Synthesis of New Thieno[*b*]azepinediones from α-Methylene Ketones

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Abstract: New substituted 6,7-dihydro-4*H*-thieno[3,2-*b*]azepine-5,8-diones were synthesized in seven steps, starting from substituted α-methylene ketones, via 3-aminothiophene-2-carboxylic acid alkyl esters.

Key words: heterocycles, thieno[*b*]azepinediones, α-methylene ketones, 3-aminothiophene-2-carboxylic acid alkyl esters

Benzoazepinediones and their heterocyclic analogues are interesting compounds because they are precursors of potential antitumor molecules such as paullones **1**, reported by Kunick and co-workers over the last decade (Figure 1).[1–3]

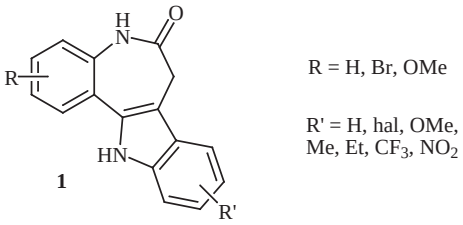
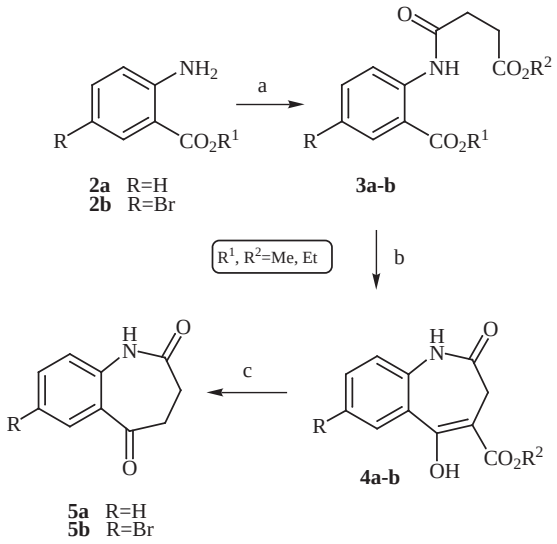


Figure 1 The structure of paullones **1**

In 1991, Kunick[4] described for the first time the synthesis of benzoazepinediones **5** from alkyl 2-aminobenzoates **2** (Scheme 1). Diesters **3** were prepared by the reaction of amines **2** with a 3-chlorocarbonylpropionic acid alkyl ester. The Dieckmann reaction from **3** using potassium hydride furnished compounds **4**. Heating **4** in wet dimethyl sulfoxide yielded benzoazepinediones **5**.

To our knowledge, Kunick's report[4] is the only reference available in the literature regarding the preparation of a thieno[*b*]azepinedione. The 5,6,7,8-tetrahydro-4*H*-thieno[3,2-*b*]azepine-5,8-dione (**6**) (Figure 2) was obtained from the 3-aminothiophene-2-carboxylic acid methyl ester in three steps in 33% yield, using the experimental conditions shown in Scheme 1.

We present here the synthesis of new thieno[*b*]-azepinediones substituted on the thiophene ring. Starting materials were the corresponding substituted 3-aminothiophene-2-carboxylic acid alkyl esters, prepared from α-methylene ketones.



Scheme 1 *Reagents and conditions*: (a) $ClCO(CH_2)_2CO_2R^2$, $CaCO_3$, toluene; (b) KH, toluene, DMF; (c) H_2O, DMSO

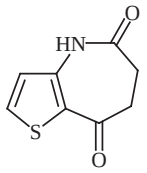


Figure 2 The structure of 5,6,7,8-tetrahydro-4*H*-thieno[3,2-*b*]azepine-5,8,dione (**6**)

