On the Synthesis and Reactivity of 4,10-Dihydrobenzo-[*b*]thieno[2,3-*e*]thiepin-10-acetic Acid and 5,10-Dihydrobenzo[*e*]thieno[3,2-*b*]thiepin-10-acetic Acid

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A simple method to synthesize 4,10-dihydrobenzo[*b*]thieno[2,3-*e*]thiepin-10-acetic acid (**8a**) and 5,10-dihydrobenzo[*e*]thieno[3,2-*b*]thiepin-10-acetic acid (**8b**) starting from ketones **1a,b** is described. The reactivity of the acid **8a** has been investigated and some derivatives are reported.

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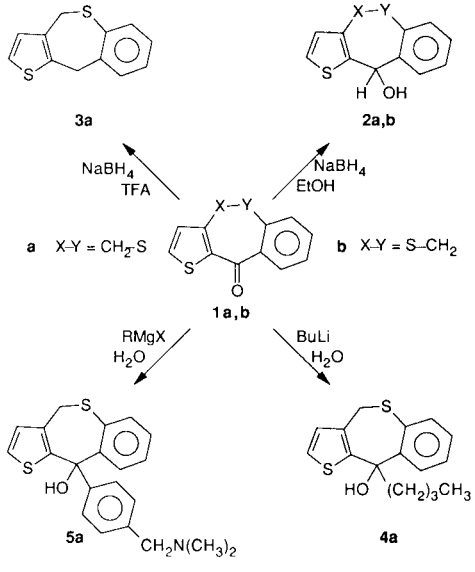
In the course of the synthesis of fused heterocyclic compounds we described in a previous paper [1] the synthesis of thienobenzothiepinones and their Schmidt rearrangement and the Beckmann rearrangement of the corresponding oximes. We report herein another view of the reactivity of these cyclic ketones, particularly the esters derivatives **7a,b** precursors of tetracyclic systems.

Firstly, we studied the reduction of 4,10-dihydrobenzo-[*b*]thieno[2,3-*e*]thiepin-10-one **1a** and 5,10-dihydrobenzo-[*e*]thieno[3,2-*b*]thiepin-10-one **1b** with sodium borohydride (Scheme I). In ethanol we obtained quantitatively the alcohols **2a,b**, while in trifluoroacetic acid [2] the corresponding alkane **3a** was formed in an excellent yield of 89%. Also, we showed from **1a** that addition of an organometallic such as butyllithium or 4-dimethylaminomethylbenzenemagnesium bromide [3] was easy and led respectively to the tertiary alcohol **4a** or the aminoalcohol **5a** precursors of a structure close to the biological active prothiaden [4].

Scheme I

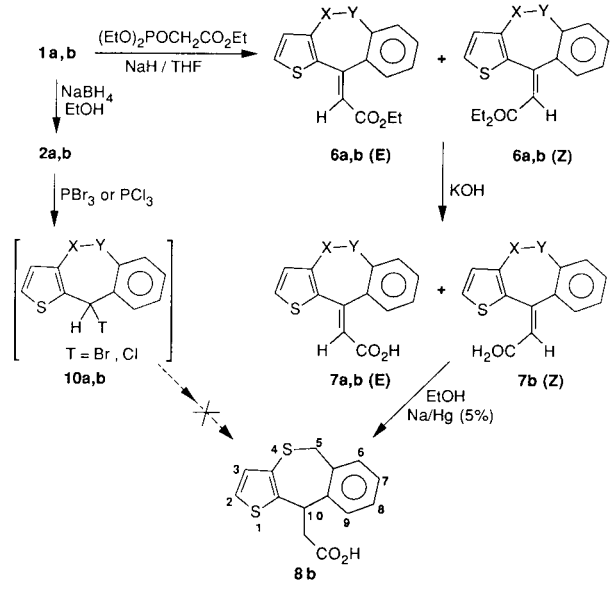


Functionalization of the tricyclic ketones **1a,b** at the 10-position using Wittig chemistry afforded the unsaturated esters **6a,b** as a mixture of *E* and *Z* isomers (Table 1). The reaction mixture was readily analysed using ^{1}H nmr spectroscopy. The *Z* minor form for both cases would be due to an unfavourable interaction between the electron pair of the sulfur atom of the thiophene ring and the close carboxylate group in the intermediate betaïne. The **6a** (*Z*) and **6a** (*E*) isomers have been separated by chromatography but only **6b** (*E*) was isolated pure under the same conditions. The chemical shifts of the α and β protons of the thiophene ring are in accordance with those observed elsewhere [5] for α-phenyl-β-(thien-2-yl)acrylic acid.

Table 1

Compound No.	**6a**		**6b**	
Crude yield %	75		65	
Configuration	*E*	*Z*	*E*	*Z*
%	75-66	25-34	66-50	34-50
	^{1}H NMR thiophene-H and vinyl-H			
H_α thiophene	7.05(d)	7.20(d)	7.25(d)	7.15(d)
H_β thiophene	6.65(d)	6.80(d)	6.65(d)	6.70(d)
Vinyl-H	6.35(s)	6.05(s)	6.40(s)	6.00(s)

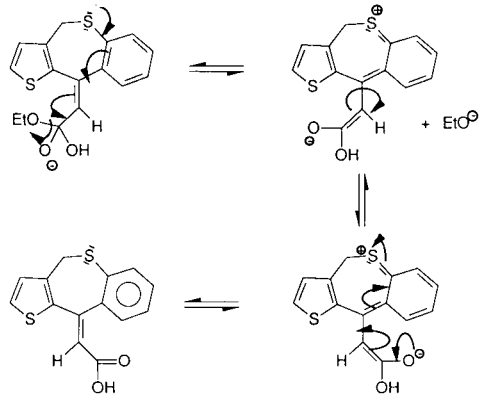
Scheme II



The 4,10-dihydrobenzo[*b*]thieno[2,3-*e*]thiepin-10-acetic acid (**8a**) and the 5,10-dihydrobenzo[*e*]thieno[3,2-*b*]thiepin-10-acetic acid (**8b**) were synthesized from vinylesters **6a,b** (Scheme II).

