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AN EFFICIENT AND CONVENIENT SYNTHESIS OF 4,5,6,7-TETRAHYDROTHIENO[3,2-*c*]PYRIDINES BY A MODIFIED PICTET-SPENGLER REACTION *VIA* A FORMYLIMINIUM ION INTERMEDIATE

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Abstract – A synthesis of *N*-formyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridines (**5**) was achieved in a highly efficient manner *via* trifluoroacetic acid catalyzed cyclization of formyliminium ion (**4**), which was produced by imination of 2-(2-thienyl)ethylamine (**1**) and a carbonyl compound (**2**) using titanium(IV) tetraisopropoxide followed by formylation with acetic-formic anhydride in a one-pot procedure. This modified Pictet-Spengler reaction provides a convenient method for preparing 4,5,6,7-tetahydrothieno[3,2-*c*]pyridines (**6**) possessing various substituents at C-4.

INTRODUCTION

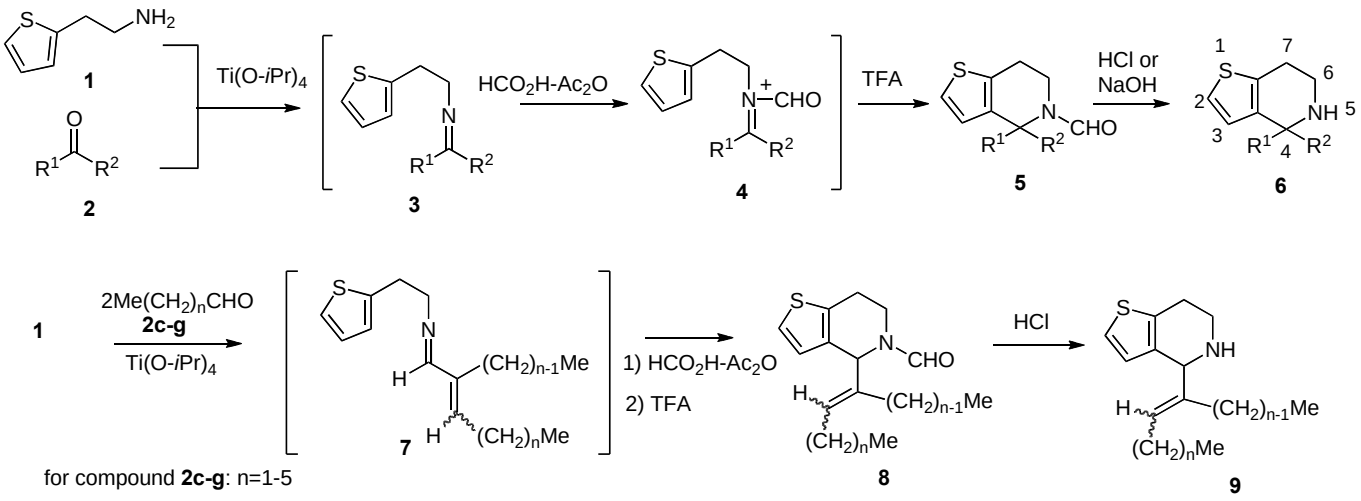
The Pictet-Spengler reaction is a well-known method for constructing 1,2,3,4-tetrahydroisoquinoline and heteroaryl homologs, which constitute important motifs of naturally occurring bioactive compounds.[1] The synthesis of these compounds by the Pictet-Spengler reaction consists of two steps: the formation of an imine by condensation of an arylethylamine with a carbonyl compound, and the acid-catalyzed cyclization of the *in situ* generated imine. We recently modified both the imination and the cyclization steps. We discovered that imination in titanium(IV) tetraisopropoxide[2] proceeded in a highly effective manner and that cyclization readily occurred in trifluoroacetic acid (TFA) when the imine was converted

into a formyliminium ion.[3] This modified method effectively enables the Pictet-Spengler reaction to be applied to ketones, which is known to be difficult,[4] providing 1,1-disubstituted 1,2,3,4-tetrahydroisoquinolines[3] and 1,1-disubstituted tetrahydro-β-carbolines.[5] This modified method also induced the Pictet-Spengler reaction of phenylethylamine with aldehydes, although the benzene ring lacks electron-donating groups, providing 1-substituted 1,2,3,4-tetrahydroisoquinolines in high yields.[6] Yokoyama *et al.* reported that no cyclization of imines proceeded in TFA.[7]

In this paper we describe the modified Pictet-Spengler reaction of 2-(2-thienyl)ethylamine (**1**) with aldehydes and ketones, which should provide a convenient method for preparing 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridines[8] with various substituents at the C-4 position. Some 4-substituted derivatives have been reported to have biological activities. For example, 4-methyl-4-phenyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (**6k**) is a known *N*-methyl-D-aspartate (NMDA) antagonist,[9] and 4-aryl-5-aroyl derivatives containing this ring system are glucose-6-phosphatase catalytic enzyme inhibitors.[10]

RESULTS AND DISCUSSION

The Pictet-Spengler reaction was carried out in a one-pot procedure as follows (Scheme 1). 2-(2-Thienyl)ethylamine (**1**) (1.2 mol equiv) and a carbonyl compound (**2**) (1.0 mol equiv) were condensed at 80 °C in titanium(IV) tetraisopropoxide (1.8 mol equiv) for 3 h, and the *in situ* formed imine (**3**) was treated with acetic-formic anhydride (100 mol equiv) at 70 °C for 2 h to produce the formyliminium ion (**4**). To this solution, a large excess (100 mol equiv) of TFA was added at 0 °C and then the solution was heated at 70 °C for an appropriate time, thus producing *N*-formyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridines (**5**). This modified Pictet-Spengler reaction was applied not only to aldehydes (**2a-j** and **2q**) and but also to ketones (**2k-o**), which produced various derivatives with different substitution patterns at the C-4 position. The structure of the product (**5**) was assigned by observation of the characteristic C_4 carbon signals at δ 52.6 and 58.8 ppm (in the case of **5a**) in the ^{13}C NMR spectrum. The results are summarized in Table 1.



Scheme 1: Synthesis of 4-substituted 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridines using modified Pictet-Spengler reaction

Benzaldehyde (**2a**), cyclopropanecarboxaldehyde (**2h**), cyclopentanecarboxaldehyde (**2i**), and cyclohexanecarboxaldehyde (**2j**) gave the corresponding 4-monosubstituted *N*-formyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridines (**5a, 5h, 5i, 5j**) in yields of 93, 72, 83, and 91%, respectively. The cyclization of imines (**3a** and **3j**), as already reported by Madsen *et al.*, proceeded in TFA at room temperature, but the yields of the products (**5a** and **5j**) were only 24% and 8%, respectively.[9] This indicated that our modified method has an advantage over the conventional one.

On the other hand, paraldehyde, a trimer of acetaldehyde (**2b**) and propionaldehyde (**2c**) gave the expected products (**5b**, **5c**), although in 24, 12% yields, respectively. This unsatisfactory result of the reaction may be attributed to the high reactivity of these aldehydes for aldol condensation. In fact, the reaction of **2c** yielded the *N*-formyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (**8c**) having a pent-2-en-2yl side chain at the C4 as a major product in 31% yield. The formation of **8c** is readily explained by assuming the formation of the imine (**7c**) that is formed from 1 mol eqiv of amine (**1**) and 2 mol eqiv of propionaldehyde (**2c**) as shown in Scheme 1. Other alkyl aldehydes, *n*-butanal (**2d**), *n*-pentanal (**2e**), *n*-hexanal (**2f**), and *n*-heptanal (**2g**), gave the similar results, thus yielding the corresponding 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine derivative (**5d, 5e, 5f, 5g**) in yields of 49-56% together with the minor one (**8d, 8e, 8f, 8g**) in yields of 12-14%.