α-Methylene ketones **7** led to β-chloroacroleins **8** by a Vilsmeier–Haack–Arnold reaction, using phosphorus oxychloride and DMF[5] (Scheme 2). They were obtained in good to excellent yields and used without further purification in the next step (Table 1). The corresponding oximes were prepared by reacting **8** with hydroxylamine hydrochloride in DMF.[6] The oximes were dehydrated by refluxing in acetic anhydride to give the β-chloroacrylonitriles **9** in moderate to good yields. Condensation of β-chloroacrylonitriles **9** with alkyl thioglycolate (R = Me, Et) in a basic medium, in a mixture of the appropriate alcohol and tetrahydrofuran yielded 3-aminothiophene-2-carboxylic acid alkyl esters **10** in moderate to excellent yields.[7]

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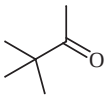
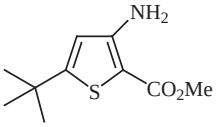
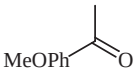
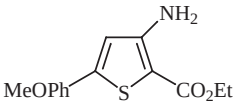
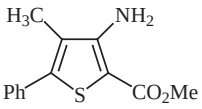
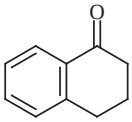
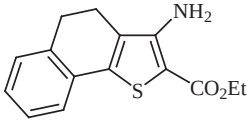
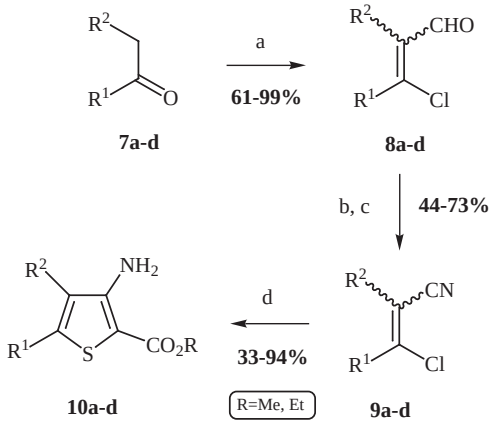
Table 1 Preparation of β-Chloroacroleins **8**, β-Chloroacrylonitriles **9** and Thiophenes **10**

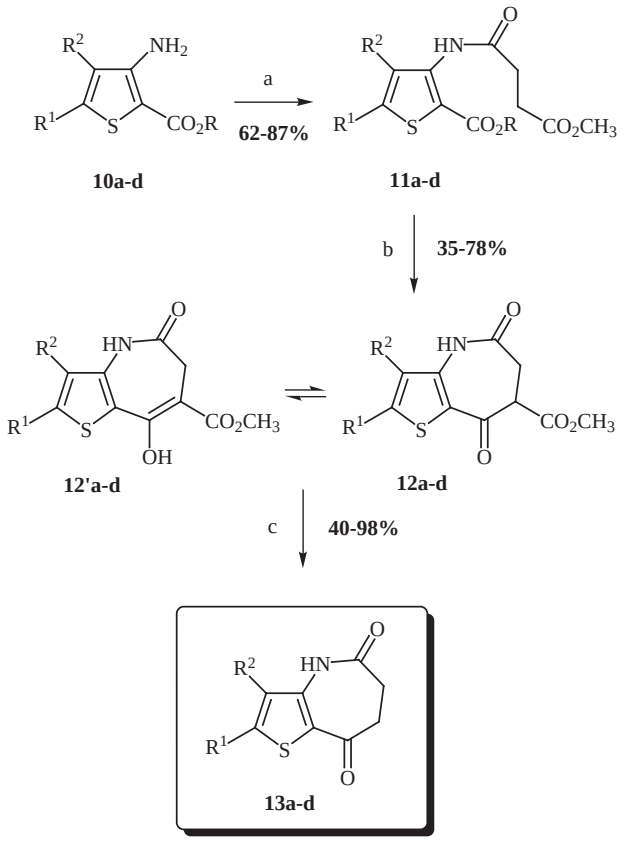
Entry	Ketone **7**	Yield (%)		Thiophene **10**	Yield (%)
		8	**9**		
a		61[a]	73[a]		94[a]
b		72[a]	50[b]		33[c]
c		99[a]	44[a]		48[a]
d		88[a]	55[a]		82[a]

[a] Crude product, analytically pure and used without further purification.
[b] Product purified by recrystallization in aq EtOH.
[c] Product purified by chromatography column using CH_2Cl_2 as eluent.