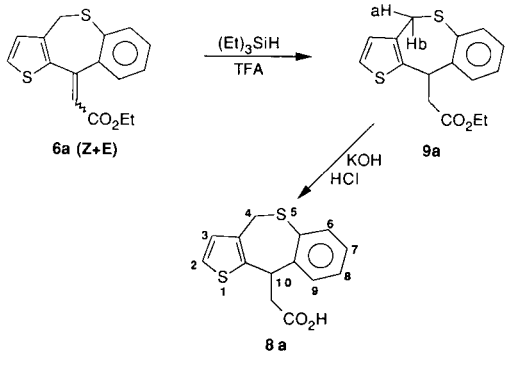
Saponification of the mixture **6a** (*Z*+*E*) isomers producted an isomerization because only the acid **7a** (*E*) was isolated. From the esters **6b** (*Z*+*E*) the expected mixture of acids **7b** (*Z*+*E*) was obtained, no isomerization was observed in this case. We suggest for this isomerization process a better conjugation in **6a** compared to **6b** between the sulfur atom of the thiepine ring with the carboxylate group (see Scheme III) leading to a free rotation. Then the more stabe *E* isomer is preferentially formed.

Scheme III



The selective reduction [6] of the double bond of the acid **7b** (*Z*+*E*) was achieved with a sodium-amalgam but the reaction of **7a** (*E*) was not observed, whatever the conditions the acid was unchanged. So, another way has been explored from the vinylester **6a** (Scheme IV). The selective reduction of the double bond was carried out using triethylsilane in trifluoroacetic acid [7]. The resultant saturated ester **9a** was isolated in a 86% yield. Other methods of reduction such as zinc/acetic acid, chromium sulfate in water [8], hydrogen with palladium on carbon, alkali metal in hexamethylphosphotriamide [9] were unsuccessful; the starting material was generally recovered.

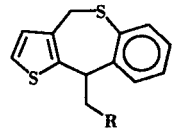
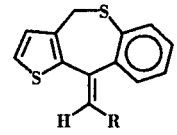
Scheme IV



Saponification of the ester **9a** afforded the expected saturated acid **8a** in a 87% yield. The acids **8a,b** could be prepared from alcohols **2a,b**, unfortunately the halogeno derivatives **10a,b** were very unstable and it was not possible to proceed in this way.

The reactivity of the acid **8a** has been investigated (see Table 2). Treatment of this acid with successively triethylamine, ethyl chloroformate and sodium azide [10] furnished the carbonylazide **11**. When heated in benzene or *o*-dichlorobenzene **11** led to the isocyanate **13**. This compound was not isolated, but heated in ethanol gave the ethyl carbamate **15**. Reaction of this product with a hot solution of hydrochloric acid [6], or with sodium borohydride in dioxane or tetrahydrofuran [11] afforded the aminomethyl **17**. This amine treated either with acetic anhydride or benzoyl chloride was converted to its amide derivative **18** or **19**. All attempts to realize a cyclization with the benzene ring by reaction of compounds **15**, **18** and **19** with phosphorus pentachloride were unsuccessful. It seems that the benzene ring was not activated enough for an electrophilic attack while a similar reaction with a thiophene ring has been described [6]. On the other hand as we have previously showed elsewhere [12], the isocyanate **13** with aluminium chloride did not give a cyclic lactam but the substituted urea **20**.

Table 2

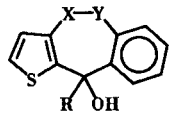
R		
CO_2H	**8a**	**7a**
CON_3	**11**	**12**
N=C=O	**13**	**14**
$NHCO_2R_1$	**15** ($R_1 = C_2H_5$)	**16** ($R_1 = CH_3$)
NH_2	**17**	-
$NHCOCH_3$	**18**	-
$NHCOC_6H_5$	**19**	-
-NH-C(=O)-NH-	**20**	**21**
$CONHNH_2$	**22**	-
CONHN=CHOEt	**23**	-
	**24**	-

Similar reactions have been investigated from the acid **7a**. Then, we isolated the carbonylazide **12**, the isocyanate **14**, the carbamate **16** and the substituted urea **21**. No product of cyclization have been observed in this series.

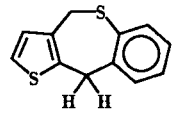
Finally, it is known that some oxadiazole structures have interesting pharmacology activities [13,14,15], so it prompted us to synthesize the oxadiazole **24** substituted with our tricyclic thiepin system. Then, treatment of the ester **9a** with hydrazine monohydrate in warm ethanol [16]

Table 3

Physical and Spectral Data of Compounds **2a, 2b, 3a** and **4a**



2a, 2b and **4a**



3a

Product No.	X / Y	R	Yield (%)	Mp (°C)	IR (KBr) ν cm^{-1} (O-H) broad	Formula	Analyses: Calcd./Found C, %	H,%
2a	CH_2/S	H	96	144-148	3800-2900	$C_{12}H_{10}OS_2$	C, 61.51	H, 4.30
							C, 61.47	H, 4.20
2b	S/CH_2	H	94	154-158	3550-3050	$C_{12}H_{10}OS_2$	C, 61.51	H, 4.30
							C, 61.42	H, 4.22
3a	CH_2/S	-	89	71-72	----------	$C_{12}H_{10}S_2$	C, 66.01	H, 4.62
							C, 65.95	H, 4.38
4a	CH_2/S	Bu	91	oil [a]	3240-2740	$C_{16}H_{18}OS_2$	C, 66.17	H, 6.24
							C, 66.05	H, 6.05

