THIENO[3,4-b][1,4]DIAZEPINES: SYNTHESIS AND STEREOCHEMISTRY

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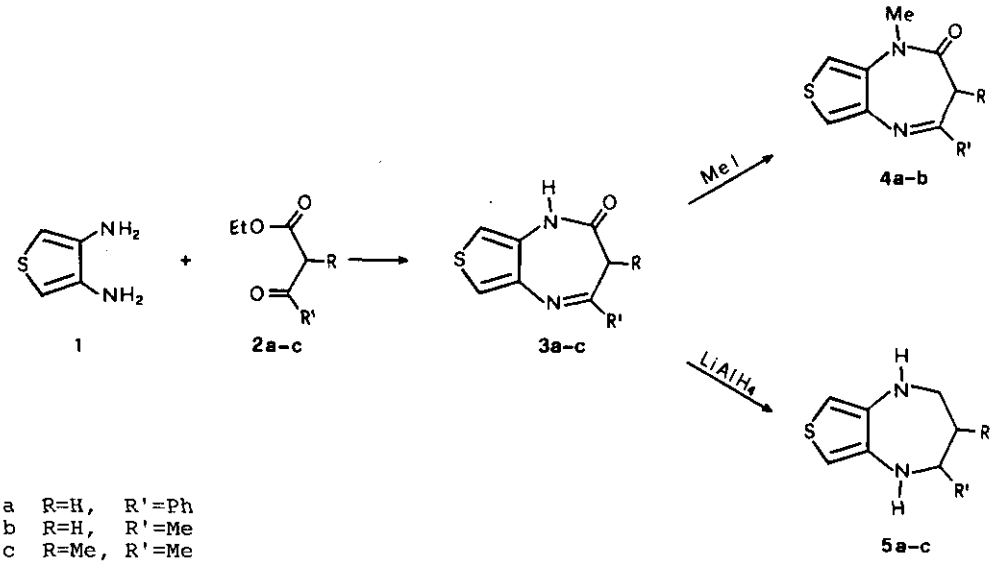
Abstract - The synthesis of 1,3-dihydro-2H- and 2,3,4,5-tetrahydro-1H-thieno[3,4-b][1,4]diazepine derivatives from 3,4-diaminothiophene and ß-keto esters is described.

Following our interest in the chemistry of benzodiazepines with particular reference to the configurational and conformational properties of the system, we have been interested in the synthesis and spectroscopic characteristics of compounds containing a heterocyclic five-membered ring fused to the diazepine ring.[1-4] We report here the synthesis and the stereochemical features of novel thieno[3,4-b][1,4]diazepines; these compounds are structurally related to several thieno[2,3-e][1,4]diazepines which show very remarkable pharmacological activity on CNS and have been introduced in therapy as Clotiazepam® and Brotizolam®.

We have also extended our investigations to tetrahydrothieno[3,4-b][1,4]-diazepines in the aim of correlating the stereochemistry of the obtained derivatives with the potential biological activity of the system.

The synthetic approach to thieno[3,4-b][1,4]diazepin-2-ones (**3a-c**) is based on the condensation-cyclization reaction of 3,4-diaminothiophene (**1**) with an equimolar amount of ß-keto esters (**2a-c**) in refluxing xylene (Scheme 1): the process afforded in one-step the 1,3-dihydro-2H-thieno[3,4-b][1,4]-diazepin-2-ones (**3a-c**) in good yields. The N-methyl derivatives (**4a-b**) were prepared by treatment of **3a-b** with an excess of methyl iodide in DMF in the presence of potassium carbonate or NaH. 2,3,4,5-Tetrahydro-1H-thieno-[3,4-b][1,4]diazepines (**5a-c**) were synthesized by treatment of **3a-c** with lithium aluminum hydride; the reduction process involves both the carbonyl group and the C=N moiety of the heptatomic nucleus.