Table1 Synthesis of *N*-formyl-4,5,6,7-tetrahydrothieno[3.2-*c*]pyridines (**5**) using the Modified Pictet-Spengler reaction of 2-(2-thienyl)ethylamine (**1**)

Run	Aldehydes/ Ketones	R^1	R^2	Cyclization of *N*-formyliminium ion (**4**) Acid	Temp (¡C)	Time (h)	Products **5**	Yields (%)	**8**	Yields (%)
1	**2a**	H	Ph	TFA	70	16	**5a**	93		
2	**2b**	H	Me	TFA	70	1.5	**5b**	24		
3	**2c**	H	Et	TFA	70	1.5	**5c**	12	**8c** (n=1)	31
4	**2d**	H	*n*-propyl	TFA	70	1.5	**5d**	53	**8d** (n=2)	14
5	**2e**	H	*n*-butyl	TFA	70	1.5	**5e**	56	**8e** (n=3)	13
6	**2f**	H	*n*-pentyl	TFA	70	1.5	**5f**	49	**8f** (n=4)	14
7	**2g**	H	*n*-hexyl	TFA	70	1.5	**5g**	56	**8g** (n=5)	12
8	**2h**	H	cyclopropyl	TFA	70	6	**5h**	72		
9	**2i**	H	cyclopentyl	TFA	70	3	**5i**	83		
10	**2j**	H	cyclohexyl	TFA	70	3	**5j**	91		
11	**2k**	Me	Ph	TFA	70	3	**5k**	84		
12	**2l**	Me	Me	TFA	70	3	**5l**	74		
13	**2m**	Me	Et	TFA	70	16	**5m**	74		
14	**2n**			TFA	70	16	**5n**	65		
15	**2o**			TFA	70	16	**5o**	51		
16	**2p**	Ph	Ph	TFA	70	3	**5p**	0		
17	**2q**	H	H	TFA	70	1.5	**5q**	69		

Acyclic ketones such as acetophenone (**2k**), acetone (**2l**), and 2-butanone (**2m**) gave the corresponding, 4,4-disubstituted *N*-formyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridines (**5k**, **5l**, and **5m**) in high yields (74-84%). Cyclic ketones such as cyclopentanone (**2n**) and cyclohexanone (**2o**) also yielded the corresponding 4-spirocycloalkyl *N*-formyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridines (**5n**) and (**5o**) in yields of 65% and 51%, respectively. The gradually decreased yields observed in the reactions of cyclic ketones suggested that the cyclization was sensitive to steric congestion. In the case of benzophenone

Table 2 Synthesis of 4-Substitued 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridines (**6**) and (**9**)

				Hydrolysis			
Run	Substrate (**5**)	R^1	R^2	Reagent	Time (h)	Products	Yields (%)
1	**5a**	H	Ph	NaOH[c)]	18	**6a**	84
2	**5b**	H	Me	HCl[a)]	4	**6b**	100
3	**5c**	H	Et	HCl[a)]	4	**6c**	100
4	**5d**	H	*n*-propyl	HCl[a)]	4	**6d**	76
5	**5e**	H	*n*-butyl	HCl[a)]	4	**6e**	100
6	**5f**	H	*n*-pentyl	HCl[a)]	4	**6f**	100
7	**5g**	H	*n*-hexyl	HCl[a)]	4	**6g**	63
8	**5h**	H	cyclopropyl	NaOH[c)]	18	**6h**	94
9	**5i**	H	cyclopentyl	HCl[b)]	4	**6i**	94
10	**5j**	H	cyclohexyl	NaOH[c)]	18	**6j**	83
11	**5k**	Me	Ph	NaOH[c)]	18	**6k**	100
12	**5l**	Me	Me	NaOH[b)]	18	**6l**	67
13	**5m**	Me	Et	HCl[a)]	4	**6m**	85
14	**5n**			HCl[a)]	18	**6n**	100
15	**5o**			HCl[a)]	4	**6o**	47
16	**5q**	H	H	HCl[a)]	4	**6q**	93
	Substrate (**8**)		n	Reagent	Time (h)	Products	Yields (%)
17	**8c**		1	HCl[a)]	4	**9c**	100
18	**8d**		2	HCl[a)]	4	**9d**	90
19	**8e**		3	HCl[a)]	4	**9e**	100
20	**8f**		4	HCl[a)]	4	**9f**	44
21	**8g**		5	HCl[a)]	4	**9g**	79

a) 10% HCl-EtOH-H_2O solution. b) 20% HCl-EtOH-H_2O solution.
c) 10% NaOH-EtOH-H_2O solution.

(**2p**) possessing two bulky phenyl groups, the expected product (**5p**) was not obtained at all. We previously showed that the reaction of tryptamine with benzophenone (**2p**) under similar conditions yielded *N*-formyl-1,1-diphenyl-1,2,3,4-tetrahydro-β-carboline, albeit in low yield (24%),[4] indicating that the inhibition of the reaction is attributable to the steric hindrance in the cyclization step, not in the imination one.

Interestingly, paraformaldehyde (**2q**) afforded *N*-formyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (**5q**), the skeletal compound of the ring system, in yield of 69%.

Alkaline or acidic hydrolysis of *N*-formyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridines (**5** and **8**) afforded the corresponding 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridines (**6** and **9**) in excellent to good yields as shown in Table 2.

The 4-methyl-4-phenyl derivative (**6k**) of the NMDA antagonist was prepared previously in a multi-step operation but in low overall yield (27%).[9] This method gave **6k** in 84% overall yield by these simple manipulations.

Thus, the modified Pictet-Spengler reaction of 2-(2-thienyl)ethylamine (**1**) with carbonyl compounds provides a convenient and effective method for synthesizing 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridines (**6**) with various substituents at the C-4 position. Particularly, this modified method is of great value in preparing the sterically congested 4,4-disubstituted derivatives by simple one-pot manipulation.

EXPERIMENTAL

Unless otherwise noted, the following procedures were adopted. Melting points were taken on a Yanagimoto SP-M1 hot-stage melting point apparatus and are uncorrected. IR spectra were measured as KBr disks with a HORIBA FT-710 spectrophotometer or Nicolet iS10 spectrophotometer and the values are given in cm^{-1}. NMR spectra were measured on a JEOL JNM-AL 300 (^{1}H-NMR, 300 MHz; ^{13}C-NMR, 75 MHz) NMR spectrometer in $CDCl_3$ or DMSO-d_6 with tetramethylsilane as an internal standard and the chemical shifts are given in δ values. LR-MS were taken on JMS-AM20, and high resolution MS (HR-MS) on a JEOL JMS-D300 spectrometer at 70 eV (EI-MS) using direct inlet systems. HRFAB-MS spectra were recorded with JEOL-MS700 spectrometer using glycerol as a matrix. Elemental analyses were recorded on a ThermoFisherScientific model EA1112 IRMS NC-plus CHNS. TLC was performed

on Merck precoated Silica gel 60 F_{254} plates (Merck). Column chromatography was carried out with silica gel (Wakogel C-200). The organic extract from each reaction mixture was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to dryness.

The Pictet-Spengler reaction of 2-(2-thienyl)ethylamine (1) with carbonyl compound (2) : General procedure.

Method A: A mixture of **1** (1.00 g, 7.86 mmol), carbonyl compound (**2**) (6.4 mmol) and Ti(O-*i*Pr)$_4$ (3.2 g, 11.3 mmol) was heated at 80 °C for 3 h under an argon atmosphere. To the reaction mixture, a solution of acetic-formic anhydride [prepared from HCO_2H (29.46 g, 0.64 mol) and Ac_2O (65.34 g, 0.64 mol)] was added at 0 °C, then the mixture was heated at 70 °C for 2 h. To this reaction mixture CF_3CO_2H (72.97 g, 0.64 mol) was added and heated at 70 °C for 3-16 h (Table 1). The reaction mixture was diluted with MeOH (100 mL) and passed through a short SiO_2 column ($CHCl_3$-MeOH) to remove TiO_2. The eluent was concentrated *in vacuo* to *ca*. 50 mL and the residue was extracted with $CHCl_3$. After removal of the solvent of extract *in vacuo*, the residue was purified by chromatography over SiO_2 eluted with AcOEt-hexane (1:1-1:3) to give **5**.

Method B: A mixture of **1** (1.00 g, 7.86 mmol), carbonyl compound (**2**) (7.86 mmol) and Ti(O-*i*Pr)$_4$ (2.68 g, 9.43 mmol) was heated at 80 °C for 2 h under an argon atmosphere. To the reaction mixture, a solution of acetic-formic anhydride [prepared from HCO_2H (9.05 g, 196.5 mmol) and Ac_2O (20.1 g, 196.5 mmol)] was added at 0 °C, then the mixture was heated at 70 °C for 0.5 h. To this reaction mixture CF_3CO_2H (22.41 g, 196.5 mmol) was added and heated at 70 °C for 1.5 h. The reaction mixture was diluted with MeOH (100 mL) and passed through a short SiO_2 column ($CHCl_3$-MeOH) to remove TiO_2. The eluent was concentrated *in vacuo* to *ca*. 50 mL and the residue was extracted with $CHCl_3$. After removal of the solvent of extract *in vacuo*, the residue was purified by chromatography over SiO_2 (AcOEt-hexane (2:1-1:3)) to give **5** and **8**.

5-Formyl-4-phenyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (5a) : Method A

Pale yellow prisms recrystallized from hexane-Et_2O. mp 80-83 °C IR:1662. ^{1}H-NMR: 2.87-3.00, 3.42-3.52, 3.65-3.71, 4.48-4.52 (total 4H, each m, H-6 and H-7), 5.74, 6.63 (total 1H, each s, H-4), 6.70, 6.71 (total 1H, each d, *J*=5 Hz, H-3), 7.14-7.19 (2H, m, H-2 and Ph-H), 7.26-7.38 (4H, m, Ph-H), 8.18, 8.51 (total 1H, each s, -CHO). ^{13}C-NMR: 24.5, 26.1 (C_7), 34.4, 40.2 (C_6), 52.6, 58.8 (C_4), 123.6 (C_3),

125.9, 126.3 (C_2), 127.7, 127.9 (Ph-CH), 128.3, 128.4 (2 x Ph-CH), 128.5, 128.7 (2 x Ph-CH), 132.6, 132.9 (Ph-C), 133.6, 135.2 (C_{3a}), 139.9, 140.5 (C_{7a}), 161.1, 161.2 (-CHO). LR-EIMS: *m/z* 243 (M^+), 243 (base peak). HR-EIMS *m/z* (M^+): Calcd for $C_{14}H_{13}NOS$: 243.0718. Found: 243.0669.

