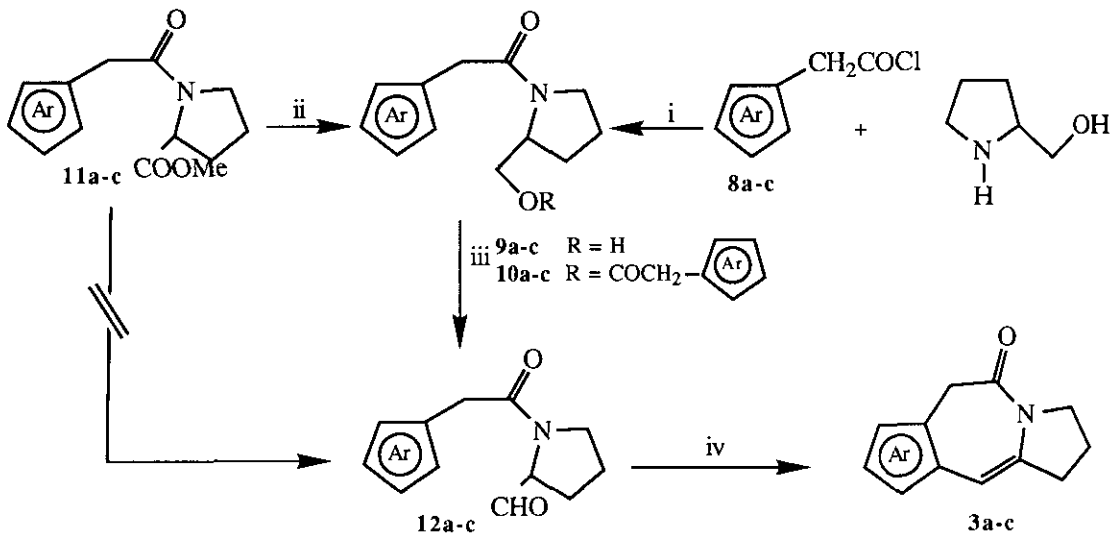
Product	Yield	% of ester α	% of ester β	J_{Ha-Hb} α	J_{Ha-Hb} β	$J_{H6peq-Ha}$
 **6aα or 7aβ**	92%	44% –	– 56%	2 Hz –	– 12 Hz	2 Hz 2 Hz
 **6bα or 7bβ**	95%	47% –	– 53%	2 Hz –	– 12 Hz	2 Hz 2 Hz
 **6cα or 7cβ**	87%	100% –	– 0%	2 Hz –	– –	2 Hz 2 Hz
 **6dα or 7dβ**	90%	90% –	– 10%	2 Hz –	– 12 Hz	2 Hz 2 Hz

On the other hand, α-and β-amido alcohols had an equal chemical behavior against dehydration in contrast to the observation made by Rapoport in the indolizidine series.[2] Actually, when the mixture of alcohols (**4+5**) (α+β) was treated under reflux of toluene with a catalytic amount of *p*-toluenesulfonic acid and azeotropic elimination of water[5] a dehydration occurred leading to the enamides (**3a,d**) in excellent yields (90 to 96%) . After twenty min of reaction all the starting materials had disappeared. If a longer reaction time (12 h) was used, we observed a large degradation of the formed enamide. This thermal unstability had been reported for indolizidines.[6] Structural assignments of enamides (**3a-d**) are obtained by usual spectrometric methods (IR, ^1H and ^{13}C NMR) and are reported in the Experimental. Actually, compounds (**3a-d**) display a characteristic singlet for the two protons H_6 and a triplet for the proton H_{10} (or H_{12}) coupled with the two protons H_1 (J_{H10-H1} = 2 Hz) and in the ^{13}C NMR a supplementary quaternary carbon (C_{10a} or C_{12a}) appears.

Although, this pathway gave good results, an alternative approach could be investigated starting from the ready available prolinol derivatives (**9a-c**) (Scheme 2). Treatment of the previously reported aromatic acid

chlorides (**8a-c**)[1] with L-prolinol in acetonitrile at -20°C in the presence of two equivalents of anhydrous potassium carbonate[7] gave the amido alcohols (**9a-c**) contaminated with a small amount of amide esters (**10a-c**) (10%). This mixture was submitted to an aqueous potassium carbonate solution under the reflux of methanol and saponification of the ester occurred. This method produced pure amide alcohols (**9a-c**) in 70-76% yields as colorless oils.

Scheme 2



i) K_2CO_3, MeCN ii) $LiBH_4$, EtOH iii) DMSO, DCC, Cl_2HCO_2H iv) BF_3-Et_2O, CH_2Cl_2

One additional approach was attempted and consisted of a selective reduction of esters (**11a-c**) using lithium chloride and sodium borohydride in ethanol.[8] Thus, the ester function of the reported amide esters (**11a-c**)[1] was reduced to afford compounds (**9a-c**) in comparative yields (60-82%).