Scheme 1



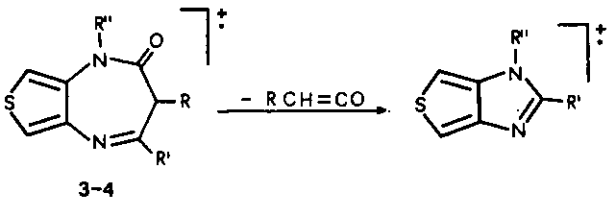
a R=H, R'=Ph
b R=H, R'=Me
c R=Me, R'=Me

The structures of the diazepines (**3-5**) were confirmed by the elemental analyses and spectroscopic measurements (ir, ms, ^{1}H- and ^{13}C-nmr). The ir spectra of compounds (**3**) and (**5**) exhibit a characteristic absorption at 3200-3100 cm^{-1} due to the NH stretching. For compounds (**3**) and (**4**) a strong carbonyl band is also observed at 1678-1660 cm^{-1}. An additional band is present for **3** and **4** at 1615-1605 cm^{-1} due to C=N absorption of the heptatomic ring.

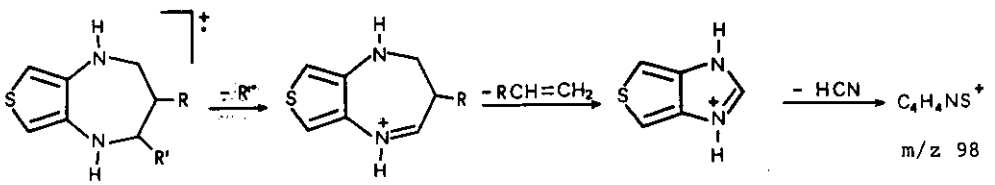
The mass spectra of all the synthesized compounds show correct molecular ions and the formation of diagnostic fragmentations (Scheme 2). In particular, for dihydrothienodiazepinones (**3** and **4**) thienoimidazole fragments originate from molecular ions by loss of RCH=CO, with retention of the N-1 and C-4 substituents present in the thienodiazepinone precursors.

In the mass spectra of tetrahydrothienodiazepines (5) the initial cleavage process occurs by removal of an electron from a nitrogen atom with loss of the substituent at C-2. An olefin molecule can then break away to yield the stable thienoimidazole ion which appears as the base peak. Subsequent loss of HCN yields the m/z 98 ion.

Scheme 2



3-4



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The ^{1}H-nmr spectra (Table 1) of the 1,3-dihydro-2H-thieno[3,4-b][1,4]-diazepin-2-ones (**3a-b** and **4a-b**) show a single line for the methylene protons at C-3. The heptatomic ring of **3** and **4** can be regarded as a cycloheptadiene-like system showing two limit pseudo-boat conformers which can interconvert through a "quasi"-planar transition state; the observed magnetic equivalence of diastereotopic protons at C-3 can be explained in terms of a conformational mobility of the heptatomic ring in solution at room temperature, so that the methylene resonances are the averaged values

resulting from the rapid conformational equilibrium. Analogously to dihydro-1,4-benzodiazepin-2-one systems,[5] the introduction of a methyl group at C-3 exerts a restricting effect on conformational inversion. In fact, the ^{1}H-nmr spectra in various solvents of compound (**3c**) allow to rule out the presence of two conformers interconverting at room temperature; furthermore, shifts induced by the addition of Eu(fod)$_3$ as lanthanide shift reagent are consistent with the existence of one pseudo-boat conformer in which the C-3 methyl group adopts the more stable quasi-equatorial position. These conclusions are supported by dynamic nmr experiments: at a series of temperatures between -60° and 120°C, apart from some line broadening which occurred at high temperature, no changes consistent with the inversion of the heterocyclic ring were observed.

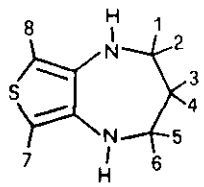
2,3,4,5-Tetrahydro-1*H*-thieno[3,4-*b*][1,4]diazepines (**5**) show ^{1}H-nmr spectra indicative of a fixed conformation at room temperature. All the alicyclic protons are non-equivalent and give rise to a complex resonance pattern which have been analyzed by iterative computer fitting (Table 2).