5-Formyl-4-methyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (5b) : Method B (Using paraldehyde 1.04 g, 7.86 mmol) instead of acetaldehyde as a carbonyl compound)

Yellow oil. IR: 1664. ^{1}H-NMR: 1.43, 1.50 (total 3H , each d, *J*=7 Hz, -CH_3), 2.77-3.14, 3.49-3.58, 3.74-3.81, 4.60-4.67 (total 4H, each m, H-6, H-7), 4.77, 5.42 (total 1H, each q, *J*=7 Hz, H-4), 6.79, 6.80 (total 1H, each d, *J*=5 Hz, H-3), 7.14 (1H, d, *J*=5 Hz, H-2), 8.16, 8.29 (total 1H, each s, -CHO). ^{13}C-NMR: 20.1, 22.9 (CH_3), 24.7, 26.1 (C_7), 34.2, 40.5 (C_6), 46.2. 51.6 (C_4), 123.6 (C_3),124.7, 125.2 (C_2), 131.7, 133.4 (C_{3a}), 136.0, 136.5 (C_{7a}), 161.30, 161.33 (-CHO). LR-EIMS: *m/z* 243 (M^+), 243(base peak). HR-EIMS *m/z* (M^+): Calcd for $C_9H_{11}NOS$:181.0561. Found: 181.0555.

4-Ethyl-5-formyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (5c) : Method B

Yellow oil. IR: 1672. ^{1}H-NMR: 1.00 (3H , t, *J*=7 Hz, -CH_2CH_3), 1.65-1.95 (2H, m, -C$H_2$$CH_3$), 2.82-3.04, 3.50-3.60, 3.76-3.83, 4.64-4.74, (total 4H, each m, H-6, H-7), [4.41 (dd, *J*=4, 10 Hz), 5.42 (dd, *J*=5, 9 Hz) total 1H, H-4], 6.80, 6.81 (total 1H, each d, *J*=5 Hz, H-3), 7.13, 7.14 (total 1H, each d, *J*=5 Hz, H-2), 8.22, 8.24 (total 1H, each s, -CHO). HR-EIMS *m/z* (M^+): Calcd for $C_{10}H_{13}NOS$: 195.0718. Found: 195.0710.

5-Formyl-4-(pent-2-en-2-yl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (8c): Method B

Yellow oil. IR: 1672. ^{1}H-NMR: 0.91, 0.94 (total 3H, each t, *J*=7 Hz, -C=CHCH_2CH_3), 1.67, 1.70 (total 3H, each s, -CH_3) 2.01, 2.06 (total 2H, each q, *J*=7 Hz, -C$H_2$$CH_3$), 2.77-2.97 (2H, m, H-7), 3.23-3.32, 3.46-3.56, 3.66-3.72, 4.30-4.37 (total 2H, each m, H-6), 4.94, 5.82 (total 1H, each s, H-4), 5.10-5.14, 5.22-5.26 (total 1H, each m, -C=CH$CH_2$$CH_3$), 6.70 , 6.71 (total 1H, each d, *J*=3 Hz, H-3), 7.11, 7.13 (total 1H, each d, *J*=3 Hz, H-2), 8.23, 8.30 (total 1H, each s, -CHO). HR-FABMS *m/z* (MH^+): Calcd for $C_{12}H_{18}NOS$: 208.1160. Found: 208.1158.

5-Formyl-4-propyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (5d) : Method B

Yellow oil. IR: 1672. ^{1}H-NMR: 0.91, 1.00 (total 3H , each t, *J*=7 Hz, - CH_2CH_2CH_3), 1.38-1.50, 1.68-1.79 (total 4H, each m, -CH_2C$H_2$$CH_3$), 2.81-3.00 (2H, m, H-7), 3.02-3.10, 3.50-3.58, 3.57-3.76, 4.65-4.69 (total 2H, each m, H-6), 4.50, 5.40 (total 1H, each dd, *J*=5, 9 Hz, H-4), 6.79, 6.81 (total 1H, each, d, *J*=5

Hz, H-3), 7.13, 7.16 (total 1H, each , d, *J*=5 Hz, H-2), 8.20, 8.21 (total 1H, each s, -CHO). HR-FABMS *m/z* (MH^+): Calcd for $C_{11}H_{16}NOS$: 210.0953. Found: 210.0953.

5-Formyl-4-(hept-3-en-3-yl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (8d): Method B

Yellow oil. IR: 1675. ^{1}H-NMR: 0.82, 0.85, 1.00, 1.07 (total 6H, each t, *J*=7Hz, -CH_2CH_3, -C=CH$(CH_2)_2CH_3$), 1.23-1.36 (2H, m, -CH_2CH_3), 1.96-2.05, 2.10-2.26 (total 4H, each m, -C=CH$(CH_2)_2CH_3$), 2.77-2.92 (2H, m, H-7), 3.07-3.15, 3.45-3.56, 3.62-3.67, 4.40-4.46 (total 2H, each m, H-6), 4.93, 5.03 (total 1H, each t, *J*=7 Hz, -C=CH$(CH_2)_2CH_3$), 5.01, 5.96 (total 1H, each s, H-4), 6.65-6.68 (1H, m, H-3), 7.10-7.12 (1H, m, H-2), 8.22, 8.30 (total 1H, each s, -CHO). HR-FABMS *m/z* (MH^+): Calcd for $C_{15}H_{22}NOS$: 264.1423. Found: 264.1440.

4-Butyl-5-formyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (5e) : Method B

Yellow oil. IR: 1672. ^{1}H-NMR: 0.95, 0.97 (total 3H , each t, *J*=7 Hz, -$(CH_2)_3CH_3$), 1.26-1.54, 1.63-1.83 (total 6H, each m, $(CH_2)_3CH_3$), 2.87-2.97 (2H, m, H-7), 2.97-3.16, 3.50-3.57, 3.74-3.77, 4.65-4.71 (total 2H, each m, H-6), 4.51, 5.40 (total 1H, each dd, *J*=5, 9 Hz, H-4), 6.79, 7.14 (total 1H, each, d, *J*=5 Hz, H-3), 7.12, 7.17 (total 1H, each , d, *J*=5 Hz, H-2), 8.20, 8.21 (total 1H, each s, -CHO). HR-FABMS *m/z* (MH^+): Calcd for $C_{12}H_{18}NOS$: 224.1110. Found: 224.1103.

5-Formyl-4-(non-4-en-4-yl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (8e): Method B

Yellow oil. IR: 1675. ^{1}H-NMR: 0.86, 0.89, 0.93, 0.94 (total 6H, each t, *J*=7 Hz, -$(CH_2)_2CH_3$, -C=CH$(CH_2)_3CH_3$), 1.25-1.27, 1.34-1.48 (total 6H, each m, -$(CH_2)_2CH_3$, -C=CH$(CH_2)_3CH_3$), 1.90-2.10, 2.10-2.21 (total 4H, each m, -$(CH_2)_2CH_3$, -C=CH$(CH_2)_3CH_3$), 2.77-2.96, 3.04-3.14, 3.45-3.52, 3.54-3.66, 4.42-4.47 (total 4H, each m, H-6, H-7), 4.96, 5.06 (total 1H, each t, *J*=7 Hz, -C=CH$(CH_2)_3CH_3$), 5.00, 5.94 (total 1H, each s, H-4), 6.64, 6.67 (total 1H, each d, *J*=5 Hz, H-3), 7.10, 7.11 (total 1H, each d, *J*=5 Hz, H-2), 8.21, 8.29 (total 1H, each s, -CHO). HR-FABMS *m/z* (MH^+): Calcd for $C_{17}H_{26}NOS$: 292.1735 Found: 292.1736.

5-Formyl-4-pentyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (5f) : Method B

Yellow oil. IR: 1672. ^{1}H-NMR: 0.88, 0.39 (total 3H , each t, *J*=7 Hz, -$(CH_2)_4CH_3$), 1.23-1.44 (6H, m, $(CH_2)_4CH_3$), 1.67-1.77 (2H, m, $(CH_2)_4CH_3$), 2.75-3.05, 3.48-3.58, 3.73-3.81, 4.45-4.50 (total 4H, each m, H-6, H-7), 4.64-4.69, 5.36-5.39 (total 1H, each m, H-4), 6.79 (1H, d, *J*=4 Hz, H-3), 7.10, 7.11 (total 1H, each d, *J*=4 Hz, H-2), 8.188, 8.190 (total 1H, each s, -CHO). HR-FABMS *m/z* (MH^+): Calcd for

$C_{13}H_{20}NOS$: 238.1266. Found: 238.1274.

