# SIMPLE SYNTHESES OF THIENO[4,3,2-*d,e*]ISOQUINOLINE-3,5-DIONES AND THEIR HOMOLOGUES

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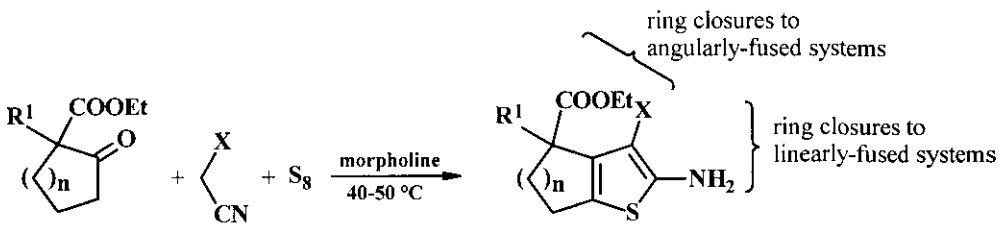
**Abstract** — Simple, convenient syntheses of thieno[4,3,2-*d,e*]isoquinoline-3,5-diones (**7a-d**) and their homologues (**8a-c**) were achieved starting from ethyl 2-amino-3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophene-4-carboxylate (**2**) and its homologue derivatives (**5**) by sulfuric acid treatment.

The biological and chemical importance of heterocyclic β-enamino esters provides strong motivation for investigations of this family of compounds.[1-6] The synthesis of 2-aminothiophene-3-carboxylic acid derivatives by Gewald's reaction is a well-known procedure[7,8] to obtain biologically active and chemically widely applicable compounds.[7-9] We recently reported[10] that the reactions of ethyl 2-oxo-1-cyclopentane-, -cyclohexane- or -cycloheptanecarboxylate or their 1-methyl or 1-ethyl derivatives (**1**) with malononitrile or ethyl cyanoacetate plus elementary sulfur in the presence of morpholine afforded new trifunctional compounds (**2**) and (**3**) (Scheme 1).




**1** **2**: X = CN; **3**: X = COOEt

n = 1– 3; $R^1$ = H, Me, Et

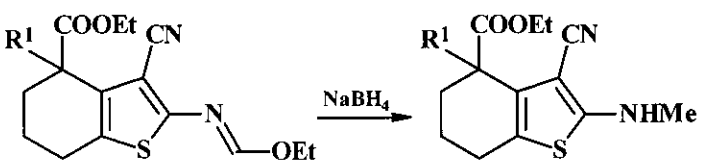
Scheme 1

Compounds (**2**) and (**3**) are suitable starting materials for the synthesis of both linearly- and angularly-fused heterocycles of potential biological and chemical interest. *Via* the ring closures of 3-substituted 2-aminothiophenes, a number of linearly-fused derivatives have been prepared (see *e.g.* ref. 11). In the present paper, we describe the ring closures of **2** in the angular direction. The ester function at position 4

and the nitrile group at position 3 provide a good possibility for the preparation of pyridine-2,6-diones by hydrolytic ring closure.

## RESULTS AND DISCUSSION

Homologues of **2** (n = 1-3; $R^1$ = H, Me, Et) were prepared from ethyl 2-oxo-1-cyclopentane-, -cyclohexane- and -cycloheptanecarboxylate and their 1-methyl and 1-ethyl derivatives under Gewald conditions.[10] Since our aim was to investigate the ring closure of 2-methylamino derivatives in parallel, **5a** and **5b** were prepared by a standard *N*-methylation procedure.[12] The ethoxymethylenamino derivatives (**4a**) and (**4b**) were prepared from **2** by reaction with triethyl orthoformate, and were subsequently reduced to *N*-methyl derivatives (**5a**) and (**5b**) with sodium borohydride.