Table 1. ^{1}H-Nmr spectral data of 1,3-dihydro-2*H*-thieno[3,4-*b*][1,4]diazepin-2-ones **3-4**.

Compd	δ ($CDCl_3$)
3a	3.69 (s, 2H, CH_2), 6.84 (d, J=3.7, 1H, H-6), 7.34 (d, J=3.7, 1H, H-8), 7.42-8.12 (m, 5H, ArH), 8.30 (br s, 1H, NH).
3b	2.34 (s, 3H, CH_3), 3.24 (s, 2H, CH_2), 6.80 (d, J=3.7, 1H, H-6), 7.17 (d, J=3.7, 1H, H-8), 8.77 (br s, 1H, NH).
3c	1.22 (d, J=7.0, 3H, CH_3-3), 2.10 (s, 3H, CH_3-4), 3.09 (q, J=7.0, 1H, CH), 6.70 (d, J=3.7, 1H, H-6), 7.07 (d, J=3.7, 1H, H-8), 9.68 (br s, 1H, NH).
4a	3.38 (s, 3H, N-CH_3), 3.68 (s, 2H, CH_2), 6.94 (d, J=3.8, 1H, H-6), 7.29 (d, J=3.8, 1H, H-8), 7.41-8.14 (m, 5H, ArH).
4b	2.32 (s, 3H, CH_3), 3.23 (s, 2H, CH_2), 3.35 (s, 3H, N-CH_3), 6.88 (d, J=4, 1H, H-6), 7.14 (d, J=4, 1H, H-8).

The heptatomic ring adopts a chair-like conformation, as reported for analogous tetrahydro-1,5-benzodiazepines;[6] furthermore, owing to asymmetrical substitution, the chair conformation involves synaxial interference, thus inhibiting the ring inversion. Analysis of proton coupling constants and chemical shifts allowed to determine that for compounds (**5a**) and (**5b**) the substituent at C-4 is situated in a nearly equatorial position. For compound (**5c**), the higher value of chemical shift for proton at C-4, with respect to the analogous proton in derivative (**5b**), is consistent with its pseudoequatorial stereochemistry. Proton at C-3 resonates as a multiplet and assumes a pseudoequatorial situation as confirmed by the coupling constants values with two diastereotopic methylene protons at C-3 which appear equivalent for accidental isochrony.

Table 2. ^{1}H-Nmr spectral data of 2,3,4,5-tetrahydro-1H-thieno[3,4-b][1,4]-diazepines 5.



Compd	ν_1	ν_2	ν_3	ν_4	ν_5	ν_6	ν_7 - ν_8	NH
5a	2.91 Hax $J_{1,2}$ -12.6 $J_{1,3}$ 8.9 $J_{1,4}$ 3.5 $J_{1,5}$ 2.0	3.32 Heq $J_{2,3}$ 3.5 $J_{2,4}$ 4.8 $J_{2,5}$ 0.2	2.15 Hax $J_{3,4}$ -12.6 $J_{3,5}$ 9.0	2.00 Heq $J_{4,5}$ 3.2	3.90 Hax	7.21-7.54 Pheq	6.24	3.65
5b	2.80 Hax $J_{1,2}$ -12.7 $J_{1,3}$ 9.6 $J_{1,4}$ 3.5 $J_{1,5}$ 1.5	3.22 Heq $J_{2,3}$ 3.5 $J_{2,4}$ 4.5 $J_{2,5}$ 0.2	1.67 Hax $J_{3,4}$ -12.7 $J_{3,5}$ 10.2 $J_{3,6}$ 1.2	1.85 Heq $J_{4,5}$ 2.9	2.92 Hax $J_{5,6}$ 6.6	1.23 CH_3eq	6.18	3.59
5c	2.98 Hax $J_{1,3}$ 4.9	2.98 Heq $J_{2,3}$ 5.5	1.00 CH_3ax $J_{3,4}$ 6.7	1.88 Heq $J_{4,5}$ 2.6	1.14 CH_3ax $J_{5,6}$ 6.7	3.32 Heq	6.11	3.51

Table 3. ^{13}C-Nmr spectral data of compounds **3-5**.