Product No.	X / Y	R	Recrystallization	^{1}H NMR (deuteriochloroform) δ in ppm
2a	CH_2/S	H	hexane	3.95 (s, 2H, CH_2-S), 4.1 (d, 1H, OH (CH)), 6.27 (d, 1H, CH (OH)), 6.72 (d, 1H, J = 5 Hz, H_4 thiophene), 7.2 (d, 1H, J = 5 Hz, H_5 thiophene), 7.25-7.55 (m, 3H, benzene-3H), 7.7 (m, 1H, benzene-1H)
2b	S/CH_2	H	cyclohexane	3.8 (s, 2H, CH_a (CH_b)), 4.9 (d, 1H, CH_b (CH_a)), 5.9 (s, 1H, CH-OH), 6.7 (d, 1H, J = 5.2 Hz, H_4 thiophene), 7.2 (d, 1H, J = 5.2 Hz, H_5 thiophene), 7.25 (s, 4H, benzene-4H), 7.7 (s, 1H, O-H)
3a	CH_2/S	-	ethanol	3.7 (s, 2H, CH_2), 4.27 (s, 2H, CH_2-S), 6.65 (d, 1H, J = 5.6 Hz, H_4 thiophene), 7.1-7.35 (m, 4H, benzene-4H and H_5 thiophene), 7.65 (m, 1H, benzene-1H)
4a	CH_2/S	Bu	oil	0.55-1.65 (m, 9H, -$(CH_2)_3$-CH_3 (butyl), 3.40 (s, 1H, O-H), 3.87 (s, 2H, CH_2-S), 6.6 (d, 1H, J = 6 Hz, H_4 thiophene), 6.95 (d, 1H, J = 6 Hz, H_5 thiophene), 7.0-7.9 (s, 4H, benzene-4H)

[a] The ir spectra of this compound was recorded neat.

afforded the carbonylhydrazine **22** in 83% yield. This reacted with an excess of ethyl orthoformate [17] gave compound **23**. Thermolysis of this compound in toluene or xylene afforded the expected 4,10-dihydro-10-(1,3,4-oxadiazol-2-yl)benzo[*b*]thieno[2,3-*e*]thiepine (**24**) in a 69% yield.

All of the new products were identified by elemental analyses, ir and nmr spectra.

EXPERIMENTAL

The ir spectra were run on a Beckmann IR-20 spectrometer. The ^{1}H nmr spectra were recorded on a Varian EM-360 (60 MHz) spectrometer or Bruker AC-200 (200 MHz) with TMS as internal standard. Elemental analyses were performed by laboratoire de microanalyse de l'I.N.S.A de Rouen, place Emile Blondel, 76130 Mont-Saint-Aignan, France. All melting points were determined on a Leitz melting point microscope and are uncorrected.

Reduction of Ketones **1a,b** with Sodium Borohydride in Ethanol.

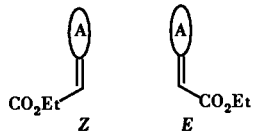
A solution of ketone **1a** or **1b** (1 g, 4.31 mmoles) in 30 ml of ethanol was heated at 60° and sodium borohydride (0.33 g, 8.62 mmoles) was added in portions. The mixture was refluxed for 2 hours. The reaction mixture was poured into water (30 ml) and the precipitate was filtered and recrystallized to give **2a,b** as white solids. Physical constants are given in Table 3.

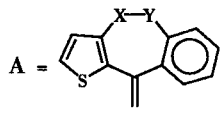
Reduction of Ketone **1a** with Borohydride in Trifluoroacetic Acid.

To a magnetically stirred trifluoroacetic acid (0.8 ml, 10 mmoles) in 20 ml of anhydrous tetrahydrofuran at 0-5° and under nitrogen, was added 0.38 g (10 mmoles) of sodium borohydride pellets over 30 minutes. After 0.5 hour of reaction at the same temperature, 2.32 g (10 mmoles) of ketone **1a** in 20 ml of dry tetrahydrofuran was added dropwise over a period of 30 minutes. After 5 hours of reaction at 20°, the mixture was treated cautiously with ice water (50 ml) below 10°, made basic with 50 ml of 50% potassium carbonate and extracted with methylene chloride (100 ml). The organic extract was washed with water, dried and evaporated to provide after recrystallization **3a** in good yield (Table 3).