**4a:** $R^1$ = H
**4b:** $R^1$ = Me

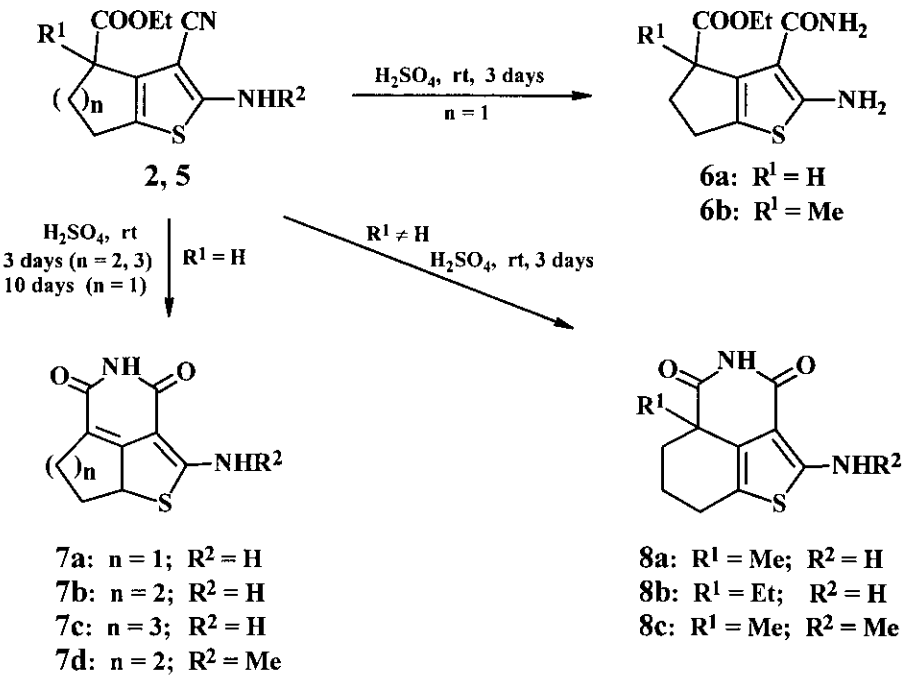
**5a:** $R^1$ = H
**5b:** $R^1$ = Me

Scheme 2

Depending on the ring size and the substituent $R^1$, considerable differences were found in the reactions of **2** and **5** with sulfuric acid (Scheme 3). When the cyclopentane derivatives (**2**) (n = 1, $R^1$ = H, Me) were left to stand in the presence of a large excess of sulfuric acid at room temperature for 3 days, a clear solution was obtained, from which, after extraction with chloroform, the hydrolysed carboxamides (**6a**) and (**6b**) were isolated. In the reactions of the cyclohexane- and cycloheptane-fused homologues of **2** with sulfuric acid under the same reaction conditions, two different ring-closed products were isolated. When the starting materials were the 4-unsubstituted derivatives of **2** ($R^1$ = H) and **5a**, the products were **7b**, **7c** and **7d**. In the reactions of the 4-substituted derivatives (**2**, $R^1$ = Me, Et, and **5b**), the colored products (**8a**), (**8b**) or (**8c**) containing a thiophene ring were obtained (Scheme 3).

On increase of the reaction time to 10 days, the five-membered derivatives of **2**, or the hydrolysed **6a**, could also be transformed to the ring-closed product (**7a**). The formation of different products depending on the size of the fused ring can be rationalized in terms of the different distances between the reacting groups. On reaction with sulfuric acid, the nitriles are hydrolysed to carboxamides, which give the corresponding pyridine-2,6-dione derivatives with the neighboring ester group. In the case of the five-membered derivatives, the distance between the reacting groups is definitely larger in the cyclohexane derivatives, which results in slower formation of the ring-closed products. As the reaction temperature was elevated, the reaction rate increased, and the formation of hydrolytic products was also observed.

Merely a few thieno[4,3,2-*d*,*e*]isoquinolines have been synthesized previously.[13] As far as we are aware, the cyclopentane- and cycloheptane-fused homologues (**7a** and **7d**) are not known.




Scheme 3

The characteristic $^{1}$H- and $^{13}$C-NMR chemical shifts of the compounds prepared are given in the EXPERIMENTAL section. The spectral data are self-explanatory and require only a few additional comments. The $^{1}$H-NMR spectra of **7** and **8** show the lactam proton signal (9.89-10.46 ppm) at very low field, suggesting the existence of an intramolecular hydrogen-bond. The signals of the amino group of **7a-7c** are split because of the hindered rotation caused by the angular substitution on C8a and another possible hydrogen-bond between the amino group and the C3 carbonyl group. The signal of the amino proton in the *N*-methyl-substituted compound (**7d**) remains at low field, *i.e.* the hydrogen-bond exists between the two groups. In consequence of the C5a substitution in **8a-8c**, the amino signals are shifted upfield and joined because of the shielding of the aromatic thiophene ring and the free rotation of the amino group. The high chemical shift of the signal at 4.71-4.94 ppm for **7** indicates the presence of a proton on C8a. The sterically close-lying sulfur atom and the conjugation across the molecule can play a role in this high shift and the transfer of H-5a to become H-8a during the ring closure.