Compd	δ ($CDCl_3$)
3a	39.51 (C-3), 109.29 (C-6), 118.41 (C-8), 127.07 (C-2',6'), 128.39 (C-3',5'), 130.53 (C-4'), 131.14 (C-5a), 137.47 (C-1'), 141.15 (C-8a), 157.90 (C-4), 164.68 (C-2).
3b	27.85 (CH_3-4), 43.73 (C-3), 107.82 (C-6), 115.65 (C-8), 133.93 (C-5a), 140.24 (C-8a), 160.87 (C-4), 163.45 (C-2).
3c	11.31 (CH_3-3), 23.27 (CH_3-4), 44.04 (C-3), 109.34 (C-6), 116.94 (C-8), 130.45 (C-5a), 141.06 (C-8a), 166.32 (C-4), 167.88 (C-2).
4a	34.83 (NCH_3), 39.93 (C-3), 109.95 (C-6), 117.79 (C-8), 127.43 (C-2',6'), 128.47 (C-3',5'), 130.74 (C-4'), 132.40 (C-5a), 137.61 (C-1'), 142.47 (C-8a), 159.57 (C-4), 164.57 (C-2).
4b	27.98 (CH_3-4), 34.76 (NCH_3), 43.98 (C-3), 108.21 (C-6), 115.12 (C-8), 132.13 (C-5a), 142.05 (C-8a), 162.12 (C-4), 163.30 (C-2).
5a	42.11 (C-3), 46.94 (C-2), 63.18 (C-4), 103.66 (C-8), 104.44 (C-6), 126.60 (C-2',6'), 127.61 (C-4'), 128.74 (C-3',5'), 137.79 (C-1'), 141.39 (C-8a), 143.60 (C-5a).
5b	23.16 (CH_3-4), 40.99 (C-3), 46.59 (C-2), 52.95 (C-4), 103.25 (C-8), 103.87 (C-6), 142.53 (C-5a,8a).
5c	11.21 (CH_3-3), 18.83 (CH_3-4), 39.80 (C-3), 52.21 (C-2), 54.79 (C-4), 102.30 (C-8), 102.72 (C-6), 142.25 (C-8a,5a).

In conclusion, an easy synthetic approach to 1,3-dihydro-2H-thieno[3,4-b]-[1,4]diazepin-2-ones and 2,3,4,5-tetrahydro-1H-thieno[3,4-b][1,4]diazepines has been described. The nmr spectral analysis shows for compounds (**3-4**) the existence of a rapid equilibrium between two limiting pseudo-boat conformers. The introduction of a methyl group at C-3 inhibits the conformational inversion which would require the transposition of the methyl group from the pseudoequatorial position, in the more stable diastereomeric conformation, to the pseudoaxial position of the alternative less stable conformation. Conversely, tetrahydrothienodiazepines (**5**) exist as only one

chair-like conformer at room temperature: this conformational preference is interpretable on the basis of the steric requirements of the system.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Elemental analyses (C, H, N, S) were carried out on a C.Erba Model 1106 Elemental Analyzer. Merck silica gel 60 F_{254} plates were used for tlc; preparative silica gel chromatography was performed using a Chromatotron apparatus. Ir specra were determined in nujol on a Perkin Elmer mod. 257 spectrophotometer. ^{1}H- and ^{13}C-nmr spectra were measured with a Bruker WP 80 SY spectrometer in $CDCl_3$ (internal lock) with TMS as the internal standard: chemical shifts are expressed in δ (ppm) and coupling constants (J) in hertz. Lanthanide induced shifts measurements were performed with a $CDCl_3$ solution of $Eu(fod)_3$. For compounds (5), the resonance pattern of the alicyclic moiety was analyzed with the aid of a version of the LAOCN3 program.[7] Mass spectra were recorded on a Hewlett-Packard Model 5995 GC/MS.