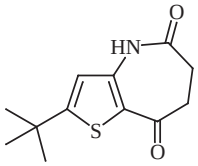
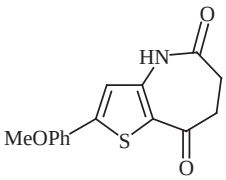
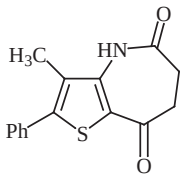
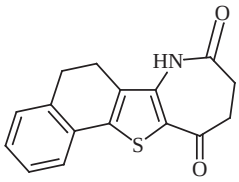
Scheme 2 *Reagents and conditions*: (a) $POCl_3$, DMF, 60 °C, 5 h; (b) $NH_2OH{\cdot}HCl$, DMF, 110 °C, 8 h; (c) Ac_2O, reflux, 18 h; (d) $HSCH_2CO_2R$, K_2CO_3, ROH, THF, reflux, overnight

The reaction of 3-aminothiophene-2-carboxylic acid alkyl esters **10** with 3-chlorocarbonylpropionic acid methyl ester in the presence of calcium carbonate or potassium carbonate in toluene[2,4] yielded the corresponding amides **11** (Scheme 3) in good yields (Table 2). The Dieckmann reaction of **11** with a large excess of potassium hydride in a mixture of toluene and DMF gave the cyclized compounds **12** in moderate to good yields.[2,4] The ^1H NMR spectra indicated that compounds **12** are in equilibrium with the corresponding enolic forms **12′** in DMSO-d_6 solution. The proportion of each form was not determined as it changes over time. Nevertheless, it was observed that



Scheme 3 *Reagents and conditions*: (a) $ClCO(CH_2)_2CO_2CH_3$, $CaCO_3$ or K_2CO_3, toluene, reflux, 2 h; (b) KH, toluene, DMF, 80 °C, 3 h, argon; (c) H_2O, DMSO, 140 °C, 4–8 h

Table 2 Preparation of Amides **11**, Compounds **12** and **12′** and Thienoazepinediones **13**

Entry	Yield (%)		Thienoazepinedione **13**	Yield (%)
	11	**12** and **12′**		
a	87[a]	78[a]		40[a]
b	66[b]	47[c]		98[a]
c	67[a]	35[a]		98[a]
d	62[b]	76[a]		97[a]

[a] Crude product, analytically pure and used without further purification.
[b] Product purified by recrystallization.
[c] Product purified by trituration in hot methanol and filtration.

intermediates **12** are usually the existing major form after workup of the reaction mixture.

It should be noted that the thiophene ring in the amides **11b** and **11d** was substituted in position 2 by a carboxylic acid ethyl ester group, whereas 3-chlorocarbonylpropionic acid methyl ester was always used to prepare the amides. Hence, the presence of two different ester groups could involve a transesterification reaction during cyclization with potassium hydride. This phenomenon was not observed for compounds **12b** and **12′b**. However, for derivatives **12d** and **12′d,** the presence of other signals which could correspond to transesterification compounds was noticed in the ^{1}H NMR spectrum. All the isomers could not be separated in order to be characterized and the dealkoxycarbonylation was carried out on the mixture. By heating compounds **12** in dimethyl sulfoxide–water,[2,4] the expected 6,7-dihydro-4*H*-thieno[3,2-*b*]azepine-5,8-diones **13** were obtained in moderate to excellent yields.

In conclusion, we have described a synthesis of new substituted 6,7-dihydro-4*H*-thieno[3,2-*b*]azepine-5,8-diones in seven steps from α-methylene ketones via 3-aminothiophene-2-carboxylic acid alkyl esters. These thieno[*b*]azepinediones and all intermediates of this synthesis, prepared in acceptable yields, were usually obtained analytically pure and no further purification was needed.