Oxidation of alcohols (**9a-c**) with a combination of dimethyl sulfoxide and dicyclohexylcarbodiimide in dichloroacetic acid[7] afforded aldehydes (**12a,b**) as oils in 70% yield after silical gel chromatography or **12c** as a solid after recrystallization from ether. Attempts to obtain these aldehydes by a dIRect reduction of the ester function of **11a-c** using diisobutylaluminium hydride[9] or the corresponding acid with *N,N'*-carbonyl-diimidazole and lithium aluminium hydride[10] failed. In all cases unchanged starting material was recovered. Finally, aldehydes (**12a-c**) were cyclized to the corresponding crystalline cyclic enamides (**3a-c**) upon stirring during three days at room temperature in dichloromethane containing boron trifluoride etherate. The yields (60-90%) were inferior to those observed during the dehydration of alcohol (**4a-c**) (91-96%). Nevertheless, it is an attractive sequence since the yield calculated from the starting acid chlorides (**8a-c**) is 13,12 and 24% respectively for the process using keto amides (**1a-c**) as intermediates and 45,29 and 38% respectively for the process described in Scheme 2. The particularly low yields (12% and 14%) observed in the first procedure are essentially due to the cyclization step (preparation of **1a-c**).[1]

In conclusion, we have described two short syntheses of pyrrolidinothieno (or [1]benzothieno)[3]azepinones (**3a-c**) in an interesting overall yield of 29 to 45%. Furthermore, the reduction of ketones (**1a-d**) furnished a diastereomeric mixture of α-(**4a-d**) and β-(**5a-d**) alcohols. This mixture depended of

the nature of the heterocycle since the β-alcohol was the major product in the thiophene series and the minor one in the [1]benzothiophene series.

EXPERIMENTAL

Melting points were measured on a Boetius micro hot-stage and are uncorrected. The IR spectra were recorded on a Perkin Elmer FTIR Paragon Spectrophotometer (potassium bromide). The NMR (^{1}H NMR and ^{13}C NMR) were recorded on a Brucker AC-200 spectrometer (200 MHz) in deuteriochloroform using tetramethylsilane as the internal standard. Ascending TLC was performed on precoated of silica gel 60 F 254 (Merck) and the spots were visualized using UV lamp or iodine vapor. E. Merck silica gel 60 F (70-300 mesh) was used for column chromatography. The elemental analyses were carried out by the microanalysis laboratory of INSA of Rouen, F 76130 MT.ST.Aignan. MS spectral measurements were recorded on a AEI MS 902 S Spectrometer.

General procedure for compounds (9a-c).

Method A : To a solution of L-prolinol (4 g, 0.04 mol) in acetonitrile (50 mL) was added anhydrous potassium carbonate (10 g, 0.07 mol), and the mixture was cooled to -10°C. Appropriate acid chloride (0.06 mol) in 10 mL of acetonitrile was added dropwise and the reaction mixture was stirred for 1 h at 10°C then 30 min at rt.Suspension was filtered off and the solution was concentrated. A NMR analysis showed the presence of ester (**10a-c**) (10%). These latter were transformed into the alcohol by means of the following procedure. The above oil was dissolved in a mixture of ethanol (20 mL), sodium hydroxide (1 g, 0.025 mol) and water (5 mL) and was stirred at rt for 12 h. The mixture was evaporated, diluted with water, and extracted with dichloromethane. The organic layer was dried over magnesium sulfate and concentrated to give **9a-c**.

Method B : The L-methyl *N*-acylprolinates (**11a-c**) (10 mmol) were dissolved in THF (30 mL) under argon, and anhydrous lithium chloride (0.85g, 20 mmol) and sodium borohydride (0.75g, 20 mmol) were added. Ethanol (30 mL) was added dropwise below 5°C during 20 min, and the mixture was stirred at 0°C for 1 h, then at rt for 24 h. The mixture was cooled with ice-water, adjusted to pH 2 by addition of 10% hydrochloric acid solution and concentrated in *vacuo*. Water was added and the mixture was extracted with dichloromethane. The organic layer was dried over magnesium sulfate, evaporated in *vacuo*, the crude product was purified by column chromatography (silica gel-dichloromethane) to give **9a-c**.

***N*-(Thien-3-ylacetyl)prolinol (9a)**. This compound was obtained as an oil in 72% (A) or 64% (B) yield; $[\alpha]_D$ = -61° (c = 1 in CH_2Cl_2); IR : 3383 (OH), 1620 (C=O) cm^{-1}; ^{1}H NMR : δ 1.55-2.05 (m, 4H, prolinol), 3.34-3.56 (m, 5H, 4H and OH prolinol), 4.09-4.22 (m, 1H, prolinol), 6.96-7.05 (m, 2H, thiophene), 7.22-7.26 (m, 1H, thio-phene). Anal. Calcd for $C_{11}H_{15}NO_2S$: C, 58.64 ; H, 6.71; N, 6.22. Found: C, 58.80; H, 6.71; N, 6.22.