Table 4

Analytical and Spectral Data of Isomeric Vinylesters **6a** (*E*+*Z*) and **6b** (*E*+*Z*)





X, Y = CH_2, S

X = CH_2, Y = S **6a**

X = S, Y = CH_2 **6b**

Product No.	Isomer	Mp °C	Yield (%)	% isomers [a]	Analyses: Calcd./Found $C_{16}H_{14}O_2S_2$: C%, 63.53; H%, 4.66	
6a	*E*	87-88	75	75-66	63.51	4.32
	Z	127-128		34-25	63.30	4.58
6b	*E*	121	65	66-50	63.08	4.52
	Z	118		50-34	63.47	4.50

Product No.	Isomer	IR (KBr) ν in cm^{-1} C=O	^1H NMR (deuteriochloroform) δ in ppm
6a	*E*	1645	1.05 (t, 3H, CH_3(Et)), 3.8 (s, 2H, CH_2-S), 4.0 (q, 2H, CH_2(Et)), 6.35 (s, 1H, vinyl-H), 6.65 (d, 1H, J = 6 Hz, H_4 thiophene), 7.05-7.4 (m, 4H, benzene-3H and H_5 thiophene), 7.5-7.7 (m, 1H, benzene-1H)
	Z	1640	1.24 (t, 3H, CH_3(Et)), 4.05 (s, 2H, CH_2-S), 4.12 (q, 2H, CH_2(Et)), 6.05 (s, 1H, viny,-H), 6.8 (d, 1H, J = 5.2 Hz, H_4 thiophene), 7.20-7.70 (m, 5H, benzene-4H and H_5 thiophene)
6b	*E*	1675	1.1 (t, 3H, CH_3(Et)), 4.0 (q, 2H, CH_2(Et)), 4.0 (s, 2H, CH_2-S), 6.4 (s, 1H, vinyl-H), 6.65 (d, 1H, J = 6 Hz, H_4 thiophene), 7.25 (d, 1H, J = 6 Hz, H_5 thiophene), 7.4 (m, 4H, benxene-4H)
	Z	1665	1.3 (t, 3H, CH_3(Et)), 4.13 (s, 2H, CH_2-S), 4.25 (q, 2H, CH_2(Et)), 6.0 (s, 1H, vinyl-H), 6.7 (d, 1H, J = 5.4 Hz, H_4 thiophene), 7.15-7.5 (m, 5H, benzene-4H and H_5 thiophene)

[a] Are determined by ^1H nmr spectroscopy.

Addition of Butyllithium to Ketone **1a**. Tertiary Alcohol **4a**.

A solution of butyllithium (6.6 ml of an hexane solution, 1.65*N*) was added dropwise under nitrogen at −70° to a stirred solution of **1a** (2.32 g, 10 mmoles) in anhydrous diethyl ether. After 2 hours of reaction at the same temperature, the mixture was allowed to stir at −10° for 1.5 hours and poured onto crushed ice. The product was extracted several times with diethyl ether. The combined organic layers were washed with water, dried over anhydrous magnesium sulfate and concentrated to give **4a** as an oil. Physical and spectral data of this compound are given in Table 3.

The Grignard Reaction of Ketone **1a** with 4-Dimethylaminomethylphenylmagnesium Bromide.

The Grignard reagent was prepared from *N,N*-dimethyl-4-bromobenzylamine according to the reported procedure [3] (3.57 g, 16.7 mmoles) and magnesium (0.75 g, 32.5 g-atoms) in 40 ml of dry tetrahydrofuran. Then it was treated dropwise under stirring with a solution of **1a** (1.95 g, 8.41 mmoles) in 25 ml of dry tetrahydrofuran. The mixture was refluxed for 4 hours, allowed to stand overnight at room temperature, diluted with ether, and decomposed by 20% ammonium chloride (50 ml). The organic layer was shaken with 10% hydrochloric acid, the resultant precipitated hydrochloride of **5a** was filtered, washed with diethyl ether and recrystallized from ethanol-diethyl ether (66%), mp 229-231°.

The free base **5a** was obtained after treatment of the hydrochloride salt with a solution of potassium hydroxide 4*N* below 15° in a 62% yield, mp 142-143°; ir (potassium bromide): ν 3360-2950 (O-H) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.12 (s, 6H, $N(CH_3)_2$), 3.15 (s, 2H, CH_2-N), 3.35 (s, 2H, CH_2-S), 7.15-8.05 (m, 10H, benzene-8H, H_4 and H_5 thiophene), 8.9 (s, 1H, O-H).

Anal. Calcd. for $C_{21}H_{21}NOS_2$: C, 68.63; H, 5.72; N, 3.83. Found: C, 68.39; H, 5.51; N, 3.59.

The Wittig Reaction of Ketones **1a,b** with Triethyl phosphonacetate.

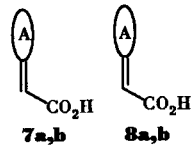
To a stirred suspension of sodium hydride (0.74 g, 18.5 mmoles as a 60% dispersion in mineral oil) in 20 ml of dry tetrahydrofuran, triethyl phosphonacetate (3.95 g, 17.4 mmoles) under nitrogen was added at a rate such that the reaction temperature was maintained at 30-35°. The mixture was stirred at room temperature for 1 hour and a solution of ketone **1a** or **1b** (2 g, 8.6 mmoles) in 40 ml of tetrahydrofuran was added dropwise over 30 minutes. The mixture was refluxed for 70 hours and poured into ice-water. The product was extracted with diethyl ether washed with water, dried and concentrated to give a mixture of *Z* and *E* isomeric ethyl esters **6a,b** as an oil. The residue was separated by chromatography on a fluorisil column eluting with hexane-benzene. The first fractions gave pure **6a,b** (*E*-isomer) and the second fractions gave a mixture of *E* and *Z* isomers separated by recrystallization from ethanol. All physical and spectral data of these products are summarized in Table 4.

Saponification of Unsaturated Esters **6a,b** (*Z*+*E*).