KH was purchased from Acros. β-Chloroacroleins[5] and β-chloroacrylonitriles[6] were prepared according to literature procedures. Melting points were determined on a Stuart SMP3 melting point apparatus and are uncorrected. IR spectra were performed on a Mattson 3000 FTIR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a AC Bruker 250 MHz spectrometer in $CDCl_3$ or DMSO-d_6. Mass spectra were performed on a Hewlett-Packard 5971 A GC-MS spectrometer.

3-Aminothiophenes 10; General Procedure

β-Chloroacrylonitriles **9** (0.109 mol) were dissolved in a mixture of the appropriate alcohol (MeOH or EtOH, 170 mL) and THF (30 mL). Then, alkyl thioglycolate (methyl thioglycolate or ethyl thioglycolate, 0.109 mol) was added in one portion with stirring, followed by K_2CO_3 (15.15 g, 0.109 mol) and the reaction mixture was refluxed overnight. After cooling to r.t., the crude mixture was filtered over Celite and the filtrate evaporated to furnish thiophenes **10**.

3-Amino-5-*tert*-butylthiophene-2-carboxylic Acid Methyl Ester (10a)

Orange solid; yield: 21.76 g (94%); analytically pure and used without further purification; mp 71–72 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.33 [s, 9 H, $C(CH_3)_3$], 3.80 (s, 3 H, CO_2CH_3), 5.39 (br s, 2 H, NH_2, D_2O exchangeable), 6.33 (s, 1 $H_{thiophene}$).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 31.2 [$(CH_3)_3$], 34.4 (C), 50.5 (CH_3), 97.4 (C), 114.9 (CH), 153.9 (C), 163.3 (C), 164.6 (C=O).

GC-MS: *m*/*z* (%) = 213 (59), 198 (100).

3-Amino-5-(4-methoxyphenyl)thiophene-2-carboxylic Acid Ethyl Ester (10b)

Orange solid; yield: 5.01 g (33%); purified by column chromatography on silica gel using CH_2Cl_2 as eluent; mp 148–150 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.37 (t, 3 H, *J* = 7.1 Hz, CH_3), 3.84 (s, 3 H, OCH_3), 4.31 (q, 2 H, *J* = 7.1 Hz, CH_2), 5.45 (br s, 2 H, NH_2, D_2O exchangeable), 6.67 (s, 1 $H_{thiophene}$), 6.91 (d, 2 H_{phenyl}, *J* = 8.7 Hz), 7.52 (d, 2 H_{phenyl}, *J* = 8.7 Hz).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.5 (CH_3), 55.3 (OCH_3), 60.0 (CH_2), 114.3 (2 CH), 114.5 (CH), 116.2 (C), 126.2 (C), 127.2 (2 CH), 149.0 (C), 154.3 (C), 160.3 (C), 164.6 (C=O).

3-Amino-4-methyl-5-phenylthiophene-2-carboxylic Acid Methyl Ester (10c)

Orange oil; yield: 21.44 g (48%); analytically pure and used without further purification.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.21 (s, 3 H, CH_3), 3.60 (s, 3 H, CO_2CH_3), 7.35–7.44 (m, 5 H_{phenyl}), NH_2 signal not present in the spectrum.

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 18.6 (CH_3), 52.6 (CH_3), 128.6 (C), 128.9, 129.0, 129.1 (5 CH), 129.8 (C), 130.0 (C), 130.3 (C), 135.1 (C), 161.5 (C=O).

GC-MS: *m*/*z* (%) = 247 (35), 174 (100).

3-Amino-4,5-dihydronaphtho[1,2-*b*]thiophene-2-carboxylic Acid Ethyl Ester (10d)
Orange solid; yield: 20.73 g (82%); analytically pure and used without further purification; mp 114–115 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.38 (t, 3 H, *J* = 7.1 Hz, CH_3), 2.60 (m, 2 H, CH_2), 3.00 (m, 2 H, CH_2), 4.33 (q, 2 H, *J* = 7.1 Hz, CH_2), 5.43 (br s, 2 H, NH_2, D_2O exchangeable), 7.22–7.23 (m, 3 H_{arom}), 7.38–7.41 (m, 1 H_{arom}).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.5 (CH_3), 20.8 (CH_2), 28.3 (CH_2), 60.0 (CH_2), 123.6 (CH), 126.7 (C), 127.1 (CH), 128.1 (CH), 128.4 (CH), 128.5 (C), 130.6 (C), 135.5 (C), 141.2 (C), 151.7 (C), 164.9 (C=O).