***N*-(Thien-2-ylacetyl)prolinol (9b)**. This compound was obtained as an oil in 70% (A) or 60% (B) yield; $[\alpha]_D$ = -54° (c = 1 in CH_2Cl_2) IR: 3383 (OH), 1621 (C=O) cm^{-1}; ^{1}H NMR : δ 1.49-2.09 (m, 4H, prolinol), 3.42-3.64 (m, 4H, prolinol), 3.83 (s, 2H, CH_2-CO), 4.12-4.25 (m, 1H, prolinol), 4.82 (broad,

1H, OH), 6.87-6.95 (m, 2H, thiophene), 7.17-7.19 (m, 1H, thiophene). Anal. Calcd for $C_{11}H_{15}NO_2S$: C, 58,64 ; H, 6,71 ; N, 6,22. Found: C, 58.74; H, 6.78 ; N, 6.20.

***N*-([1]Benzothien-3-ylacetyl)prolinol (9c).** This compound was obtained as an oil in 76% (A) or 82% (B) yield, mp 108°C (ethanol); $[\alpha]_D$ = -46° (c = 1 in CH_2Cl_2); IR : 3406 (OH), 1625 (C=O) cm^{-1}; ^1H NMR : δ 1.51-2.09 (m, 4H, prolinol), 3.36-3.73 (m, 5H, 4H and OH prolinol), 3.85 (s, 2H, CH_2-CO-), 4.18-4.30 (m, 1H, prolinol), 7.24-7.38 (m, 3H, H arom), 7.74-7.86 (m, 2H, H arom). Anal. Calcd for $C_{15}H_{17}NO_2S$: C, 65.43 ; H, 6.22 ; N, 5.09. Found: C, 65.60; H, 6.28; N, 5.16.

General procedure for compounds (12a-c).

A mixture of alcohol (**9a-c**) (8 mmol), dicyclohexylcarbodiimide, (3.30 g, 16 mmol), dichloroacetic acid (0.3 mL, 4 mmol) in dimethyl sulfoxide (20 mL) was stirred for 30 min at 0°C, then 4 h at rt. Oxalic acid (3 g) was added slowly and cautiously at 0°C, and the mixture was filtered. The filtrate was diluted with dichloromethane and washed with water, 10% sodium hydrogen carbonate solution and water. The organic layer was evaporated, the crude product was purified by column chromatography (silica gel-dichloromethane) to give **12a-c**.

***N*-(Thien-3-ylacetyl)prolinal (12a).** This compound was obtained as an oil in 70% yield; $[\alpha]_D$ = -39° (c = 1 in CH_2Cl_2); IR : 1732 (C=O), 1640 (C=O) cm^{-1}; ^1H NMR : δ 1.85-1.92 (m, 4H, prolinal), 3.45-3.56 (m, 2H, prolinal), 3.65 (s, 2H, CH_2-CON), 4.32-4.35 (m, 1H, prolinal), 6.96 (dd, 1H, thiophene, J = 1.2 and 5 Hz), 7.08-7.10 (m, 1H, thiophene), 7.22 (dd, 1H, thiophene, J = 1.2 and 5 Hz), 9.41 (d, 1H, CHO, J = 1.6 Hz). Anal. Calcd for $C_{11}H_{13}NO_2S$: C, 59.17 ; H, 5.87 ; N, 6.27. Found: C, 59.30; H, 6.01; N, 6.32.

***N*-(Thien-2-ylacetyl)prolinal (12b).** This compound was obtained as an oil in 70% yield; $[\alpha]_D$ = -46° (c = 1 in CH_2Cl_2); IR : 1730-(C=O), 1641 (C=O) cm^{-1}; ^1H NMR : δ 1.86-2.08 (m, 4H, prolinal), 3.54-3.69 (m, 2H, prolinal), 3.89 (s, 2H, CH_2-CON), 4.43-4.49 (m, 1H, prolinal), 6.92-6.94 (m, 2H, thiophene), 7.18-7.21 (m, 1H, thio-phene), 9.51, (d, 1H, CHO, J = 1.6 Hz). Anal. Calcd for $C_{11}H_{13}NO_2S$: C, 59.17 ; H, 5.87 ; N, 6.27. Found: C 59.17; H, 5.90; N, 6.29.

***N*-([1]Benzothien-3-ylacetyl)prolinal (12c).** This compound was obtained in 70% yield, mp 102-104°C (ethanol) ; $[\alpha]_D$ = -74° (c = 1 in CH_2Cl_2); IR : 1720 (C=O), 1630 (C=O) cm^{-1}; ^1H NMR : δ 1.75-2.16 (m, 2H, prolinal), 3.51-3.59 (m, 2H, prolinal), 3.89 (s, 2H, prolinal), 4.80-4.55 (m, 1H, prolinal), 7.30-7.42 (m, 3H, H arom), 7.76-7.86 (m, 2H, H arom), 9.52 (d, 1H, CHO, J = 1.6 Hz). Anal. Calcd for $C_{15}H_{15}NO_2S$: C, 65.91 ; H, 5.53 ; N, 5.12. Found: C, 66.20; H, 5.66; N, 5.20.

Azepinones (3a-d).

Method A: To a solution of aldehyde (**12a-c**) (2 mmol) in dry dichloromethane (20 mL) was added borontrifluoride etherate (4 mL, 30 mmol). The reaction mixture was stirred at rt for 12 h and quenched with water then washed with 10% sodium hydrogen carbonate solution. The organic layer was dried over magnesium sulfate, evaporated and recrystallization of the residue from ethanol gave **3a-c**.