5-Formyl-4-(undec-5-en-5-yl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (8f): Method B

Yellow oil. IR: 1675. ^{1}H-NMR: 0.81-0.95 (6H, m, -$(CH_2)_3C\underline{H}_3$, -C=CH$(CH_2)_4C\underline{H}_3$), 1.24-1.58 (10H, m, -$(C\underline{H}_2)_3CH_3$, -C=CH$(C\underline{H}_2)_4CH_3$), 1.92-2.24 (4H, m, -$(C\underline{H}_2)_3CH_3$, -C=CH$(C\underline{H}_2)_4CH_3$), 2.76-4.47 (4H, m, H-6, H-7), 4.93-5.07 (1H, m, -C=C$\underline{H}(CH_2)_3CH_3$), 5.95 (1H, s, H-4), 6.64, 6.65 (total 1H, each d, *J*=5 Hz, H-3), 7.08, 7.10 (total 1H, each d, *J*=5 Hz, H-2), 8.21, 8.29 (total 1H, each s, -C$\underline{H}$O). HR-FABMS *m/z* (MH^+): Calcd for $C_{19}H_{30}NOS$: 320.2048. Found: 320.2062

5-Formyl-4-hexyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (5g) : Method B

Yellow oil. IR: 1672. ^{1}H-NMR: 0.85-0.89 (3H, m, -$(CH_2)_5C\underline{H}_3$), 1.23-1.46 (8H, m, $(C\underline{H}_2)_5CH_3$), 1.71-1.81 (2H, m, $(C\underline{H}_2)_5CH_3$), 2.80-3.07, 3.49-3.59, 3.74-3.81, 4.47-4.51 (total 4H, each m, H-6, H-7), 5.36-5.40, 4.64-4.70 (total 1H, each m, H-4), 6.81, 6.79 (total 1H, each d, *J*=3 Hz, H-3), 7.11, 7.13（total 1H, each d, *J*=3 Hz, H-2), 8.20, 8.21 (total 1H, each s, -C$\underline{H}$O). HR-FABMS *m/z* (MH^+): Calcd for $C_{14}H_{22}NOS$: 252.1422. Found: 252.1432.

5-Formyl-4-(tridec-6-en-6-yl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (8g): Method B

Yellow oil. IR: 1675. ^{1}H-NMR: 0.80-0.90 (6H, m, -$(CH_2)_4C\underline{H}_3$, -C=CH$(CH_2)_5C\underline{H}_3$), 1.23-1.33 (14H, m, -$(C\underline{H}_2)_4CH_3$, -C=CH$(C\underline{H}_2)_5CH_3$), 1.89-2.02, (4H, m, -$(C\underline{H}_2)_4CH_3$, -C=CH$(C\underline{H}_2)_5CH_3$), 2.74-4.46 (4H, m, H-6, H-7), 4.92-5.07 (1H, m, -C=C$\underline{H}(CH_2)_3CH_3$), 5.94 (1H, s, H-4), 6.64, 6.66 (total 1H, each d, *J*=5 Hz, H-3), 7.09, 7.10 (total 1H, each d, *J*=5 Hz, H-2), 8.21, 8.29 (total 1H, each s, -C$\underline{H}$O). HR-FABMS *m/z* (MH^+): Calcd for $C_{21}H_{34}NOS$: 348.236. Found: 348.2357.

4-Cyclopropyl-5-Formyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (5h) : Method A

Colorless prisms recrystallized from hexane-Et_2O. mp 88-90 °C IR: 1672. ^{1}H-NMR: 0.36-0.81(4H, m, cyclopropyl-C$\underline{H}_2$), 1.75 (1H, m, cyclopropyl-C$\underline{H}$), 2.81-2.99 (2H, m, H-7), 3.20-3.30, 4.62-4.69 (total 2H, each m, H-6), 3.68-3.86 (1H, m, H-4), 6.92, 6.93 (total 1H, each d, *J*=5 Hz, H-3), 7.14, 7.15 (total 1H, each , *J*=5 Hz, H-2), 8.20 (1H, d, *J*=4 Hz, -CHO). ^{13}C-NMR: 2.85, 3.68, 4.91(2 x cyclopropyl-$\underline{C}H_2$), 16.6, 17.2 (cyclopropyl-$\underline{C}$H), 24.7, 26.2 (C_7), 35.3, 41.3 (C_6), 54.1, 60.7 (C_4), 123.2, 123.3 (C_3), 125.1, 125.7 (C_2), 132.1, 133.8 (C_{3a}), 134.6, 135.0 (C_{7a}), 161.1, 161.6 ($\underline{C}$HO). LR-EIMS: *m/z* 207 (M^+), 166 (base peak). HR-EIMS *m/z* (M^+): Calcd for $C_{11}H_{13}NOS$: 207.0718. Found: 207.0735.

4-Cyclopentyl-5-Formyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (5i) : Method A

Yellow oil. IR: 1670. ^{1}H-NMR: 1.25-1.79 (8H, m, cyclopentyl-C<u>H</u>$_2$), 2.80-3.01 (2H, m, H-7), 3.05-3.15, 3.59-3.69 (total 2H, each m, H-6), 3.75-3.79, 4.66-4.72 (total 1H, each m, cyclopentyl-C<u>H</u>), 4.23, 5.24 (total 1H, each d, *J*=10 Hz, H-4), 6.85 (1H, d, *J*=5 Hz, H-3), 7.10, 7.11 (total 1H, each d, *J*=5 Hz, H-2), 8.17, 8.22 (total 1H, each s, -CHO). ^{13}C-NMR: 24.1, 25.2 (cyclopentyl-<u>C</u>H$_2$), 24.3, 25.4 (cyclopentyl-<u>C</u>H$_2$), 24.6, 26.3 (cyclopentyl-<u>C</u>H$_2$), 30.0, 30.6 (cyclopentyl-<u>C</u>H$_2$), 31.0, 34.7 (C_7), 40.8 (C_6), 45.5 (cyclopentyl-<u>C</u>H), 53.9, 60.7 (C_4), 122.8 (C_3), 125.7, 126.2 (C_2), 132.1, 133.8 (C_{3a}), 135.2, 135.6 (C_{7a}), 161.3, 161.5 (-<u>C</u>HO). LR-EIMS: *m/z* 235 (M^+), 166 (base peak). HR-EIMS *m/z* (M^+): Calcd for $C_{13}H_{17}NOS$: 235.1031. Found: 235.1010.

4-Cyclohexyl-5-Formyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (5j) : Method A

Yellow oil. IR: 1670. ^{1}H-NMR: 0.95-2.05 (10H, m, cyclohexyl-C<u>H</u>$_2$), 2.79-3.11, 3.57-3.67 (total 4H, each m, H-6 and H-7), 3.75-3.82, 4.69-4.75 (total 1H, each m, cyclohexyl-C<u>H</u>), 4.21, 5.17 (total 1H, each d, *J*=7 Hz, H-4), 6.82, 6.83 (total 1H, each d, *J*=5 Hz, H-3), 7.11, 7.13 (total 1H, each d, *J*=5 Hz, H-2), 8.16, 8.21 (total 1H, each s, -C<u>H</u>O). LR-EIMS: *m/z* 249 (M^+), 166 (base peak). HR-EIMS *m/z* (M^+): Calcd for $C_{14}H_{19}NOS$: 249.1187. Found: 249.1175.

5-Formyl-4-methyl-4-phenyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (5k) : Method A

Colorless plate recrystallized from AcOEt. mp 139-141 °C. IR: 1666. ^{1}H-NMR: 2.02 (3H, s, -C<u>H</u>$_3$), 2.89-3.05 (2H, m, H-7), 3.75-3.83 (1H, m, H-6), 3.96-4.04 (1H, m, H-6), 6.58 (1H, d, *J*=5 Hz, H-3), 7.08 (1H, d, *J*=5 Hz, H-2), 7.21-7.36 (5H, m, Ph-<u>H</u>), 8.25 (1H, s, -C<u>H</u>O). ^{13}C-NMR: 24.6 (C_7), 27.7 (<u>C</u>H$_3$), 35.8 (C_6), 62.6 (C_4), 123.2 (C_3), 125.6 (C_2), 126.7 (2 x Ph-<u>C</u>H), 127.7 (Ph-CH), 128.6 (2 x Ph-<u>C</u>H), 133.5 (C_{3a}), 139.7 (C_{7a}), 144.2 (Ph-<u>C</u>), 162.1 (-<u>C</u>HO). LR-EIMS: *m/z* 257 (M^+), 242 (base peak). HR-EIMS *m/z* (M^+): Calcd for $C_{15}H_{15}NOS$: 257.0874. Found: 257.0862.

5-Formyl-4,4-dimethyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (5l) : Method A

Colorless plates recrystallized from hexane-Et_2O. mp 88-90 °C. IR: 1641. ^{1}H-NMR: 1.69 (6H, s, 2 x -C<u>H</u>$_3$), 2.83 (2H, t, *J*=5 Hz, H-7), 3.92 (2H, t, *J*=5 Hz, H-6), 6.85 (1H, d, *J*=5 Hz, H-3), 7.12 (1H, d, *J*=5 Hz, H-2), 8.57 (1H, s, -C<u>H</u>O). ^{13}C-NMR: 24.8 (C_7), 29.9 (2x- <u>C</u>H$_3$), 35.4 (C_6), 57.4 (C_4), 123.3 (C_3), 124.2 (C_2), 133.1 (C_{3a}), 140.7 (C_{7a}), 160.6 (-<u>C</u>HO). LR-EIMS: *m/z* 195 (M^+), 180 (base peak). HR-EIMS *m/z* (M^+): Calcd for $C_{10}H_{13}NOS$: 195.0718. Found: 195.0708. *Anal*. Calcd for $C_{10}H_{13}NOS$: C, 61.50; H, 6.71; N, 7.17 Found: C, 61.59; H, 6.79; N, 7.33.