GC-MS: *m*/*z* (%) = 273 (100), 226 (54).

Amides 11; General Procedure
A solution of 3-chlorocarbonylpropionic acid methyl ester (17.33 g, 0.115 mol) in toluene (50 mL) was added dropwise to a stirred and cooled (0 °C) suspension of the appropriate substituted 3-aminothiophene-2-carboxylic acid alkyl ester **10** (0.096 mol) and $CaCO_3$ (19.19 g, 0.192 mol) or K_2CO_3 (26.50 g, 0.192 mol) in toluene (200 mL). The reaction mixture was allowed to stand at that temperature for an additional 15 min. After warmimg to r.t. gradually, the mixture was refluxed for 2–3 h (progress of the reaction was monitored by TLC) and then filtered to remove the inorganic salts. The filtrate was evaporated to give amides **11**.

5-*tert*-Butyl-3-(3-methoxycarbonylpropionylamino)thiophene-2-carboxylic Acid Methyl Ester (11a)
Orange solid; yield: 27.24 g (87%); analytically pure and used without further purification; mp 66–68 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.37 [s, 9 H, $C(CH_3)_3$], 2.74 (br s, 4 H, CH_2CH_2), 3.71 (s, 3 H, CO_2CH_3), 3.86 (s, 3 H, CO_2CH_3), 7.91 (s, 1 $H_{thiophene}$), 10.23 (br s, 1 H, NH, D_2O exchangeable).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 28.9 (CH_2), 31.7 (CH_2), 31.8 [$(CH_3)_3$], 35.2 (C), 51.7 (CH_3), 51.9 (CH_3), 107.0 (C), 117.6 (CH), 144.4 (C), 164.5 (C), 164.9 (C=O), 168.9 (C=O), 172.8 (C=O).

3-(3-Methoxycarbonylpropionylamino)-5-(4-methoxyphenyl)thiophene-2-carboxylic Acid Ethyl Ester (11b)
Orange crystals; yield: 3.45 g (66%); purified by recrystallization from MeOH; mp 112–113 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.40 (t, 3 H, *J* = 7.1 Hz, CH_3), 2.77 (s, 4 H, CH_2CH_2), 3.72 (s, 3 H, CO_2CH_3), 3.84 (s, 3 H, OCH_3), 4.36 (q, 2 H, *J* = 7.1 Hz, CH_2), 6.92 (d, 2 H_{phenyl}, *J* = 8.9 Hz), 7.60 (d, 2 H_{phenyl}, *J* = 8.9 Hz), 8.26 (s, 1 $H_{thiophene}$), 10.30 (br s, 1 H, NH, D_2O exchangeable).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.3 (CH_3), 28.9 (CH_2), 31.9 (CH_2), 51.8 (CH_3), 55.3 (OCH_3), 60.9 (CH_2), 108.2 (C), 114.4 (2CH), 117.1 (CH), 126.0 (C), 127.5 (2CH), 145.0 (C), 149.8 (C), 160.5 (C), 164.4 (C=O), 169.0 (C=O), 172.8 (C=O).

3-(3-Methoxycarbonylpropionylamino)-4-methyl-5-phenylthiophene-2-carboxylic Acid Methyl Ester (11c)
Orange oil; yield: 1.87 g (67%); analytically pure and used without further purification.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.16 (s, 3 H, CH_3), 2.61–2.70 (m, 2 H, CH_2), 2.88–2.97 (m, 2 H, CH_2), 3.68 (s, 3 H, CO_2CH_3), 3.85 (s, 3 H, CO_2CH_3), 7.41–7.51 (m, 5 H_{phenyl}), NH signal not present in the spectrum.