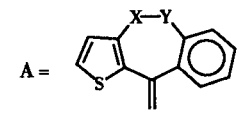
The esters **6a,b** (*Z*+*E*) (3.4 g, 11.3 mmoles) was hydrolyzed by refluxing for 5 hours in a mixture of ethanol (40 ml) and 10% aqueous sodium hydroxide (40 ml). The ethanol was evaporated and the residue was acidified with 2*N* aqueous hydrochloric acid. The white solid precipitated was filtered, washed with water, air

Table 5

Yields and Physical Data of Saturated Acids **8a,b** and Unsaturated Acids **7a,b**



7a,b **8a,b**



X, Y = CH_2, S

X = CH_2, Y = S **a**

X = S, Y = CH_2 **b**

Product No.	Isomer	Mp °C	Yield (%)	Recrystallizaion [a]	Formula	Analyses: Calcd./Found C, %	H, %
7a	*E*	210-212	85	A	$C_{14}H_{10}O_2S_2$	61.29 61.18	3.67 3.37
7b	*Z+E*	229-231	87	B-C (3/2)	$C_{14}H_{10}O_2S_2$	61.29 61.21	3.67 3.52
8a	-	169	87	B-C	$C_{14}H_{12}O_2S_2$	60.84 60.70	4.38 4.35
8b	-	204	83	D-E (2/1)	$C_{14}H_{12}O_2S_2$	60.84 60.65	4.38 4.30

Product No.	Isomer	IR (KBr) ν in cm^{-1} C=O	O-H	^1H NMR (deuteriochloroform) δ in ppm
7a	*E*	1670	3400-2200	3.0-4.2 (broad, 1H, OH), 4.02 (s, 2H, CH_2-S), 6.30 (s, 1H, vinyl-H), 6.9 (d, 2H, J = 6.2 Hz, H_4 thiophene), 7.2-7.5 (m, 4H, benzene-4H), 7.55 (d, 1H, J = 6.2 Hz, H_5 thiophene)
7b	*Z+E*	1635	3300-2400	4.0-4.5 (broad, 2H, OH (*Z+E*)), 4.2 (s, 4H, S-CH_2 (*Z+E*)), 6.0 (s, 1H, vinyl-H (*Z*)), 6.35 (s, 1H, vinyl-H (*E*)), 6.85 (d, 2H, J = 5.9 Hz, H_4 thiophene (*Z+E*)), 7.1-7.8 (m, 10H, benzene-4H (*Z+E*) and H_5 thiophene (*Z+E*))
8a	-	1675	3300-2300	2.8-4.7 (broad, 1H, OH), 3.32 (d, 2H, CH_2(CH)), 4.1 (s, 2H, CH_2-S), 5.2 (t, 1H, CH(CH_2)), 6.8 (d, 1H, J = 5.2 Hz, H_4 thiophene), 7.15-7.76 (m, 5H, benzene-4H and H_5 thiophene)
8b	-	1630	3350-2200	2.85-3.75 (broad, 1H, OH), 3.15 (d, 2H, CH_2 (CH)), 4.15 (d, 1H, J = 14 Hz, CH_a (CH_b)), 4.65 (d, 1H, J = 14 Hz, CH_b (CH_a)), 5.05 (t, 1H, CH (CH_2)), 6.75 (d, 1H, J = 5 Hz, H_4 thiophene), 7.1-7.55 (m, 5H, benzene-4H and H_5 thiophene)

[a] Solvents: A = Pentane, B = Ethanol, C = Water, D = Benzene, E = Hexane.

dried and recrystallized from suitable solvent (Table 5). We obtained the acids **7b** (*Z+E*) in the corresponding ratio of the starting esters **6b** (*Z+E*) and only the acid **7a** (*E*) in the case of the starting esters **6a** (*Z+E*).

Selective Reduction of the Double Bond of Unsaturated Acid **7b** (*Z+E*).

The above acids **7b** (*Z+E*) (2 g, 7.3 mmoles) in 40 ml of hot ethanol was added to a flask containing 5% sodium/amalgam (40 g). The mixture was stirred for 4 hours at 60-70°, the ethanol layer was decanted and the residue was washed with ethanol. The combined ethanol solutions were diluted with an equal volume of water and acidified with 2*N* aqueous hydrochloric acid. The resultant solid was filtered, washed with water, dried and recrystallized to give **8b**. The physical constants are given in Table 5.

The Selective Reduction of the Double Bond of Unsaturated Esters **6a** (*Z+E*).

A solution of **6a** (*Z+E*) (3.02 g, 10 mmoles) in 30 ml of trifluoroacetic acid was stirred under an atomosphere of nitrogen and cooled in an ice bath. The solution was treated with 1.2 g (10.3 mmoles) of triethylsilane, added dropwise over a period of 5 minutes. After removal of this ice bath, the stirring was continued for 30 minutes. The mixture was then poured into ice-water, made alkaline by the addition of ammonia and extracted with dichloromethane. The extracts were combined, dried and evaporated. The residue was chromatographed on a fluorisil column eluting with hexane-benzene (4:1) to give **9a** as an oil (86%); ir (neat): ν 1635 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.05 (t, 3H, CH_3 (Et)), 3.30 (d, 1H, J = 8.2 Hz, -CH_a-S (-CH_b-S)), 3.45 (d, 1H, J = 8.2 Hz, -CH_b-S (-CH_a-S)), 3.76 (d, 2H, CH_2-CO_2 Et (C-H)), 3.98 (q, 2H, CH_2 (Et)), 4.95 (t, 1H, C-H (CH_2-CO_2Et)), 6.50 (d, 1H, J = 6.2 Hz, H_4 thiophene), 6.9 (d, 1H, J = 6.2 Hz, H_5 thiophene), 6.95-7.70 (m, 4H, benzene-4H).

Anal. Calcd. for $C_{16}H_{16}O_2S_2$: C, 63.11; H, 5.29. Found: C, 63.02; H, 5.10.