*X-Ray Discussion.* In the solid state, the asymmetric unit of **7b** is formed of two independent molecules and a water molecule, which are hydrogen-bonded to each other. Molecule A (S1...C8b) displays disorder, with C8 and C8a in two positions. C81 and C8a1 have a population parameter 0.69(1) and thus C82 and C8a2 have the value 0.31(1). Molecule B (S11...C18b) does not clearly display similar disorder, but the thermal ellipsoids of C18 and C18a indicate that the molecule is flexible in this region.

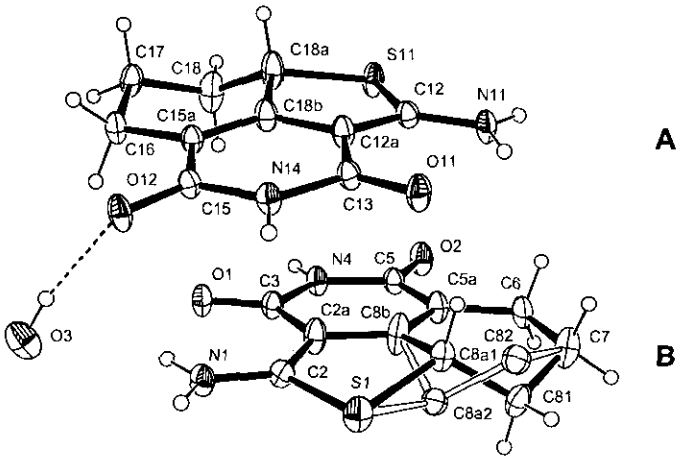



**Fig. 1.** ORTEP perspective view of **7b**, showing the numbering system. Thermal ellipsoids are drawn at a 30% probability level. The hydrogen atoms of the minor component of the disordered part of the molecule are not included.

The interesting point in both molecules of **7b** is the planar arrangement of all heavy atoms except C8a1, C8a2, C81 and C82 in molecule A and C18 and C18a in molecule B. Due to this aromatic ring system, the compound is orange-red.

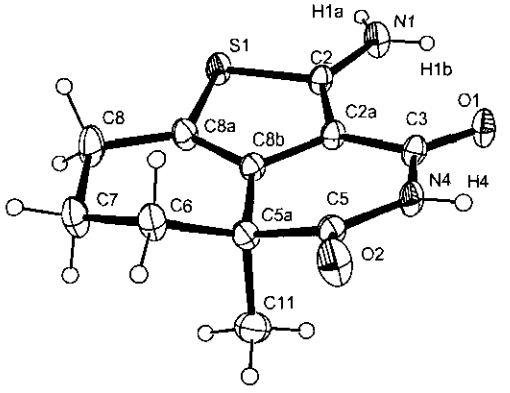



**Fig. 2.** ORTEP perspective view of **8a**, showing the numbering system. Thermal ellipsoids are drawn at a 30% probability level.

The solid-state structure of **8a** is formed of asymmetric units each containing a single molecule, which are hydrogen-bonded to each other. The molecule in **8a** differs from that in **7b** by a methyl group. The proton on C8a (C18a) in **7b** is replaced by a methyl group on C5a in **8a** and the aromaticity of the ring C2a, C3... C5a, C8b is destroyed. Thus, in **7b** C(8a1)-C(8b) = 1.508(5) Å and in **8a** C(18a)-C(18b) = 1.504(4) Å, while C(8a)-C(8b) = 1.343(3) Å. The loss of aromaticity is also indicated by the fact that **8a** is colourless.