Method B: A mixture of alcohol (**4+5(a-d)**) and a catalytic amount of *p*-toluenesulfonic acid in toluene (20 mL) was heated at reflux (Dean Stark) for 20 min. The reaction mixture was allowed to cool to rt,diluted

with dichloromethane, washed with 10% sodium hydrogen carbonate solution. The organic layer was dried, evaporated in *vacuo* and recrystallization of the residue from ethanol gave **3a-d**.

2,3,5,6-Tetrahydro-*1H*-pyrrolo[2,1-*b*]thieno[3,2-*f*][3]azepin-5-one(3a). This compound was obtained in 90% (A) or 94% (B) yield, mp 96-98°C; IR : 1647 (C=O) cm^{-1}; ^1H NMR : δ 1.87-2.01 (m, 2H, H_2), 2.74 (td, 2H, H_1, J = 2 and 8 Hz), 3.48 (s, 2H, H_6), 3.76 (t, 2H, H_3, J = 8 Hz), 6.17 (t, 1H, H_{10}, J = 2 Hz), 6.78 (d, 1H, H_7, J = 5 Hz), 7.16 (d, 1H, H_8, J = 5 Hz); ^{13}C NMR : δ 20.9 (CH_2), 33.2 (CH_2), 38.2 (CH_2), 49.2 (CH_2), 101.6 (CH), 124.8 (CH thiophene), 127.9 (CH thiophene), 128.5 (C), 134.8 (C thiophene), 139.5 (C thiophene), 166.1 (C=O). Anal. Calcd for $C_{11}H_{11}NOS$: C, 64.36 ; H, 5.40 ; N, 6.82. Found: C, 64.42; H, 5.51; N, 6.92.

2,3,5,6-Tetrahydro-*1H*-pyrrolo[2,1-*b*]thieno[2,3-*f*][3]azepin-5-one(3b). This compound was obtained in 60% (A) or 91% (B) yield, mp 130-132°C ; IR : 1646 (C=O) cm^{-1}; ^1H NMR : δ 1.87-2.02 (m, 2H, H_2), 2.74 (td, 2H, H_1, J = 2 and 8 Hz), 3.58 (s, 2H, H_6), 3.75 (t, 2H, H_3, J = 8 Hz), 6.16 (t, 1H, H_{10}, J = 2 Hz), 6.83 (d, 1H, H_9, J = 5.4 Hz), 7.08 (d, 1H, H_8, J = 5.4 Hz); ^{13}C NMR : δ 20.9 (CH_2) 33.2 (CH_2), 37.2 (CH_2), 49.1 (CH_2), 104.0 (CH), 123.5 (CH thiophene), 126.2 (CH thiophene), 126.3 (C) 135.1 (C thiophene), 139.5 (C thiophene), 165.3 (C=O). Anal. Calcd for $C_{11}H_{11}NOS$: C, 64.36 ; H, 5.40 ; N, 6.82. Found: C, 64.52; H, 5.48; N, 7.01.

2,3,5,6-Tetrahydro-*1H*-pyrrolo[2,1-*b*][1]benzothieno[3,2-*f*][3]azepin-5-one(3c). This compound was obtained in 72% (A) or 96% (B) yield, mp 118-120°C; IR : 1639 (C=O) cm^{-1}; ^1H NMR : δ 1.91-2.06 (m, 2H, H_2), 2.83 (td, 2H, H_1, J = 2 and 8 Hz), 3.65 (s, 2H, H_6), 3.82 (t, 2H, H_3, J = 8 Hz), 6.22 (t, 1H, H_{12}, J = 2 Hz), 7.27-7.36 (m, 2H, H arom), 7.71-7.78 (m, 2H, H arom); ^{13}C NMR : δ 20.9 (CH_2), 33.5 (CH_2), 35.7 (CH_2), 49.5 (CH_2), 101.8 (CH), 120.9 (CH arom), 121.8 (C), 122.4 (CH arom), 124.2 (CH arom), 124.4 (CH arom), 135.2 (C arom), 138.4 (C arom), 140.2 (C arom), 141.8 (C arom), 165.5 (C=O). Anal. Calcd for $C_{15}H_{13}NOS$: C, 70.56 ; H, 5.13 ; N, 5.49. Found: C, 70.80; H, 5.22; N, 5.56.

2,3,5,6-Tetrahydro-*1H*-pyrrolo[2,1-*b*][1]benzothieno[2,3-*f*][3]azepin-5-one(3d). This compound was obtained in 90% (B) yield, mp 133-135°C ; IR : 1653 (C=O) cm^{-1}; ^1H NMR : δ 1.92-2.07 (m, 2H, H_2), 2.85 (td, 2H, H_1, J = 2 and 8 Hz), 3.67 (s, 2H, H_6), 3.79 (t, 2H, H_3, J = 8 Hz), 6.44 (t, 1H, H_{12}, J = 2 Hz), 7.26-7.40 (m, 2H, H arom) 7.69 (d, 1H, H arom, J = 8 Hz), 7.76 (d, 1H, H arom, J = 8 Hz); ^{13}C NMR : δ 20.6 (CH_2), 33.0 (CH_2), 37.7 (CH_2), 49.0 (CH_2), 101.8 (CH), 121.1 (CH arom), 122.9 (CH rom), 124,6 (CHarom), 124.7 (CH arom),127.4 (C), 129.9 (Carom), 137.7 (C arom), 139.3 (C arom), 140.9 (C arom), 165.4 (C=O). Anal. Calcd for $C_{15}H_{13}NOS$: C, 70.56 ; H, 5.13 ; N, 5.49 . Found: C, 70.82; H, 5.21; N, 5.56.