4,10-Dihydrobenzo[*b*]thieno[2,3-*e*]thiepin-10-acetic Acid (**8a**).

In a similar manner as described for the synthesis of carboxylic acids **7a,b**, the above ester **9a** (3.04 g, 10 mmoles) with 3 g (50 mmoles) of potassium hydroxide pallets in 60 ml of alcohol-water (1:1) solution was converted to the corresponding acid **8a**. The physical constants are summarized in Table 5.

General Procedure for the Synthesis of Carbonylazides **11** and **12**.

A solution of 10 mmoles of carboxylic acid **7a** or **8a** in 75 ml of dry acetone and 11 moles of triethylamine was cooled in a ice-salt

bath. To the well stirred and cold solution, under an atmosphere of nitrogen, a solution of 11 mmoles of ethyl chloroformate in 7.5 ml of acetone was added dropwise over a period of 30 minutes. The reaction mixture was allowed to stir at 0° for an additional 15 minutes and a solution of 11 mmoles of sodium azide in 10 ml of water was added dropwise over 20 minutes. The mixture was allowed to stir at 0° for 30 minutes then poured onto crushed ice.

The solid azide **12** was filtered and recrystallized from diethyl ether-hexane to give **12** (*Z*+*E*, ¼) in a 88% yield, mp 118-120° dec; ir (potassium bromide): ν 2215 (CO-N_3), 1635 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.85 (s, 2H, CH_2-S (*E*)), 4.0 (s, 2H, CH_2-S (*Z*)), 6.05 (s, 1H, vinyl-H (*Z*)), 6.3 (s, 1H, vinyl-H (*E*)), 6.75 (d, 1H, J = 4.8 Hz, H_4 thiophene (*E*)), 6.85 (d, 1H, J = 4.8 Hz, H_4 thiophene (*Z*)), 7.1-7.8 (m, 10H, benzene-4H (*Z*+*E*) and H_5 thiophene (*Z*+*E*)).

Anal. Calcd. for $C_{14}H_9N_3OS_2$: C, 56.16; H, 3.03; N, 14.03. Found: C, 56.02; H, 3.01; N, 14.00.

The oily azide **11** was extracted several times with carbon tetrachloride, washed with water and dried. Evaporation of the solvent yielded 2.39 g (80%) pure **11** as an orange oil. This azide was used for the next reaction without further purification; ir (neat): ν 2125 (CO-N_3), 1760 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.25 (d, 2H, CH_2 (C-H)), 3.75 (s, 2H, CH_2-S), 4.89 (t, 1H, C-H (CH_2)), 6.5 (d, 1H, J = 5 Hz, H_4 thiophene), 6.8-7.7 (m, 5H, H_5 thiophene and benzene-4H).

General Procedure for the Synthesis of Isocyanates **13** and **14**.

The above saturated azide **11** (1 g, 3.32 mmoles) or unsaturated azide **12** (1 g, 3.35 mmoles) was dissolved in 20 ml of dry benzene or *ortho*-dichlorobenzene and was refluxed for 2.5 hours. The mixture was treated with charcoal and evaporated to leave the isocyanate **13** as an orange oil (0.79 g, 87%); ir (neat): ν 2250 (N=C=O), 1690 (C=O) cm^{-1}, or the unsaturated isocyanate **14** as an oil (0.86 g, 95%); ir (neat): ν 2255 (N=C=O), 1670 (C=O) cm^{-1}.

These compounds were shown to be somewhat unstable.

General Procedure for obtaining Carbamates **15** and **16**.

The foregoing isocyanate **13** (1 g, 3.66 mmoles) in 30 ml of ethanol was refluxed for 12 hours. The hot mixture was filtered and the filtrate evaporated. Trituration of the residual oil with diethyl ether afforded the carbamate **15** (1 g, 86%) as white needles, mp 203-204°; ir (potassium bromide): ν 3360-2800 (NH-C=O), 1590 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.12 (t, 3H, CH_3 (Et)), 3.5 (d, 1H, CH_a-S (CH_b)), 3.7 (d, 1H, CH_b-S (CH_a)), 3.8 (d, 2H, CH_2-NH (C-H)), 3.85-4.22 (m, 3H, CH_2 (Et) and C-H (CH_2-N-H)), 4.36-4.9 (broad, 1H, N-H), 6.55 (d, 1H, J = 5.2 Hz, H_4 thiophene), 6.9-7.27 (m, 5H, benzene-4H and H_5 thiophene).

Anal. Calcd. for $C_{16}H_{17}NO_2S_2$: C, 60.16; H, 5.36; N, 4.38. Found: C, 60.05; H, 5.18; N, 4.38.

In a similar process as described for the synthesis of **15**, the isocyanate **14** (1 g, 3.69 mmoles) with 20 ml of methanol led to compound **16** (0.9 g, 79%) after 24 hours of refluxing. Recrystallization for analysis from ethanol-water (3:2) gave colourless crystals with mp 188-189°; ir (potassium bromide): ν 3340-2900 (NH-C=O), 1680 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.7 (s, 3H, CH_3), 3.9 (s, 2H, CH_2-S), 6.7 (d, 1H, J = 5.4 Hz, H_4 thiophene); 6.95 (d, 1H, J = 5.4 Hz, H_5 thiophene), 7.15 (s, 1H, vinyl-H), 7.2-7.35 (m, 4H, benzene-3H and N-H), 7.45-7.7 (m, 1H, benzene-1H).

Anal. Calcd. for $C_{15}H_{13}NO_2S_2$: C, 59.38; H, 4.32; N, 4.62. Found: C, 59.22; H, 4.22; N, 4.26.