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 12.1 (CH_3), 28.6 (CH_2), 33.1 (CH_2), 51.8 (CH_3), 52.3 (CH_3), 126.0 (C), 128.8, 128.9, 129.1 (5CH), 133.2 (C), 133.3 (C), 140.9 (C), 144.3 (C), 161.3 (C=O), 172.8 (C=O), 173.7 (C=O).

3-(3-Methoxycarbonylpropionylamino)-4,5-dihydronaphtho[1,2-*b*]thiophene-2-carboxylic Acid Ethyl Ester (11d)
Yellow needles; 2.52 g (62%); purified by recrystallization from toluene; mp 151–152 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.39 (t, 3 H, *J* = 7.2 Hz, CH_3), 2.76–2.78 (m, 6 H, CH_2CH_2 + CH_2), 2.87–2.90 (m, 2 H, CH_2), 3.72 (s, 3 H, CO_2CH_3), 4.35 (q, 2 H, *J* = 7.2 Hz, CH_2), 7.23–7.26 (m, 3 H_{arom}), 7.39–7.40 (m, 1 H_{arom}), 9.21 (br s, 1 H, NH, D_2O exchangeable).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.3 (CH_3), 24.1 (CH_2), 28.8 (CH_2), 29.1 (CH_2), 31.4 (CH_2), 51.8 (CH_3), 61.0 (CH_2), 113.3 (C), 123.4 (CH), 127.0 (CH), 128.1 (CH), 128.7 (CH), 130.5 (C), 134.0 (C), 136.3 (C), 141.8 (C), 142.1 (C), 163.7 (C=O), 169.8 (C=O), 172.8 (C=O).

Compounds 12 and 12′; General Procedure
A solution of the appropriate amide **11** (15.5 mmol) in anhyd toluene (40 mL) and DMF (6 mL) was added dropwise to a stirred and cooled (0 °C) suspension of potassium hydride (3.73 g, 93.1 mmol) in anhyd toluene (30 mL) under argon, and the reaction mixture was allowed to stand at that temperature for an additional 30 min. After warming to r.t. gradually, the mixture was heated at 80 °C for 3 h (progress of the reaction was monitored by TLC). The mixture was hydrolysed slowly at 0 °C with AcOH (7 mL) and filtered after addition of H_2O (60 mL).

For compounds **12b** and **12′b**: the obtained residue constituted a mixture of the two isomers **12b** and **12′b**.

For the rest: the filtrate was extracted with Et_2O (3 × 50 mL). The organic layers were combined, washed with brine (100 mL), dried (Na_2SO_4) and evaporated to give a mixture of the two isomers **12** and **12′**.

2-*tert*-Butyl-5,8-dioxo-5,6,7,8-tetrahydro-4*H*-thieno[3,2-*b*]-azepine-7-carboxylic Acid Methyl Ester (12a) and 2-*tert*-Butyl-8-hydroxy-5-oxo-5,6-dihydro-4*H*-thieno[3,2-*b*]azepine-7-carboxylic Acid Methyl Ester (12′a)
Orange paste; yield: 11.50 g (78%); used without further purification. A small sample was purified by trituration in hot MeOH and filtration to give a beige solid; mp 194–195 °C.

IR (KBr): 1563 (C=O), 1603 (C=O), 1634 (C=O), 1687 (C=O) cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.32 [s, $C(CH_3)_3$ **12a**], 1.35 [s, $C(CH_3)_3$ **12′a**], 2.98–3.05 (m, CH_2 **12a** + CH_2 **12′a**), 3.66 (s, CO_2CH_3 **12a**), 3.81 (s, CO_2CH_3 **12′a**), 4.06 (m, CH **12a**), 6.69 (s, $H_{thiophene}$ **12′a**), 6.70 (s, $H_{thiophene}$ **12a**), 10.73 (br s, NH **12a** + NH **12′a**, D_2O exchangeable), 12.22 (br s, OH **12′a**, D_2O exchangeable).

2-(4-Methoxyphenyl)-5,8-dioxo-5,6,7,8-tetrahydro-4*H*-thieno[3,2-*b*]azepine-7-carboxylic Acid Methyl Ester (12b) and 8-Hydroxy-2-(4-methoxyphenyl)-5-oxo-5,6-dihydro-4*H*-thieno-[3,2-*b*]azepine-7-carboxylic Acid Methyl Ester (12′b)
Yellow solid; yield: 1.35 g (47%); purified by trituration in hot MeOH and filtration; mp 226–228 °C.