Reduction of ketones (1a-d) into alcohols (4a-d) and (5a-d).

A solution of the keto amide (**1a-d**) (1.7 mmol) in methanol (10 mL) was cooled at 0°C, and sodium borohydride (78 mg, 2.06 mmol) was added and stirring was continued at rt for 1 h. The mixture was diluted with water (15 mL), and then it was acidified with 10% hydrochloric acid solution, and extracted with dichloromethane (10 mL x3). The combined extracts were washed with brine, dried over magnesium sulfate, and concentrated. Recrystallization of the solid from ethanol gave alcohols (**4+5**).

2,3,5,6,10,10a-Hexahydro-*1H*-10-hydroxypyrrolo[2,1-*b*]thieno[3,2-*f*][3]azepin-5-one (4a+5a). These compounds were obtained in 75% yield, mp 156-158°C; IR: 3355 (OH), 1632 (C=O) cm^{-1}. **(4a)** (46%) ^1H NMR : δ 1.75-2.01 (m, 2H, H_2), 2.08-2.34 (m, 2H, H_1), 3.54-3.75 (m, 2H, H_3), 3.60 (d, 1H, H_{6pax}, J = 16 Hz), 3.76 (dd, 1H, H_{6peq}, J = 2 and 16 Hz), 4.26 (t, 1H, $H_{10a\text{-}pax}$, J = 6 Hz), 4.71 (dd, 1H, H_{10peq}, J = 2 and 10 Hz), 6.71 (d, 1H, H_7, J = 5 Hz), 7.20 (d, 1H, H_8, J = 5 Hz), ^{13}C NMR : δ 22.2 (CH_2), 29.3 (CH_2), 38.2 (CH_2), 46.4 (CH_2), 59.9 (CH), 69.4 (CH), 124.5 (CH thiophene), 129.3 (CH thiophene), 130.1 (C thiophene), 138.5 (C thiophene), 170.6 (C=O). **(5a)** (54%) ^1H NMR : δ 1.75-2.02 (m, 2H, H_2), 2.08-2.34 (m, 2H, H_1), 3.54-3.75 (m, 2H, H_3), 3.55 (d, 1H, H_{6pax}, J = 16 Hz), 3.88 (dd, 1H, H_{6peq} , J = 2 and 16 Hz), 4.05-4.15 (m, 1H, $H_{10a\text{-}pax}$), 4.53 (td, J = 2 and 10 Hz, 1H, H_{10pax}), 6.71 (d,1H, H7, J = 5 Hz), 7.21 (d, 1H, H_8, J = 5 Hz), ^{13}C NMR : δ 23.6 (CH_2), 29.5 (CH_2), 38.4 (CH_2), 47.4 (CH_2), 61.5 (CH), 69.6 (CH), 124.9 (CH thiophene), 129.5 (CH thiophene), 130.3 (C thiophene), 139.7 (C thiophene), 171.2 (C=O); ms : m/z 223(M^+). Anal. Calcd for $C_{11}H_{13}NO_2S$: C, 59.17; H, 5.87; N, 6.27.Found : C, 59.50; H, 6.02; N, 6.24.

2,3,5,6,10,10a-Hexahydro-*1H*-10-hydroxypyrrolo[2,1-*b*]thieno[2,3-*f*][3]azepin-5-one (5b). This compound was obtained in 85% yield, mp 119-121°C; IR : 3350 (OH), 1630 (C=O) cm^{-1}; ^1H NMR : δ 1.78-2.02 (m, 2H, H_2), 2.03-2.27 (m, 2H, H_1), 2.90 (d, 1H, OH, J = 8 Hz), 3.34-3.51 (m, 2H, H3), 3.45 (d, 1H, H_{6pax}, J = 16 Hz), 3.97 (dd, 1H, H_{6peq}, J = 2 and 16 Hz), 3.87-4.06 (m, 1H, $H_{10a\text{-}pax}$), 4.36 (td, 1H, H_{10pax}, J = 2 and 8 Hz), 7.05 (m, 2H, thiophene); ^{13}C NMR : δ 20.3 (CH_2), 27.5 (CH_2), 34.9 (CH_2), 44.5 (CH_2), 59.4 (CH), 67.7 (CH), 121.1 (CH thiophene), 127.4 (CH thiophene), 128.3 (C thiophene), 135.7 (C thiophene), 168.4 (C=O); ms : m/z 223(M^+). Anal. Calcd for $C_{11}H_{13}NO_2S$: C, 59.17; H, 5.87; N, 6.27. Found : C, 59,50; H, 6,01; N, 6,32.