10-Aminomethyl-4,10-dihydrobenzo[*b*]thieno[2,3-*e*]thiepine (**17**).

Method A. Hydrolysis of the Urethane **15**.

A mixture of carbamate **15** (1 g, 3.13 mmoles) and 20 ml of concentrated hydrochloric acid was refluxed for 18 hours. The hot mixture was filtered and the filtrate evaporated. The residual oil was treated with 50 ml of 20% potassium hydroxide below 10° and extracted with 50 ml of diethyl ether. The organic layer was washed with water, dried and evaporated. Trituration of the residue with diethyl ether-hexane (1:3) led to amine **17** (0.36 g, 46%) as an orange solid, mp 52-55°; ir (potassium bromide): ν 3600-2830 (NH_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.5 (s, 2H, NH_2), 3.55 (d, 1H, J = 18 Hz, CH_a-S (CH_b)), 3.65 (d, 1H, J = 18 Hz, CH_b-S (CH_a)), 3.9 (d, 2H, CH_2-NH_2 (C-H)), 4.3 (t, 1H, CH (CH_2-NH_2)), 6.6 (d, 1H, J = 5.6 Hz, H_4 thiophene), 7.1 (d, 1H, J = 5.4 Hz, H_5 thiophene), 7.2-7.4 (m, 3H, benzene-3H), 7.5-7.8 (m, 1H, benzene-1H).

This product was used directly for the next step.

Method B. Reduction of Urethane **15** with Sodium Borohydride.

To a suspension of carbamate **15** (1 g, 3.13 mmoles) and 0.12 g (3.13 mmoles) of sodium borohydride in 30 ml of dry dioxane, a solution of acetic acid (1.88 g, 31.13 mmoles) in 10 ml of dry dioxane was added dropwise during 10 minutes at 10°. The mixture was refluxed for 2 hours, hydrolyzed with 50 ml of 10% potassium carbonate and extracted with chloroform. The organic layer was dried and evaporated to yield the amine **17** (0.52 g, 67%) identical with that described above.

N-(4,10-Dihydrobenzo[*b*]thieno[2,3-*e*]thiepin-10-ylmethyl)-acetamide (**18**).

A solution of the aminomethyl derivative **17** (1 g, 3.63 mmoles) in 15 ml of ethanol, anhydride acetic (0.85 g, 8 mmoles) in 2 ml of acetic acid was added at 25°. The mixture was stirred for 4 hours at 60°, 2 hours at room temperature and then extracted with benzene. The extracts were washed with water, dried over magnesium sulfate and evaporated to yield the acetamide **18** (0.9 g, 77%), mp 121-124° (benzene-hexane); ir (potassium bromide): ν 3290-2450 (NH-C=O), 1650 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.95 (s, 3H, NH-$COCH_3$), 3.90 (d, 2H, CH_2-N-H (C-H)), 4.1 (s, 2H, CH_2-S), 4.25 (t, 1H, C-H (CH_2-N-H)), 5.6 (broad, 1H, N-H), 6.95 (d, 1H, J = 5.8 Hz, H_4 thiophene), 7.15 (d, 1H, J = 5.8 Hz, H_5 thiophene), 7.20-7.35 (m, 4H, benzene-4H).

Anal. Calcd. for $C_{15}H_{15}NOS_2$: C, 62.25; H, 5.22; N, 4.84. Found: C, 62.09; H, 5.05; N, 4.76.

N-(4,10-Dihydrobenzo[*b*]thieno[2,3-*e*]thiepin-10-ylmethyl)benzamide (**19**).

To a suspension of the 10-aminomethyl derivative **17** (2.75 g, 10 mmoles) in 15 ml of 10% sodium hydroxide, benzoyl chloride (2.2 g, 16 mmoles) was added dropwise at 15°. The mixture was stirred for 3 hours at the same temperature and the white precipitate was filtered, washed with water and dried. Recrystallization from acetic acid afforded the benzamide in a 83% yield as white needles, mp 152-153°; ir (potassium bromide): δ 3500-2800 (NH-C=O), 1620 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.85 (d, 2H, CH_2-N-H (C-H)), 4.2-4.7 (m, 3H, CH_2-S and C-H (CH_2-N-H)), 6.65 (d, 1H, J = 5 Hz, H_4 thiophene), 6.95-7.9 (m, 10H, benzene-4H, benzene-5H (benzamide) and H_5 thiophene), 8.76 (s, 1H, N-H).

Anal. Calcd. for $C_{20}H_{17}NOS_2$: C, 68.34; H, 4.88; N, 3.99. Found: C, 68.21; H, 4.73; N, 3.89.

N,N-Di-(4,10-dihydrobenzo[*b*]thieno[2,3-*e*]thiepin-10-ylmethyl)-urea (**20**) and *N,N*-Di-(4,10-dihydrobenzo[*b*]thieno[2,3-*e*]thiepin-10-ylidene)urea (**21**).

A mixture of the preceding isocyanate **13** (1 g, 3.66 mmoles) and 30 ml of anhydrous *ortho*-dichlorobenzene was treated with 1.5 g (11 mmoles) of anhydrous aluminum chloride at room temperature. The mixture was heated at 140-145° for 2 hours and hydrolyzed with 40 ml of water after cooling. The mixture was treated with 30% aqueous potassium carbonate and extracted with diethyl ether. The organic layer was dried over magnesium sulfate and concentrated. Trituration of the residual oil with toluene-ligroine furnished urea **20** (0.9 g, 47%) as colorless pellets, mp 109-110°; ir (potassium bromide): ν 3400-2900 (NH-C=O), 1590 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.8 (d, 4H, 2-CH_2-N-H (C-H)), 4.0 (s, 4H, 2-CH_2-S), 4.12-4.8 (broad, 2H, 2-N-H), 4.24 (t, 2H, 2-C-H (CH_2-N-H)), 6.65 (d, 2H, J = 6.4 Hz, 2-H_4 thiophene), 7.1-7.25 (m, 10H, 2-benzene-4H and 2-H_5 thiophene).