IR (KBr): 1567 (C=O), 1605 (C=O), 1630 (C=O), 1697 (C=O) cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.03–3.10 (m, CH_2 **12b** + CH_2 **12′b**), 3.68 (s, CO_2CH_3 **12b**), 3.82 (s, CO_2CH_3 **12′b** + OCH_3 **12b** + OCH_3 **12′b**), 4.12 (m, CH **12b**), 7.04–7.10 (m, 2 H_{phenyl} **12b** + 2 H_{phenyl} **12′b** + $H_{thiophene}$ **12b** + $H_{thiophene}$ **12′b**), 7.61–7.65 (m, 2 H_{phenyl} **12b** + 2 H_{phenyl} **12′b**), 10.88 (br s, NH **12′b**, D_2O exchangeable), 10.90 (br s, NH **12b**, D_2O exchangeable), OH **12′b** signal not present in the spectrum.

3-Methyl-5,8-dioxo-2-phenyl-5,6,7,8-tetrahydro-4*H*-thieno[3,2-*b*]azepine-7-carboxylic Acid Methyl Ester (12c) and 8-Hydroxy-3-methyl-5-oxo-2-phenyl-5,6-dihydro-4*H*-thieno[3,2-*b*]azepine-7-carboxylic Acid Methyl Ester (12′c)

Yellow solid; yield: 242 mg (35%); analytically pure and used without further purification; mp 202–203 °C.

IR (KBr): 1589 (C=O), 1639 (C=O), 1655 (C=O), 1673 (C=O) cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 2.18 (s, CH_3 **12c**), 2.22 (s, CH_3 **12′c**), 3.08 (m, CH_2 **12c** + CH_2 **12′c**), 3.70 (s, CO_2CH_3 **12c**), 3.83 (s, CO_2CH_3 **12′c**), 4.15 (m, CH **12c**), 7.52 (m, 5 H_{phenyl} **12c** + 5 H_{phenyl} **12′c**), 10.40 (br s, NH **12c** + NH **12′c**, D_2O exchangeable), OH **12′c** signal not present in the spectrum.

8,11-Dioxo-5,7,8,9,10,11-hexahydro-6*H*-12-thia-7-azanaphtho-[2,1-*a*]azulene-10-carboxylic Acid Methyl Ester (12d) and 11-Hydroxy-8-oxo-5,7,8,9-tetrahydro-6*H*-12-thia-7-azanaphtho-[2,1-*a*]azulene-10-carboxylic Acid Methyl Ester (12′d)

Yellow solid; yield: 4.19 g (76%); analytically pure and used without further purification; mp 178–179 °C.

IR (KBr): 1560 (C=O), 1601 (C=O), 1644 (C=O), 1681 (C=O) cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 2.80 (m, CH_2 **12d** + CH_2 **12′d**), 2.93 (m, CH_2 **12d** + CH_2 **12′d**), 3.08 (m, CH_2 **12d** + CH_2 **12′d**), 3.69 (s, CO_2CH_3 **12d**), 3.83 (s, CO_2CH_3 **12′d**), 4.14 (m, CH **12d**), 7.32 (m, 3 H_{arom} **12d** + 3 H_{arom} **12′d**), 7.45 (m, 1 H_{arom} **12d** + 1 H_{arom} **12′d**), 10.31 (br s, NH **12′d**, D_2O exchangeable), 10.56 (br s, NH **12d**, D_2O exchangeable), 12.34 (br s, OH **12′d**, D_2O exchangeable).