4-Ethyl-5-formyl-1-methyl-4,5,6,7-tetrahydtothieno[3,2-*c*]pyridine (5m) : Method A

Pale yellow prisms recrystallized from AcOEt-hexane. mp 55-57 °C. IR: 1658. ^{1}H-NMR: 0.58, 0.73 (total 3H, each t, *J*=7 Hz, -$CH_2C\underline{H}_3$), 1.64 (3H, s, -$C\underline{H}_3$), 2.02 (2H, qd, *J*=7, 2 Hz, -$C\underline{H}_2CH_3$), 2.76-2.88 (2H, m, H-7), 3.81-3.95 (2H, m, H-6), 6.79 (1H, d, *J*=5 Hz, H-3), 7.13 (1H, d, *J*=5 Hz, H-2), 8.47 (1H, s, -C<u>H</u>O). ^{13}C-NMR: 7.72, 8.13 (-$CH_2\underline{C}H_3$), 24.3, 25.5 (-$\underline{C}H_2CH_3$), 25.8, 28.2 (-$\underline{C}H_3$), 32.1, 34.0 (C_7), 35.5, 44.3 (C_6), 60.3, 62.4 (C_4), 122.9, 123.0 (C_3), 124.0, 124.1 (C_2), 132.7, 133.7 (C_{3a}), 139.3, 140.6 (C_{7a}), 161.0, 162.2 (-<u>C</u>HO). LR-EIMS: *m/z* 209 (M^+), 180 (base peak). HR-EIMS *m/z* (M^+): Calcd for $C_{11}H_{15}NOS$: 209.0874. Found: 209.0871. *Anal*. Calcd for $C_{11}H_{15}NOS$: C, 63.12; H, 7.22; N, 6.69. Found: C, 63.11; H, 7.31; N, 6.90.

5-Formyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine-4-spirocyclopentane (5n) : Method A

Colorless plates recrystallized from AcOEt-hexane. mp 108-110 °C. IR: 1643. ^{1}H-NMR: 1.75-2.26 (8H, m, cyclopentyl), 2.84 (2H, t, *J*=6 Hz, H-7), 3.91 (2H, t, *J*=6 Hz, H-6), 6.82 (1H, d, *J*=5 Hz, H-3), 7.12 (1H, d, *J*=5 Hz, H-2), 8.33 (1H, s, -C<u>H</u>O). ^{13}C-NMR: 23.8 x 2 (2 x cyclopentyl-$\underline{C}H_2$), 24.9 (C_7), 36.3 (C_6), 39.6 x 2 (2 x cyclopentyl-$\underline{C}H_2$), 68.8 (C_4), 123.1 (C_3), 124.1 (C_2), 134.2 (C_{3a}), 139.4 (C_{7a}), 160.4(d, -<u>C</u>HO). LR-EIMS: *m/z* 221 (M^+), 151 (base peak). HR-EIMS *m/z* (M^+): Calcd for $C_{12}H_{15}NOS$: 221.0874 Found: 221.0856. *Anal*. Calcd for $C_{12}H_{15}NOS$: C, 65.12; H, 6.83; N, 6.33. Found: C, 65.04; H, 6.80; N, 6.46.

5-Formyl-4,5,6,7- tetrahydrothieno[3,2-*c*]pyridine-1-spirocyclohexane (5o) : Method A

Yellow prisms recrystallized from AcOEt-Et_2O. mp 156-159 °C. IR: 1643. ^{1}H-NMR: 1.33-1.97 (8H, m, cyclohexyl-$C\underline{H}_2$), 2.22 (2H, d, *J*=14 Hz, cyclohexyl-$C\underline{H}_2$), 2.85 (2H, t, *J*=6 Hz, H-7), 3.93(2H, t, *J*=6 Hz, H-6), 6.87 (1H, d, *J*=5 Hz, H-3), 7.07 (1H, d, *J*=5 Hz, H-2), 8.58(1H, s, -C<u>H</u>O). ^{13}C-NMR: 21.7 (cyclohexyl-$\underline{C}H_2$), 22.0 (cyclohexyl-$\underline{C}H_2$), 24.5 (cyclohexyl-$\underline{C}H_2$), 25.5 (C_7), 34.9 (C_6), 35.9 (2 x cyclohexyl-$\underline{C}H_2$), 60.0 (C_4), 122.7 (C_3), 124.1 (C_2), 134.1 (C_{3a}), 142.3 (C_{7a}), 162.3, 162.4(<u>C</u>HO). LR-EIMS: *m/z* 235 (M^+), 193 (base peak). HR-EIMS *m/z* (M^+): Calcd for $C_{13}H_{17}NOS$: 235.1031. Found: 235.1046. *Anal*. Calcd for $C_{13}H_{17}NOS$: C, 66.34; H, 7.28; N, 5.95. Found: C, 66.47; H, 7.58; N, 5.99.

5-Formyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (5q) : Method B (Using paraformaldehyde (0.24 g) instead of formaldehyde (7.86 mmol) as a carbonyl compound).

Yellow oil. IR: 1668. ^{1}H-NMR: 2.88, 2.92 (total 2H, each t, *J*=7 Hz and 6 Hz, H-7), 3.69, 3.86 (total 2H,

each t, *J*=6 Hz, H-6), 4.47, 4.60 (total 2H, t and s, *J*=2 Hz, H-4), 6.79, 6.80 (total 1H, each d, *J*=5 Hz, H-3), 7.15, 7.16 (total 1H, each d, *J*=5 Hz, H-2), 8.19, 8.23 (total 1H, each s, -CHO). ^{13}C-NMR: 24.3, 25.7 (C_7), 37.8, 40.5 (C_6), 43.6. 45.6 (C_4), 123.7 (C_3), 124.2, 124.9 (C_2), 130.6, 130.7 (C_{3a}), 132.1, 133.7 (C_{7a}), 161.3, 161.6 (-CHO). HR-EIMS *m/z* (M^+): Calcd for C_8H_9NOS: 167.0405. Found: 167.0416

Hydrolysis of 5-formyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine.

Typical procedure: NaOH aq hydrolysis. (see Table 2)

A solution of **5** (200 mg) in EtOH (60 mL) and 20% NaOH solution (60 mL) was refluxed for 18 h under an argon atmosphere. The reaction mixture was diluted with water, and extracted with $CHCl_3$. The residue was purified by column chromatography over SiO_2 with MeOH-$CHCl_3$ (9:1) to give **6**.

Typical procedure: HCl aq hydrolysis. (see Table 2)

A solution of **5** and **8** (200 mg) in EtOH (14 mL) and *c*-HCl (6 mL or 12 mL) was refluxed for 4-18 h under an argon atmosphere. The reaction mixture was diluted with water, alkalized with 10% NaOH solution and extracted with $CHCl_3$. The residue was purified by column chromatography over SiO_2 with MeOH-$CHCl_3$ (9:1) to give **6** and **9**.

4-Phenyl-4,5,6,7- tetrahydrothieno[3,2-*c*]pyridine (6a)

Colorless prisms recrystallized from Et_2O-hexane. mp 80-82 °C (lit.,[10] mp 79.8-80.7 °C). IR: 3255, 1655. ^{1}H-NMR : 2.83-3.04 (2H, m, H-7), 3.07~3.35 (2H, m, H-6), 5.02 (1H, s, H-4), 6.47 (1H, d, *J*=5 Hz, H-3), 7.00 (1H, d, *J*=5 Hz, H-2), 7.26-7.36 (5H, m, Ph-H). ^{13}C-NMR: 26.0 (C_7), 42.5 (C_6), 60.0 (C_4), 121.7 (C_3), 126.3 (C_2), 127.5 (PhCH), 128.2 (2 x PhCH), 128.4 (2 x PhCH), 134.9 (PhC) 136.8 (C_{3a}), 143.7 (C_{7a}). LR-EIMS: *m/z* 215 (M^+), 138 (base peak). HR-EIMS *m/z* (M^+): Calcd for $C_{13}H_{13}NS$:215.0769. Found: 215.0786.

4-Metyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (6b)

Pale yellow oil. IR: 2924, 1653. ^{1}H-NMR : 1.39 (3H, d, *J*=7 Hz, -CH_3), 1.66 (1H, brs, -NH), 2.68-2.90 (2H, m, H-7), 3.01 (1H, ddt, *J*=12, 5, 4 Hz, H-6), 3.32 (1H, ddd, *J*=13, 5, 4 Hz, H-6), 4.00 (1H, qt, *J*=7, 2 Hz, H-4), 6.80 (1H, d, *J*=5 Hz, H-3), 7.05 (1H, d, *J*=5 Hz, H-2). ^{13}C-NMR: 22.0 (-CH_3), 26.1 (C_7), 42.7 (C_6), 50.6 (C_4), 121.7 (C_3), 124.8 (C_2), 133.8 (C_{3a}), 139.3 (C_{7a}). HR-EIMS *m/z* (M^+): Calcd for $C_8H_{11}NS$:153.0612. Found: 153.0588.