Anal. Calcd. for $C_{27}H_{24}N_2OS_4$: C, 62.27; H, 4.65; N, 5.38. Found: C, 62.01; H, 4.52; N, 5.15.

In the same manner isocyanate **14** (1 g, 3.69 mmoles) with 1.47 g, (11.1 mmoles) of aluminium chloride afforded the urea **21** (0.79 g, 42%) which was crystallized from diethyl ether-hexane (1:3) as colorless needles, mp 116-117°; ir (potassium bromide): ν 3620-2750 (NH-C=O), 1695 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.9 (s, 4H, 2-CH_2-S), 4.25 (s, 2H, 2-N-H), 6.35 (s, 2H, 2-vinyl-H), 6.65 (d, 2H, J = 6.2 Hz, 2-H_4 thiophene), 6.9 (d, 2H, J = 6.2 Hz, 2-H_5 thiophene), 7.0-7.8 (m, 8H, 2-benzene-4H).

Anal. Calcd. for $C_{27}H_{20}N_2OS_4$: C, 62.76; H, 3.90; N, 5.42. Found: C, 62.71; H, 4.05; N, 5.24.

4,10-Dihydrobenzo[*b*]thieno[2,3-*e*]thiepin-10-acetic Acid Hydrazide (**22**).

A mixture of 2 g (6.58 mmoles) of saturated ester **9a** and 10 ml of hydrazine hydrate in a mixture of 10 ml of methanol and 10 ml of water was stirred and refluxed for 24 hours. After cooling to room temperature, the precipitate was collected, washed with water and air dried. The compound **22** (1.58 g, 83%) after recrystallization from methanol-diethyl ether melted at 140-142°; ir (potassium bromide): ν 3600-3100 (NH-NH_2), 2920 (C-H), 1650 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.1 (d, 2H, CH_2-CONH (C-H)), 4.05 (s, 5H, CH_2-S and (-NH-NH_2)), 5.25 (t, 1H, C-H (CH_2-CONH)), 5.75 (d, 1H, J = 6 Hz, H_4 thiophene), 7.1-7.35 (m, 4H, 3H benzene and H_5 thiophene), 7.42-7.7 (m, 1H, benzene-1H).

Anal. Calcd. for $C_{14}H_{14}N_2OS_2$: C, 57.90; H, 4.86; N, 9.64. Found: C, 57.81; H, 4.60; N, 9.30.

Ethoxyformaldehyde (4,10-Dihydrobenzo[*b*]thieno[2,3-*e*]thiepin-10-acetyl Hydrazide) **23**.

A mixture of compound **22** (2 g, 6.89 mmoles) and 20 ml of ethyl orthoformate was heated up to the boiling point for 4 hours. After cooling, the precipitate was filtered and crystallized from hexane-diethyl ether (1:3) to give 1.85 g (79%) of the title compound **23** as a white solid, mp 121-123°; ir (potassium bromide): ν 3560-2740 (CONH-N), 1660 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.15 (t, 3H, CH_3 (Et)), 1.8 (s, 1H, N-H), 3.5 (q, 2H, CH_2 (Et)), 3.8 (s, 2H, CH_2-S), 4.0 (d, 2H, CH_2-CONH- (C-H)), 5.05 (t, 1H, C-H (CH_2-CONH-)), 6.56 (d, 1H, J = 5.2 Hz, H_4 thiophene), 6.85 (d, 1H, J = 5.2 Hz, H_5 thiophene), 7.0-7.6 (m, 4H, benzene-4H), 8.1 (s, 1H, CH=N).

Anal. Calcd. for $C_{17}H_{18}N_2O_2S_2$: C, 58.93; H, 5.24; N, 8.08. Found: C, 58.79; H, 5.21; N, 8.01.

4,10-Dihydro-10-(1,3,4-oxadiazol-2-yl)benzo[*b*]thieno[2,3-*e*]thiepine (**24**).

Compound **23** (2 g, 5.78 mmoles) in 20 ml of dry xylene was heated at reflux for 24 hours. After cooling, the mixture was treated with charcoal and filtered. The precipitated was collected by filtration and recrystallized from ethyl acetate-petroleum ether (1:3) to give oxadiazole derivative **24** (1.2 g, 69%) as a white solid, mp 124-125°; ir (potassium bromide): ν 2900 (C-H), 1570 (C=N) cm^{-1}, ^1H nmr (deuteriochloroform): δ 3.9 (d, 2H, CH_2 (C-H)), 4.05 (d, 1H, CH_a-S (CH_b-S)), 4.22 (d, 1H, CH_b-S (CH_a-S)), 4.85 (t, 1H, C-H (CH_2)), 6.65 (d, 1H, J = 5.4 Hz, H_4 thiophene), 6.92-7.4 (m, 4H, benzene-3H and H_5 thiophene), 7.48-7.78 (m, 1H, benzene-1H), 8.3 (s, 1H, CH=N).

Anal. Calcd. for $C_{15}H_{12}N_2OS_2$: C, 59.97; H, 4.03; N, 9.32. Found: C, 59.90; H, 4.01; N, 9.17.

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