1,3-Dihydro-4-phenyl-2H-thieno[3,4-b][1,4]diazepin-2-one (3a)

To a suspension of 3,4-diaminothiophene (1 g, 8.8 mmol) in xylene (100 ml), ethyl benzoylacetate (1.68 g, 8.8 mmol) was added dropwise. The reaction mixture was refluxed for 30 min and then filtered. The filtrate, on cooling, afforded brown needles melting at 231-232°C (ethanol) (1.92 g, yield 90%). Anal. Calcd for $C_{13}H_{10}N_2OS$: C, 64.47; H, 4.13; N, 11.57; S, 13.22. Found: C, 64.73; H, 4.01; N, 11.38; S, 12.96. Ir: 3157, 1677, 1615 cm^{-1}. Ms m/z (%): 242 (M^+, 95), 200 (100), 199 (8), 169 (7), 128 (10), 104 (15), 77 (31).

1,3-Dihydro-4-methyl-2H-thieno[3,4-b][1,4]diazepin-2-one (3b)

Ethyl acetoacetate (1.14 g, 8.8 mmol), slightly alkaline by standing over solid sodium carbonate, and 20 drops of 10% alcoholic potassium hydroxide were added to a suspension of 3,4-diaminothiophene (1 g, 8.8 mmol) in xylene (100 ml). The resulting mixture was refluxed for 90 min with a Dean Stark apparatus and, after cooling, filtered. After removal of the solvent

under reduced pressure, the brown oily residue was recrystallized from ethanol to give yellow crystals, mp 205-206°C (1.15 g, yield 80%). Anal. Calcd for $C_8H_8N_2OS$: C, 53.34; H, 4.45; N, 15.55; S, 17.77. Found: C, 53.74; H, 4.15; N, 15.40; S, 17.45. Ir: 3138, 1662, 1606 cm^{-1}. Ms m/z (%): 180 (M^+, 43), 165 (2), 151 (4), 138 (100), 137 (25), 110 (5), 70 (5), 52 (16).

1,3-Dihydro-3,4-dimethyl-2H-thieno[3,4-b][1,4]diazepin-2-one (3c)

This compound was obtained according to the procedure described for **3b** starting from 3,4-diaminothiophene and ethyl 2-methylacetoacetate. mp 187-190°C (ethanol) (1.02 g, yield 60%). Anal. Calcd for $C_9H_{10}N_2OS$: C, 55.67; H, 5.15; N, 14.43; S, 16.49. Found: C, 55.57; H, 5.38; N, 14.24; S, 16.56. Ir: 3120, 1666, 1608 cm^{-1}. Ms m/z (%): 194 (M^+, 27), 165 (2), 151 (5), 138 (100), 137 (14), 52 (12).

1,3-Dihydro-1-methyl-4-phenyl-2H-thieno[3,4-b][1,4]diazepin-2-one (4a)

To a solution of the compound (**3a**) (242 mg, 1 mmol) in DMF (10 ml) was added dropwise a solution of methyl iodide (710 mg, 5 mmol) and potassium carbonate (170 mg) in DMF (10 ml). The resulting mixture was heated under reflux for 90 min and, after filtration, was subjected to chromatography on a Chromatotron using a silica gel rotor and eluting with ether/light petroleum (1:1). Compound (**4a**), crystallized from ether, melted at 85-87°C (154 mg, yield 60%). Anal. Calcd for $C_{14}H_{12}N_2OS$: C, 65.62; H, 4.69; N, 10.94; S, 12.50. Found: C, 65.25; H, 4.81; N, 10.78; S, 12.68. Ir: 1668, 1610 cm^{-1}. Ms m/z (%): 256 (M^+, 100), 227 (8), 214 (50), 213 (60), 199 (9), 154 (10), 135 (13), 77 (27), 51 (15).