2,3,5,6,12,12a-Hexahydro-*1H*-12-hydroxypyrrolo[2,1-*b*][1]benzothieno[3,2-*f*][3]azepin-5-one (4c+5c). These compounds were obtained in 60% yield; mp 274°C; IR : 3359(OH), 1636(C=O) cm^{-1}. **(4c)** (85%) ^1H NMR : δ 1.75-1.98 (m, 2H, H_2), 2.00-2.22 (m, 2H, H_1), 3.30-3.60 (m, 2H, H_3), 3.70 (d, 1H, H_{6pax}, J = 16 Hz), 4.00 (dd, 1H, H_{6peq}, J = 2 and 16 Hz), 4.50 (td,1H, $H_{12a\text{-}pax}$, J = 2 and 6 Hz,), 4.70 (dd, 1H, H_{12peq}, J = 2 and 8 Hz), 5.88 (d, 1H, OH, J = 8 Hz), 7.31-7.40 (m, 2H, H arom) , 7.80-7.92 (m, 2H, H arom); ^{13}C NMR : δ 23.0 (CH_2), 28.6 (CH_2), 34.7 (CH_2), 46.5 (CH_2), 58.9 (CH), 68.4 (CH), 121.4 (CH arom), 121.6 (CH arom), 122.1 (CH arom), 124.1 (CH arom), 137.6 (C arom), 138.5 (C arom), 138.7 (C arom), 140.9 (C arom), 169.1 (C=O). **(5c)** (15%) ^1H NMR : δ 1.75-1.98 (m, 2H, H_2), 2.00-2.22 (m, 2H, H_1), 3.30-3.60 (m, 2H, H_3), 3.66 (d, 1H, H_{6pax}, J = 16 Hz), 4.18 (dd, 1H, H_{6peq}, J = 2 and 16 Hz,), 4.14-4.19 (m, 1H, $H_{12a\text{-}pax}$), 4.57 (td, 1H, H_{12pax}, J = 2 and 8 Hz), 6.25 (d, 1H, OH, J = 8 Hz), 7.50-7.61 (m, 2H, H arom), 8.08-8.13 (m, 2H, H arom); ^{13}C NMR : δ 21.5 (CH_2), 26.4 (CH_2), 34.6 (CH_2), 45.8 (CH_2), 60.3 (CH), 66.3 (CH), 122.0 (CH arom), 124.0 (CH arom), 124.4 (CH arom), 124.6 (CH arom), 137.7 (C arom), 138.4 (C arom), 138.7 (C arom), 140.4 (C arom), 169.8 (C=O). Anal. Calcd for $C_{15}H_{15}NO_2S$: C, 65.91; H, 5.53; N, 5.12. Found : C, 65.88; H, 5.72; N, 5.26.

2,3,5,6,12,12a-hexahydro-*1H*-12-hydroxypyrrolo[2,1-*b*][1]benzothieno[2,3-*f*][3]azepin-5-one (4d+5d). These compounds were obtained in 80% yield; mp 184-186°C; IR : 3404 (OH), 1635(C=O) cm^{-1}. **(4d)** (70%) ^1H NMR : δ 1.83-1.89 (m, 2H, H_2), 2.10-2.37 (m, 2H, H_1), 3.33-3.63

(m, 2H, H_3), 3.70 (d, 1H, H_{6pax}, J = 16 Hz,), 4,06 (dd, 1H, H_{6peq}, J = 2 and 16 Hz), 4.28-4.38 (m, 1H, $H_{12a-pax}$), 4.88 (dd, 1H, H_{12peq}, J = 2 and 10 Hz,), 7.30-7.37 (m, 2H, H arom), 7.73 (d, 1H, H arom, J = 8 Hz), 7.84 (d, 1H, H arom, J = 8 Hz); ^{13}C NMR : δ 23.8 (CH_2), 29.6 (CH_2), 37.8 (CH_2), 47.7 (CH_2), 60.0 (CH), 69.0 (CH), 121.9 (CH arom), 122.0 (CH arom), 124.5 (CH arom), 124.6 (CH arom), 131.0 (C arom), 132.7 (C arom), 137.6 (C arom), 140.0 (C arom), 168.8 (C=O). **(5d)** (30%) ^1H NMR : δ 1.83-1.89 (m, 2H, H_2), 2.10-2.37 (m, 2H, H_1), 3.33-3.63 (m, 2H, H_3), 3.69 (d, 1H, H_{6pax}, J = 16 Hz), 4.22 (dd, 1H, H_{6peq}, J = 2 and 16 Hz), 4.10-4.25 (m, 1H, $H_{12a-pax}$), 4.76 (td, 1H, H_{12pax}, J = 2 and 10 Hz), 7.28-7.40 (m, 2H, H arom), 7.79 (d, 1H, H arom, J = 8 Hz), 7.91 (d, 1H, H arom, J = 8 Hz); ^{13}C NMR : δ 22.3 (CH_2), 29.7 (CH_2), 37.8 (CH_2), 46.3 (CH_2), 61.4 (CH), 69.3 (CH), 121.4 (CH arom), 121.8 (CH arom), 124.2 (CH arom), 124.4 (CH arom), 130.6 (C arom), 132.8 (C arom), 137.8 (C arom), 140.1 (C arom), 169.8 (C=O). Anal. Calcd for $C_{15}H_{15}NO_2S$: C, 65.91; H, 5.53; N, 5.12. Found : C, 65.92; H, 5.65; N, 5.24.