4-Ethyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (6c)

Pale yellow oil. IR: 2860, 2927, 1652. ^{1}H-NMR: 1.00 (3H , each t, *J*=7 Hz, -$CH_2C\underline{H}_3$), 1.54-1.70 (2H, m, -$C\underline{H}_2CH_3$), 1.92 (1H, dddd, *J*=15, 11, 8, 4 Hz, H-7), 270-2.91 (1H, m, H-7), 3.00 (1H, ddd, *J*= 12, 8, 5 Hz, H-6), 3.32 (1H, ddd, *J*=12, 5, 4, Hz, H-6), 3.83 (1H, ddd, *J*=8, 4, 2 Hz, H-4). 6.81 (1H, d, *J*=5 Hz, H-3), 7.05 (1H, d, *J*=5 Hz, H-2). ^{13}C-NMR: 10.3 ($\underline{C}H_3$), 26.2 (C_7), 28.6 (-$\underline{C}H_2CH_3$), 38.2, 42.5 (C_6), 56.2 (C_4), 121.6 (C_3), 124.9 (C_2), 134.3 (C_{3a}), 138.3 (C_{7a}). HR-FABMS *m/z* (MH^+): Calcd for $C_9H_{14}NS$: 168.0847. Found: 168.0858.

4-Propyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (6d)

Yellow oil. IR: 2958, 2925, 1666. ^{1}H-NMR: 0.97 (3H, t, *J*=7 Hz, -$(CH_2)_2C\underline{H}_3$), 1.36-1.65, (2H, m, -$(C\underline{H}_2)_2CH_3$), 2.78-1.89 (2H, m, -$(C\underline{H}_2)_2CH_3$), 2.72-2.89 (2H, m, H-7), 2.95-3.04 (1H, m, H-6), 3.28-3.35 (1H, m, H-6), 3.88-3.91 (1H, m, H-4), 6.81 (1H, d, *J*=5 Hz, H-3), 7.05 (1H, d, *J*=5 Hz, H-2). ^{13}C-NMR: 14.1 ($\underline{C}H_3$), 19.1 (-$(\underline{C}H_2)_2CH_3$), 26.1 (C_7), 38.2 (-$(\underline{C}H_2)_2CH_3$), 42.4 (C_6), 54.6 (C_4), 121.6 (C_3), 124.8 (C_2), 134.0 (C_{3a}), 138.4 (C_{7a}). HR-FABMS *m/z* (MH^+): Calcd for $C_{10}H_{16}NS$: 182.1003. Found: 182.1004.

4-Butyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (6e)

Yellow oil. IR: 2960, 2930, 1668. ^{1}H-NMR: 0.92 (3H, t, *J*=7 Hz, -$(CH_2)_3C\underline{H}_3$), 1.26-1.54, 1.49-1.62, 1.76-1.89 (total 6H, each m, $(C\underline{H}_2)_3CH_3$), 2.71-2.87 (2H, m, H-7), 2.96-3.03 (1H, m, H-6), 3.27-3.35 (1H, m, H-6), 3.89 (1H, dd, *J*=2, 7 Hz, H-4), 6.81 (1H, d, *J*=5 Hz, H-3), 7.05 (1H, d, *J*=5 Hz, H-2). ^{13}C-NMR: 13.9 ($\underline{C}H_3$), 22.7 (-$(\underline{C}H_2)_3CH_3$), 25.9 (C_7), 28.0 (-$(\underline{C}H_2)_3CH_3$), 35.5 (-$(\underline{C}H_2)_3CH_3$), 42.2 (C_6), 54.8 (C_4), 121.7 (C_3), 124.8 (C_2), 133.9 (C_{3a}), 138.7 (C_{7a}). HR-FABMS (MH^+): Calcd for $C_{11}H_{18}NS$: 196.1160. Found: 196.1151.

4-Pentyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (6f)

Yellow oil. IR: 2956, 2929, 1662. ^{1}H-NMR: 0.90 (3H, t, *J*=7 Hz, -$(CH_2)_4C\underline{H}_3$), 1.26-1.63 6H, m, $(C\underline{H}_2)_4CH_3$), 1.79-1.88 (2H, m, $(C\underline{H}_2)_4CH_3$), 2.71-2.88 (2H, m, H-7), 2.95-3.03 (1H, m, H-6), 3.28-3.35 (1H, m, H-6), 3.87-3.89 (1H, m, H-4), 6.81 (1H, each, d, *J*=5 Hz, H-3), 7.04-7.08 (1H, m, H-2). ^{13}C-NMR: 13.4 ($\underline{C}H_3$), 22.5 (-$(\underline{C}H_2)_4CH_3$), 25.5 (C_7), 26.1 (-$(\underline{C}H_2)_4CH_3$), 31.9 (-$(\underline{C}H_2)_4CH_3$), 35.9 (-$(\underline{C}H_2)_4CH_3$), 42.3 (C_6), 54.8 (C_4), 121.5 (C_3), 124.7 (C_2), 133.9 (C_{3a}), 138.4 (C_{7a}). HR-FABMS (MH^+): Calcd for $C_{12}H_{20}NS$: 210.1316. Found: 210.1319.

4-Hexyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (6g)

Yellow oil. IR: 2954, 2929, 1662. ^{1}H-NMR: 0.88 (3H, t, *J*=7 Hz, -$(CH_2)_5C\underline{H}_3$), 1.21-1.60 (8H, m,

($C\underline{H}_2)_5CH_3$), 1.73-1.84 (2H, m, ($C\underline{H}_2)_5CH_3$), 2.71-3.35 (4H, m, H-6, H-7), 3.86-3.89 (1H, m, H-4), 6.81 (1H, d, *J*=5 Hz, H-3), 7.05 (1H, d, *J*=5 Hz, H-2). ^{13}C-NMR: 14.0 ($\underline{C}H_3$), 22.6 (-($\underline{C}H_2)_5CH_3$), 25.9 (C_7), 26.1 (-($\underline{C}H_2)_5CH_3$), 29.4 (-($\underline{C}H_2)_5CH_3$), 31.7 (-($\underline{C}H_2)_4CH_3$), 35.9 (-($\underline{C}H_2)_4CH_3$), 42.3 (C_6), 54.9 (C_4), 121.7 (C_3), 124.9 (C_2), 134.0 (C_{3a}), 138.3 (C_{7a}). HR-FABMS (MH^+): Calcd for $C_{13}H_{22}NS$: 224.1473. Found: 224.1474.

4-Cyclopropyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (6h)

Pale yellow oil. IR: 2920, 1647. ^{1}H-NMR: 0.31-0.76 (4H, m, cyclopropyl-$C\underline{H}_2$), 0.95-1.07 (1H, m, cyclopropyl-C$\underline{H}$), 2.72-3.03 (4H, m, H-6 and H-7), 3.30-3.39 (1H, m, H-4), 7.06 (1H, d, *J*=5 Hz, H-3), 7.08 (1H, d, *J*=5Hz, H-2). ^{13}C-NMR: 2.46 (cyclopropyl-$\underline{C}H_2$), 3.84 (cyclopropyl-$\underline{C}H_2$), 17.0 (cyclopropyl-$\underline{C}$H), 26.0 (C_7), 42.9 (C_6), 60.9 (C_4), 121.7 (C_3), 125.1 (C_2), 134.0 (C_{3a}), 138.0 (C_{7a}).LR-EIMS: *m/z* 179 (M^+), 138 (base peak). HR-EIMS m/z (M^+): Calcd for $C_{10}H_{13}NS$:179.0769. Found: 179.0793.

1-Cyclopentyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (6i)

Yellow oil. IR: 2949, 2866, 1670. ^{1}H-NMR: 1.20-1.40 (1H, m, cyclopentyl-$C\underline{H}_2$), 1.45-1.80 (7H, m, cyclopentyl-$C\underline{H}_2$), 2.27-2.32 (1H, m, cyclopentyl-C$\underline{H}$), 2.79-2.81 (2H, m, H-7), 2.94-3.03 (1H, m, H-6), 3.29~3.36 (1H, m, H-6), 3.84 (1H, d, *J*=6 Hz, H-4), 6.87 (1H, d, *J*=5 Hz, H-3), 7.04 (1H, d, *J*=5 Hz, H-2). ^{13}C-NMR: 25.3 (cyclopentyl-$\underline{C}H_2$), 26.0 (cyclopentyl-$\underline{C}H_2$), 26.3 (cyclopentyl-$\underline{C}H_2$), 28.5 (cyclopentyl-$\underline{C}H_2$), 30.0 (C_7), 42.1 (C_6), 44.9 (cyclopentyl-$\underline{C}$H), 58.6 (C_4), 22.3 (C_3), 125.7 (C_2), 134.5 (C_{3a}), 138.1 (C_{7a}). LR-EIMS: *m/z* 207 (M^+), 166 (base peak). HR-EIMS *m/z* (M^+): Calcd for $C_{12}H_{17}NS$:207.1082. Found: 207.1095.