1,3-Dihydro-1,4-dimethyl-2H-thieno[3,4-b][1,4]diazepin-2-one (4b)

A 50% suspension of NaH in mineral oil (167 mg, 3.4 mmol) was added portionwise to a solution of **3b** (500 mg, 2.8 mmol) in DMF (30 ml). After stirring for 15 min at 50°C, MeI (395 mg, 3.4 mmol) was added dropwise to the ice-cooled mixture and the solution was stirred for an additional 30 min at room temperature. The suspension of the mixture in water was extracted with ethyl acetate. The extract was washed with water, dried (Na_2SO_4), and then concentrated under reduced pressure. The residue, after

radial chromatography (Chromatotron) using ether/light petroleum (1:1) as eluant, afforded **4b** (240 mg, 44% yield) as brown oil. Anal. Calcd for $C_9H_{10}N_2OS$: C, 55.67; H, 5.15; N, 14.43; S, 16.50. Found: C, 55.32; H, 5.41; N, 14.05; S, 16.21. Ir: 1674, 1607 cm^{-1}. Ms m/z (%): 194 (M^+, 75), 165 (5), 152 (100), 151 (30), 137 (50), 110 (13), 66 (14).

4-Phenyl-2,3,4,5-tetrahydro-1H-thieno[3,4-b][1,4]diazepine (5a)

A solution of 1,3-dihydro-4-phenyl-2H-thieno[3,4-b][1,4]diazepin-2-one (**3a**) (1.2 g, 5 mmol) in 50 ml of anhydrous tetrahydrofuran was added to a stirred suspension of lithium aluminum hydride (380 mg, 10 mmol) in 10 ml of the same solvent. The mixture was refluxed for 2 h and, after cooling, the solvent was evaporated off. Compound (**5a**) was obtained as brown oil (414 mg, yield 36%) after radial chromatography with ether/light petroleum (1:1) as eluant. Anal. Calcd for $C_{13}H_{14}N_2S$: C, 67.83; H, 6.09; N, 12.17; S, 13.91. Found: C, 67.51; H, 6.28; N, 12.48; S, 13.73. Ir: 3171 cm^{-1}. Ms m/z (%): 230 (M^+, 53), 201 (20), 153 (4), 125 (100), 117 (9), 115 (7), 77 (9).

4-Methyl-2,3,4,5-tetrahydro-1H-thieno[3,4-b][1,4]diazepine (5b)

Compound (**5b**) was obtained according to the same procedure employed for compound (**5a**) with 1,3-dihydro-4-methyl-2H-thieno[3,4-b][1,4]diazepin-2-one (**3b**) as starting material. The obtained compound, after recrystallization from ether, melted at 87-88°C (386 mg, yield 46%). Anal. Calcd for $C_8H_{12}N_2S$: C, 57.14; H, 7.14; N, 16.67; S, 19.05. Found: C, 57.52; H, 7.38; N, 16.30; S, 18.80. Ir: 3125 cm^{-1}. Ms m/z (%): 168 (M^+, 74), 153 (50), 140 (13), 138 (16), 136 (12), 125 (100), 98 (10), 54 (14).

3,4-Dimethyl-2,3,4,5-tetrahydro-1H-thieno[3,4-b][1,4]diazepine (5c)

The above procedure was employed for the synthesis of compound (**5c**) starting from 1,3-dihydro-3,4-dimethyl-2H-thieno[3,4-b][1,4]diazepin-2-one (**3c**). The obtained compound was isolated as a pale yellow oil (580 mg, yield 64%). Anal. Calcd for $C_9H_{14}N_2S$: C, 59.35; H, 7.69; N, 15.38; S, 17.58. Found: C, 59.26; H, 7.71; N, 15.43; S, 17.60. Ir: 3123 cm^{-1}. Ms m/z (%): 182 (M^+, 27), 167 (5), 140 (16), 125 (100), 98 (6), 54 (10).

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