Thienoazepinediones 13; General Procedure

The cyclized compounds **12** and **12′** (11 mmol) were dissolved in DMSO (40 mL) and the solution was heated at 90 °C. H_2O (0.11 mol, 2 mL) was added in one portion and the reaction mixture was heated at 140 °C for 4–8 h (progress of the reaction was monitored by TLC). At r.t., the mixture was poured into iced H_2O (50 mL). If a precipitate appeared (compounds **13a**, **13b** and **13d**), it was filtered off to give the expected thienoazepinediones **13**. Otherwise, the mixture was extracted with EtOAc (3 × 100 mL). The organic layers were combined, washed with H_2O (50 mL) and brine (50 mL), dried (Na_2SO_4) and evaporated to give the expected thienoazepinedione **13c**.

2-*tert*-Butyl-6,7-dihydro-4*H*-thieno[3,2-*b*]azepine-5,8-dione (13a)

Brown solid; 3.58 g (40%), analytically pure without further purification; mp 248–249 °C.

IR (KBr): 1643 (C=O), 1679 (C=O) cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 1.32 [s, 9 H, $C(CH_3)_3$], 2.74 (s, 4 H, CH_2CH_2), 6.70 (s, 1 $H_{thiophene}$), 10.65 (br s, 1 H, NH, D_2O exchangeable).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 30.4 (CH_2), 31.5 [$(CH_3)_3$], 34.9 (C), 35.2 (CH_2), 118.5 (CH), 121.1 (C), 141.7 (C), 165.5 (C), 173.0 (C=O), 190.8 (C=O).

2-(4-Methoxyphenyl)-6,7-dihydro-4*H*-thieno[3,2-*b*]azepine-5,8-dione (13b)

Pale brown solid; yield: 980 mg (98%); analytically pure without further purification; mp 282–284 °C.

IR (KBr): 1632 (C=O), 1672 (C=O) cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 2.79 (m, 4 H, CH_2CH_2), 3.82 (s, 3 H, OCH_3), 7.06 (d, 2 H_{phenyl}, J = 8.7 Hz), 7.09 (s, 1 $H_{thiophene}$), 7.62 (d, 2 H_{phenyl}, J = 8.7 Hz), 10.77 (br s, 1 H, NH, D_2O exchangeable).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 30.3 (CH_2), 35.1 (CH_2), 55.5 (OCH_3), 114.9 (2CH), 117.6 (CH), 121.8 (C), 124.8 (C), 127.3 (2CH), 142.5 (C), 150.5 (C), 160.6 (C), 172.9 (C=O), 190.6 (C=O).

3-Methyl-2-phenyl-6,7-dihydro-4*H*-thieno[3,2-*b*]azepine-5,8-dione (13c)

Brown solid; yield: 124 mg (98%); analytically pure without further purification; mp 219–220 °C.

IR (KBr): 1634 (C=O), 1682 (C=O) cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 2.18 (s, 3 H, CH_3), 2.80–2.85 (m, 4 H, CH_2CH_2), 7.51 (m, 5 H_{phenyl}), 9.99 (br s, 1 H, NH, D_2O exchangeable).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 13.0 (CH_3), 30.3 (CH_2), 36.0 (CH_2), 124.1 (C), 127.9 (C), 128.9 (2 CH), 129.1 (CH), 129.2 (2 CH), 133.3 (C), 140.9 (C), 145.5 (C), 173.2 (C=O), 191.4 (C=O).

5,6,9,10-Tetrahydro-7*H*-12-thia-7-azanaphtho[2,1-*a*]azulene-8,11-dione (13d)

Yellow solid; 3.30 g (97%); analytically pure without further purification; mp 281–283 °C.

IR (KBr): 1631 (C=O), 1678 (C=O) cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 2.81 (m, 6 H, 3 CH_2), 2.92 (m, 2 H, CH_2), 7.33 (m, 3 H_{arom}), 7.49 (m, 1 H_{arom}), 10.16 (br s, 1 H, NH, D_2O exchangeable).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 21.1 (CH_2), 27.7 (CH_2), 30.4 (CH_2), 35.7 (CH_2), 123.6 (C), 123.7 (CH), 127.4 (CH), 128.5 (CH), 129.5 (CH), 129.8 (C), 131.1 (C), 135.8 (C), 139.7 (C), 142.9 (C), 173.2 (C=O), 191.2 (C=O).

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