1-Cyclohexyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (6j)

Pale yellow oil. IR: 2925, 1670. ^{1}H-NMR: 0.99-1.45 (5H, m, cyclohexyl-$C\underline{H}_2$), 1.65-1.88 (6H, m, cyclohexyl-$C\underline{H}_2$, cyclohexyl-C$\underline{H}$), 2.65-2.85 (2H, m, H-7), 2.96 (1H, ddd, *J*=12, 9, 5 Hz, H-6), 3.33 (1H, dd, *J*=12, 5, 3 Hz, H-6), 3.82-3.83 (1H, m, H-4), 6.81 (1H, d, *J*=5 Hz, H-3), 7.06 (1H, d, *J*=5 Hz, H-6). ^{13}C-NMR: 26.3 (cyclohexyl-$\underline{C}H_2$), 26.60 (cyclohexyl-$\underline{C}H_2$), 26.64 (cyclohexyl-$\underline{C}H_2$), 26.8 (cyclohexyl-$\underline{C}H_2$), 26.9 (cyclohexyl-$\underline{C}H_2$), 30.5 (C_7), 42.7 (cyclohexyl-$\underline{C}$H), 43.0 (C_6), 59.9 (C_4), 121.4 (C_3), 125.0 (C_2), 134. 8 (C_{3a}), 137.2 (C_{7a}). LR-EIMS: *m/z* 221(M^+), 138 (base peak). HR-EIMS *m/z* (M^+): Calcd for $C_{13}H_{19}NS$: 221.1238. Found: 221.1193.

4-Methyl-4-phenyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (6k)

Pale yellow oil. HCl-salt, colorless prisms recrystallized from MeOH-Et_2O, mp 268-270 °C (sublimed). ^{1}H-NMR (DMSO-d_6): 2.06 (3H, s, -C<u>H</u>$_3$), 3.04-3.23 (4H, m, H-7 and H-6), 6.95 (1H, d, *J*=5 Hz, H-3), 7.33-7.46 (5H, m Ph-H), 7.54 (1H, d, *J*=5 Hz, H-2). The ^{1}H-NMR was identical with the reported one.[9] ^{13}C-NMR (DMSO-d_6): 21.6 (C_7), 26.0 (-<u>C</u>H$_3$), 37.4 (C_6), 61.3 (C_4), 125.0 (C_3), 125.7 (C_2), 127.7 (2 x Ph-<u>C</u>H), 128.6 (2 x Ph-<u>C</u>H), 128.9 (Ph-<u>C</u>H), 132.9 (Ph-<u>C</u>), 135.6 (C_{3a}), 139.8 (C_{7a}).

4,4-Dimethyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (6l)

Pale yellow oil. HCl salt mp 277-280 °C (sublimed), recrystallized from MeOH-Et_2O. IR: 2971, 2937, 2892, 1641. ^{1}H-NMR: 1.32 (6H, s, 2 x -C<u>H</u>$_3$), 2.68 (2H, t, *J*=5 Hz, H-7), 3.10 (2H, t, *J*=5 Hz, H-6), 6.76 (1H, d, *J*=5 Hz, H-3), 6.96 (1H, d, *J*=5 Hz, H-2). ^{13}C-NMR: 26.4 (C_7), 30.2 (2 x -<u>C</u>H$_3$), 40.0 (C_6), 52.6 (C_4), 121.6 (C_3), 124.9 (C_2), 133.0 (C_{3a}), 142.9 (C_{7a}). LR-EIMS: *m/z* 167 (M^+), 152 (base peak). HR-EIMS *m/z* (M^+): Calcd for $C_9H_{13}NS$:167.0769. Found: 167.0768.

4-Ethyl-4-methyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (6m)

Yellow oil. HCl salt mp 242-243 °C, recrystallized from MeOH-Et_2O. IR: 2962. ^{1}H-NMR: 0.83 (3H, t, *J*=7 Hz, -CH$_2$C<u>H</u>$_3$), 1.33 (3H, s, - C<u>H</u>$_3$), 1.62-1.84 (2H, m, -C<u>H</u>$_2$CH$_3$), 2.74 (2H, t, *J*=6 Hz, H-7), 3.14 (2H, m, H-6), 6.77 (1H, d, *J*=5 Hz, H-3), 7.03 (1H, d, *J*=5 Hz, H-2). ^{13}C-NMR: 8.26 (CH$_2$<u>C</u>H$_3$), 26.4 (-<u>C</u>H$_2$CH$_3$), 27.7 (-<u>C</u>H$_3$), 34.6 (C_7), 39.5 (C_6), 55.2 (C_4), 121.3 (C_3), 125.0 (C_2), 133.6 (C_{3a}), 142.1 (C_{7a}). LR-EIMS: *m/z* 181 (M^+), 58 (base peak). HR-EIMS *m/z* (M^+): Calcd for $C_{10}H_{15}NS$: 181.0925. Found: 181.0925. HCl salt: *Anal.* Calcd for $C_{10}H_{16}ClNOS$: C, 55.16; H, 7.41; N, 6.43. Found: C, 55.27; H, 7.48; N, 6.63.

4,5,6,7-Tetrahydrothieno[3,2-*c*]pyridine-4-spirocyclopentane (6n)

Yellow oil. HCl salt mp 264-266 °C, recrystallized from MeOH-Et_2O. IR: 2949. ^{1}H-NMR: 1.80-1.89 (8H, m, cyclopentyl-C<u>H</u>$_2$), 2.75 (2H, t, *J*=5 Hz, H-7), 3.12 (2H, t, *J*=5 Hz, H-6), 6.81 (1H, d, *J*=5 Hz, H-3), 7.03 (1H, d, *J*=5 Hz, H-2). ^{13}C-NMR: 24.7 (2 x cyclopentyl-<u>C</u>H$_2$), 26.3 (C_7), 40.5 (C_6), 41.6 (2x cyclopentyl-<u>C</u>H$_2$), 63.9 (C_4), 121.5 (C_3), 124.7 (C_2), 133.5 (C_{3a}), 142.2 (C_{7a}). LR-EIMS: *m/z* 193 (M^+), 164 (base peak). HR-EIMS *m/z* (M^+): Calcd for $C_{11}H_{15}NS$:193.0925. Found: 193.0899. HCl salt: *Anal.* Calcd for $C_{11}H_{16}ClNOS$: C, 57.50; H, 7.02; N, 6.10 Found: C, 57.47; H, 7.11; N, 6.28.

4,5,6,7-Tetrahydrothieno[3,2-*c*]pyridine-4-spirocyclohexane (6o)

Yellow oil. IR:2852, 2927. ^{1}H-NMR: 1.25-1.29 (1H, m, cyclohexyl-C<u>H</u>$_2$), 1.57-1.76 (9H, m, cyclohexyl-C<u>H</u>$_2$), 2.75 (2H, t, *J*=6 Hz, H-7), 3.11 (2H, t, *J*=6 Hz, H-6), 6.85 (1H, d, *J*=5 Hz, H-3), 7.03 (1H, d, *J*=5 Hz, H-2). ^{13}C-NMR: 21.6 (2 x cyclopentyl-<u>C</u>H$_2$), 25.7 (cyclopentyl-<u>C</u>H$_2$), 26.5 (C$_7$), 37.3 21.6 (2 x cyclopentyl-<u>C</u>H$_2$), 39.0 (C$_6$), 54.4 (C$_4$), 121.4 (C$_3$), 124.9 (C$_2$), 133.6 (C$_{3a}$), 143.7 (C$_{7a}$)LR-EIMS: *m/z* 207 (M$^+$), 58 (base peak). HR-EIMS *m/z* (M$^+$): Calcd for $C_{12}H_{17}NS$: 207.1082. Found: 207.1100.

4,5,6,7-Tetrahydrothieno[3,2-*c*]pyridine (6q)

Yellow oil. IR: 2925. ^{1}H-NMR: 1.74 (1H, brs, NH), 2.80 (2H, t, *J*=6 Hz, H-7), 3.15 (2H, t, *J*=6 Hz, H-6), 3.92 (2H, t, *J*=2 Hz, H-4), 6.74 (1H, d, *J*=5 Hz, H-3), 7.07 (1H, d, *J*=5 Hz, H-2). ^{13}C-NMR: 25.9 (C$_7$), 43.8 (C$_6$), 45.7 (C$_4$), 121.9 (C$_3$), 125.0 (C$_2$), 133.7 (C$_{3a}$), 134.4 (C$_{7a}$). HR-EIMS *m/z* (M$^+$): Calcd for C_7H_9NS:139.0453. Found: 139.0430.