Esterification of alcohols (4+5)

Acetic anhydride (2 mL, 20 mmol) was added to a solution of the appropriate alcohol (4.0 mmol) in pyridine (15 mL), and the mixture was allowed to stir at rt for 12 h. The mixture was partitioned between water (20 mL) and dichloromethane (50 mL). The organic layer was separated, washed with 10% potassium carbonate solution, dried over magnesium sulfate, and evaporated. Recrystallization from ethyl acetate gave the esters (**6+7**).

10-Acetoxy-2,3,5,6,10,10a-hexahydro-*1H*-pyrrolo[2,1-*b*]thieno[3,2-*f*][3]azepin-5-one (6a+7a). These compounds were obtained in 92% yield, mp 156-158°C; IR : 1732 (C=O), 1659 (C=O) cm^{-1}. **(6a)** (44%) ^1H NMR : δ 1.90-2.33 (m, 4H, H1 and H_2), 2.08 (s, 3H, CH_3-C=O), 3.49-3.71 (m, 2H, H3), 3.69 (d, 1H, H_{6pax}, J = 16 Hz), 3.82 (dd, 1H, H_{6peq}, J = 2 and 16 Hz), 4.33-4.43 (m, 1H, $H_{10a-pax}$), 6.05 (t, 1H, H_{10peq}, J = 2 Hz), 6.73 (d, 1H, H_7, J = 6 Hz), 7.20 (d, 1H, H_8, J = 6 Hz); ^{13}C NMR : δ 20.5 (CH_3), 22.6 (CH_2), 29.1 (CH_2), 38.0 (CH_2), 46.3 (CH_2), 57.6 (CH), 69.5 (CH), 125.3 (CH thiophene), 128.6 (CH thiophene), 131.3 (C thiophene), 133.2 (C thiophene), 168.9 (C=O), 169.9 (C=O). **(7a)** (56%) ^1H NMR : δ 1.90-2.33 (m, 4H, H_1 and H_2), 2.12 (s, 3H, CH_3-C=O), 3.49-3.71 (m, 2H, H_3), 3.58 (d, 1H, H_{6pax}, J = 16 Hz), 3.95 (dd, 1H, H_{6peq}, J = 2 and 16 Hz), 4.43-4.43 (m, 1H, H_{10a-ax}), 5.91 (dd, 1H, H_{10pax}, J = 2 and 12 Hz), 6.73 (d, 1H, H_7, J = 6 Hz), 7.22 (d, 1H, H_9, J = 6 Hz); ^{13}C NMR : δ 20.4 (CH_3), 21.6 (CH_2), 29.1 (CH_2), 37.8 (CH_2), 45.7 (CH_2), 58.1 (CH), 69.5 (CH), 124.8 (CH thiophene), 128.8 (CH thiophene), 131.6 (C thiophene), 134.1 (C thiophene), 169.7 (C=O), 170.1 (C=O). Anal. Calcd for $C_{13}H_{15}NO_3S$: C, 58.85 ; H, 5.70 ; N, 5.28. Found : C, 58.91 ; H, 5.70 ; N, 5.26.

10-Acetoxy-2,3,5,6,10,10a-hexahydro-*1H*-pyrrolo[2,1-*b*]thieno[2,3-*f*][3]azepin-5-one (6b+7b). These compounds were obtained in 95% yield, mp 166-168°C; IR : 1739 (C=O), 1660 (C=O) cm^{-1}. **(6b)** (47%) ^1H NMR : δ 1.89-2.29 (m, 4H, H_1 and H_2), 2.06 (s, 3H, CH_3-C=O), 3.47-3.68 (m, 2H, H3), 3.71 (d, 1H, H_{6pax}, J = 16 Hz), 3.94 (dd, 1H, H_{6peq}, J = 2 and 16 Hz), 4.28-4.39 (m, 1H, $H_{10a-pax}$), 6.03 (t, 1H, H_{10peq}, J = 2 Hz), 6.80 (d, 1H, H_9, J = 6 Hz), 7.04 (d, 1H, H8, J = 6 Hz); ^{13}C NMR : δ 21.2 (CH_3), 23.3 (CH_2), 29.5 (CH_2), 37.1 (CH_2), 46.9 (CH_2), 58.1 (CH), 70.4 (CH), 123.0

(CH thiophene), 129.5 (CH thiophene), 132.5 (C thiophene), 133.6 (C thiophene), 168.4 (C=O), 170.6 (C=O). **(7b)** (53%)^{1}H NMR : δ 1.89-2.29 (m, 4H, H_1 and H_2), 2.10 (s, 3H, CH_3-C=O), 3.47-3.68 (m, 2H, H_3), 3.58 (d, 1H, H_{6pax}, J = 16 Hz), 4.10 (dd, 1H, H_{6peq}, J = 2 and 16 Hz), 4.28-4.39 (m, 1H, $H_{10a-pax}$), 5.86 (dd, 1H, H_{10pax}, J = 2 and 12 Hz), 6.87 (d, 1H, H_9, J = 6 Hz), 7.04 (d, 1H, H_8, J = 6 Hz); ^{13}C NMR : δ 21.1 (CH_3), 22.2 (CH_2), 29.4 (CH_2), 37.0 (CH_2), 46.4 (CH_2), 58.6 (CH), 70.2 (CH), 123.1 (CH thiophene), 128.9 (CH thiophene), 132.0 (C thiophene), 133.7 (C thiophene), 169.9 (C=O), 170.5 (C=O). Anal.Calcd for $C_{13}H_{15}NO_3S$: C, 58.85; H, 5.70; N, 5.28. Found : C, 58.90; H, 5.72; N, 5.30.