4-(Pent-2-en-2-yl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (9c)

Pale yellow oil. IR: 2960, 2928. ^{1}H-NMR: 0.98 (3H, t, *J*=7 Hz, -C=CHCH$_2$C<u>H</u>$_3$), 1.51 (3H, t, *J*=1 Hz, -CH$_3$), 2.07 (2H, quintet *J*=7 Hz, -C=CHC<u>H</u>$_2$CH$_3$), 2.39-2.77 (1H, m, H-7), 2.85-2.95 (1H, m, H-7), 3.02 (1H, ddd, *J*=12, 10, 4 Hz, H-6), 3.26 (1H, ddd, *J*=12, 5, 3 Hz, H-6), 4.35 (1H, t, *J*=2 Hz, H-4), 5.43 (1H, td, *J*=7, 1 Hz, -C=C<u>H</u>CH$_2$CH$_3$), 6.63 (1H, d, *J*=5 Hz, H-3), 7.00 (1H, d, *J*=5 Hz, H-2). HR-FABMS *m/z* (MH$^+$): Calcd for $C_{12}H_{18}NS$: 208.1160. Found: 208.1158.

4-(Hept-3-en-3-yl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (9d)

Yellow oil. IR: 2963, 1651. ^{1}H-NMR: 0.84 (3H, t, *J*=7 Hz, -CH$_2$C<u>H</u>$_3$), 0.90 (3H, t, *J*=7 Hz, -C=CH(CH$_2$)$_2$C<u>H</u>$_3$), 1.31 (2H, sextet, *J*=7 Hz, -C<u>H</u>$_2$CH$_3$), 1.84-2.14 (4H, m, -C=CH(C<u>H</u>$_2$)$_2$CH$_3$), 2.63-2.84 (2H, m, H-7), 2.88-2.96 (1H, m, H-6), 3.16-3.24 (1H, m, H-6), 4.32 (1H, s, H-4), 5.16 (1H, t, *J*=7 Hz, -C=C<u>H</u>(CH$_2$)$_2$CH$_3$), 6.56 (1H, d, *J*=5 Hz, H-3), 6.92 (1H, d, *J*=5 Hz, H-2). ^{13}C-NMR: 13.9 (<u>C</u>H$_3$), 14.5 (<u>C</u>H$_3$), 21.4 (-<u>C</u>H$_2$CH$_3$), 22.9 (-C=CH(<u>C</u>H$_2$)$_2$CH$_3$), 26.0 (C$_7$), 29.7 (-C=CH(<u>C</u>H$_2$)$_2$CH$_3$), 42.2 (C$_6$), 62.4 (C$_4$), 121.0 (C$_3$), 124.8 (C$_2$), 129.3 (-C=<u>C</u>H(CH$_2$)$_2$CH$_3$), 134.6 (C$_{3a}$), 136.8 (C$_{7a}$), 142.4 (-<u>C</u>=CH(CH$_2$)$_2$CH$_3$). HR-FABMS *m/z* (MH$^+$): Calcd for $C_{14}H_{22}NS$: 264.1422. Found: 264.1421.

4-(Non-4-en-2-yl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (9e)

Yellow oil. IR: 2962, 1666. ^{1}H-NMR: 0.89 (6H, t, *J*=7 Hz, -(CH$_2$)$_2$C<u>H</u>$_3$, -C=CH(CH$_2$)$_3$C<u>H</u>$_3$), 1.26-1.49 (6H, m, -(C<u>H</u>$_2$)$_2$CH$_3$, -C=CH(C<u>H</u>$_2$)$_3$CH$_3$), 1.89-1.98 (4H, m, -(C<u>H</u>$_2$)$_2$CH$_3$, -C=CH(C<u>H</u>$_2$)$_3$CH$_3$), 2.71-2.90

(2H, m, H-7), 3.22-3.29 (2H, m, H-6), 4.38 (1H, s, H-4), 5.22 (1H, t, *J*=7 Hz, -C=C<u>H</u>$(CH_2)_3CH_3$), 6.62 (1H, t, *J*=5 Hz, H-3), 6.99 (1H, t, *J*=5 Hz, H-2). ^{13}C-NMR: 13.9 (<u>C</u>H_3), 14.4 (<u>C</u>H_3), 22.4 (-(<u>C</u>$H_2)_2CH_3$), 23.0 (-C=CH(<u>C</u>$H_2)_3CH_3$), 25.9 (C_7), 27.5 (-(<u>C</u>$H_2)_2CH_3$), 30.9 (-C=CH(<u>C</u>$H_2)_3CH_3$), 31.9 (-C=CH(<u>C</u>$H_2)_3CH_3$), 41.8 (C_6), 61.8 (C_4), 121.0 (C_3), 126.4 (C_2), 130.1 (-C=<u>C</u>H$(CH_2)_3CH_3$), 134.6 (C_{3a}), 136.7 (C_{7a}), 140.5 (-<u>C</u>=CH$(CH_2)_3CH_3$).HR-FABMS (MH^+): Calcd for $C_{16}H_{26}NS$: 264.1786. Found: 264.1774.

4-(Undec-5-en-5-yl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (9f)

Yellow oil. IR: 2957, 2930, 1652. ^{1}H-NMR: 0.73 (6H, m, -$(CH_2)_3C$<u>H</u>$_3$, -C=CH$(CH_2)_4C$<u>H</u>$_3$), 1.18-1.40 (10H, m, -(C<u>H</u>$_2)_3CH_3$, -C=CH(C<u>H</u>$_2)_4CH_3$), 1.82-2.10 (4H, m, -(C<u>H</u>$_2)_3CH_3$, -C=CH(C<u>H</u>$_2)_4CH_3$), 2.61-2.80 (2H, m, H-7), 2.82-2.94 (1H, m, H-6), 3.14-3.21 (1H, m, H-6), 4.30 (1H, s, H-4), 5.13 (1H, t, *J*= 7 Hz, -C=C<u>H</u>$(CH_2)_3CH_3$), 6.54 (1H, d, *J*=5 Hz, H-3), 6.91 (1H, d, *J*=5 Hz, H-2). ^{13}C-NMR: 13.9 (<u>C</u>H_3), 14.0 (<u>C</u>H_3), 22.5 (-(<u>C</u>$H_2)_3CH_3$), 23.1 (-C=CH(<u>C</u>$H_2)_4CH_3$), 26.1 (C_7), 27.7 (-(<u>C</u>$H_2)_3CH_3$), 28.5(-(<u>C</u>$H_2)_3CH_3$), 29.4 (-C=CH(<u>C</u>$H_2)_4CH_3$), 31.6 (-C=CH(<u>C</u>$H_2)_4CH_3$), 32.0 (-C=CH(<u>C</u>$H_2)_4CH_3$), 42.0 (C_6), 62.0 (C_4), 120.9 (C_3), 126.4 (C_2), 129.7 (-C=<u>C</u>H$(CH_2)_4CH_3$), 134.7 (C_{3a}), 136.9 (C_{7a}), 140.9 (-<u>C</u>=CH$(CH_2)_4CH_3$). HR-FABMS (MH^+): Calcd for $C_{18}H_{30}NS$: 292.2099. Found: 292.2092.

4-(Tridec-6-en-6-yl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (9g)

Yellow oil. IR: 2956, 2928, 1653. ^{1}H-NMR: 0.84-0.90 (6H, m, -$(CH_2)_4C$<u>H</u>$_3$, -C=CH$(CH_2)_5C$<u>H</u>$_3$), 1.18-1.42 (14H, m, -(C<u>H</u>$_2)_4CH_3$, -C=CH(C<u>H</u>$_2)_5CH_3$), 1.89-2.10 (4H, m, -(C<u>H</u>$_2)_4CH_3$, -C=CH(C<u>H</u>$_2)_5CH_3$), 2.61-2.99 (3H, m, H-6, H-7), 3.14-3.22 (1H, m, H-6), 4.39 (1H, s, H-4), 5.20 (1H, t, *J*=7 Hz, -C=C<u>H</u>$(CH_2)_3CH_3$), 6.61 (1H, d, *J*=5 Hz, H-3), 6.99 (1H, d, *J*=5 Hz, H-2). ^{13}C-NMR: 13.97 (<u>C</u>H_3), 14.0 0 (<u>C</u>H_3), 22.4 (-(<u>C</u>$H_2)_4CH_3$), 22.5 (-C=CH(<u>C</u>$H_2)_5CH_3$), 25.4 (C_7), 27.8 (-(<u>C</u>$H_2)_4CH_3$), 28.8 (-(<u>C</u>$H_2)_4CH_3$), 29.0 (-(<u>C</u>$H_2)_4CH_3$), 29.3 (-C=CH(<u>C</u>$H_2)_5CH_3$), 29.6 (-C=CH(<u>C</u>$H_2)_5CH_3$), 31.7 (-C=CH(<u>C</u>$H_2)_5CH_3$), 32.1 (-C=CH(<u>C</u>$H_2)_5CH_3$), 41.4 (C_6), 61.3 (C_4), 121.4 (C_3), 126.3 (C_2), 130.9 (-C=<u>C</u>H$(CH_2)_5CH_3$), 134.4 (C_{3a}), 135.9 (C_{7a}), 139.9 (-<u>C</u>=CH$(CH_2)_5CH_3$). HR-FABMS (MH^+): Calcd for $C_{20}H_{34}NS$: 320.2412. Found: 320.2412.

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