12-Acetoxy-2,3,5,6,12,12a-hexahydro-*1H*-pyrrolo[2,1-*b*][1]benzothieno[3,2-*f*][3]azepin-5-one (6c).This compound was obtained in 87% yield, mp 206-208°C; IR : 1739(C=O), 1653(C=O) cm^{-1}; ^{1}H NMR : δ 1.95-2.45 (m, 4H, H_1 and H_2), 2.11 (s, 3H, CH_3-C=O), 3.51-3.75 (m, 2H, H_3) 3.83 (d, 1H, H_{6pax}, J = 16 Hz), 4.10 (dd, 1H, H_{6peq}, J = 2 and 16 Hz), 4.51-4.57 (m, 1H, $H_{12a-pax}$), 6.16 (t, 1H, H_{12peq}, J = 2 Hz), 7.33-7.39 (m, 2H, H arom), 7.70-7.82 (m, 2H, H arom); ^{13}C NMR : δ 21.1 (CH_3) , 23.3 (CH_2), 29.7 (CH_2), 35.9 (CH_2), 47.1 (CH_2), 58.1 (CH), 70.4 (CH), 122.0 (CH arom), 122.3 (CH arom), 124.4 (CH arom), 125.4 (CH arom), 126.4 (C arom), 134.6 (C arom), 138.3 (C arom), 138.9 (C arom), 169.0 (C=O), 170.5 (C=O). Anal. Calcd for $C_{17}H_{17}NO_3S$: C, 64.74; H, 5.43; N, 4.44. Found : C, 64.76; H, 5.42; N, 4.45.

12-Acetoxy-2,3,5,6,12,12a-hexahydro-*1H*-pyrrolo[2,1-*b*][1]benzothieno[2,3-*f*][3]azepin-5-one (6d+7d).These compounds were obtained in 90% yield, mp:138-140°C; IR: 1739(C=O) cm^{-1}. **(6d)** (90%) ^{1}H NMR : δ 1.85-2.40 (m, 4H, H_1 and H_2), 2.06 (s, 3H, CH_3-C=O), 3.47-3.69 (m, 2H, H_3), 3.77 (d, 1H, H_{6pax}, J = 16 Hz), 4.09 (dd, 1H, H_{6peq}, J = 2 and 16 Hz), 4.41-4.47 (m, 1H, $H_{12a-pax}$), 6.45 (t, 1H, H_{12peq}, J = 2 Hz), 7.27-7.32 (m, 2H, H_8 and H_{11}), 7.55 (t, 1H, H_{10}, J = 3.6 Hz,), 7.71 (t, 1H, H_9, J = 3.6 Hz); ^{13}C NMR : δ 21.09 (CH_3), 23.2 (CH_2), 29.2 (CH_2), 37.9 (CH_2), 47.0 (CH_2), 58.7 (CH), 68.8 (CH), 120.9 (CH arom), 121.9 (CH arom), 124.5 (CH arom), 124.8 (CH arom), 127.6 (C arom), 135.0 (C arom), 137.2 (C arom), 139.4 (C arom), 167.7 (C=O), 171.1 (C=O). **(7d)** (10%) ^{1}H NMR : δ 1.85-2.40 (m, 4H, H_1 and H_2), 3.47-3.69 (m, 2H, H_3), 3.74 (d, 1H, H_{6pax}, J = 16 Hz), 4.30 (dd, 1H, H_{6peq}, J = 2 and 16 Hz), 4.48-4.54 (m, 1H, $H_{12a-pax}$), 6.25 (dd, 1H, H_{12pax}, J = 2 and 12 Hz), 7.27-7.32 (m, 2H, H_8 and H_{11}), 7.45 (t, 1H, H_{10}, J = 3.6 Hz), 7.72 (t, 1H, H_9, J = 3.6 Hz); ^{13}C NMR : δ 20.9 (CH_3), 22.3 (CH_2), 29.6 (CH_2), 37.9 (CH_2), 46.3 (CH_2), 59.1 (CH), 69.4 (CH), 120.9 (CH arom), 122.0 (CH arom), 124.3 (CH arom), 124.8 (CH arom), 127.2 (C arom), 135.0 (C arom), 137.4 (C arom), 139.6 (C arom), 169.7 (C=O), 171.0 (C=O). Anal. Calcd for $C_{17}H_{17}NO_3S$: C, 64.74; H, 5.43; N, 4.44. Found : C, 64.80; H, 5.45; N, 4.41.

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