## EXPERIMENTAL

The $^{1}$H- and $^{13}$C-NMR spectra were recorded in $CDCl_3$ or, when indicated, in DMSO-$d_6$ solution in 5 mm tubes at room temperature on a Bruker AM-400 FT-spectrometer, with TMS as internal standard. Melting points were determined on a Boetius micro melting point apparatus. 3-Cyano derivatives of **2** were prepared by a procedure described earlier.[10]

*X-Rray diffraction studies.* All data were collected on a Rigaku AFC5S diffractometer with graphite-monochromated $MoK_\alpha$ radiation ($\lambda$ = 0.71069 Å) in the $\omega$-2$\theta$ scan mode at rt. The lattice

parameters were calculated by least-squares refinements of 25 reflections. The weak reflections [$I < 10\sigma(I)$] were rescanned up to two times. For **7b** 3529 [R(int) = 0.013, $2\theta_{max} = 52$, and for **8a** 2090 [R(int) = 0.019, $2\theta_{max} = 52°$] unique reflections were obtained. The data were corrected for Lorentz and polarization effects.

The structures were solved by direct methods (SIR92)[14] and refined by full-matrix least-squares techniques (SHELXL-97)[15] to an R1 value of 0.045 (wR2 = 0.116) for **7b** and R1 = 0.040 (wR2 = 0.093) for **8a**. These final R values are based on the reflections with $I > 2\sigma(I)$. The heavy atoms were refined anisotropically, except for the carbon atoms of the minor component of the disordered part in **7b**. The hydrogen atoms were refined with fixed isotropic temperature factors (1.2 times $B_{eq}$ of the carrying atom), except that the CH hydrogens in **7b** and the methyl hydrogens in **8a** were included in calculated positions. The hydrogen atoms of the minor component of the disordered part in **7b** were not included. Calculations were performed with teXsan for Windows[16] crystallographic software. The figures were drawn with ORTEP-3 for Windows.[17] (The final atomic coordinates and full lists of bond lengths and angles for **7b** and **8a** have been deposited with the Cambridge Crystallographic Data Centre).

**Ethyl 3-cyano-2-ethoxymethyleneamino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-4-carboxylate (4a)**
To triethyl orthoformate (15 g, 0.11 mol), **2** ($R^1$ = H, n = 2) (3.00 g, 11 mmol) was added and the mixture was refluxed for 4 h. The excess of the orthoester was distilled off and the residue was crystallized by treatment with ether. The product (**4a**) was recrystallized from ether. Yield 2.0 g (59%), mp 60-63 °C. Anal. Calcd for $C_{15}H_{18}N_2O_3S$: C, 58.80; H, 5.93; N: 9.15. Found: C, 59.04; H, 6.04; N, 8.98. IR: CN: 2205; C=O: 1710; C=N: 1615. $^1$H-NMR 7.94 (*s*, =C*H*OCH$_2$CH$_3$, 1H, 89%); 7.19 (*s*, =C*H*OCH$_2$CH$_3$, 1H, 11%); 4.40 (*q*, *J* = 7 Hz, =CHOC*H*$_2$CH$_3$, 2H); 4.13-4.27 (*m*, =OC*H*$_2$CH$_3$, 2H); 2.63-2.66 (*m*, C*H*$_2$, 2H); 2.17-2.20 (*m*, C*H*$_2$, 2H); 1.85-1.88 (*m*, C*H*$_2$, 2H); 1.63 (*s*, CC*H*$_3$, 3H); 1.39 (*t*, *J* = 7 Hz, =CHOCH$_2$C*H*$_3$, 3H); 1.23 (*m*, OCH$_2$C*H*$_3$, 3H). $^{13}$C-NMR (DEPT): 175.2 (*C*=O); 157.6 (=*C*HOEt); 158.3; 135.0; 129.7; 101.4 (thiophene); 115.1 (*C*N); 64.2 (=CHO*C*H$_2$CH$_3$); 61.4 (O*C*H$_2$CH$_3$); 44.9 (*C*CH$_3$); 35.6 (*C*H$_2$); 25.1 (*C*H$_2$); 24.5 (*C*H$_3$); 20.1 (*C*H$_2$); 14.1 (OCH$_2$*C*H$_3$); 14.0 (OCH$_2$*C*H$_3$).

**Ethyl 3-cyano-2-ethoxymethyleneamino-4-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-4-carboxylate (4b)**
**4b** was prepared from **2** (n = 2, $R^1$ = Me) by the method used for the preparation of **4a**. Yield 59%, mp 60-63 °C (ether). Anal. Calcd for $C_{16}H_{20}N_2O_3S$: C, 59.97; H, 6.29; N, 8.74. Found: C, 60.42; H, 6.76; N, IR: CN: 2205; C=O: 1710; C=N: 1615. $^1$H-NMR 7.94 (*s*, =C*H*OCH$_2$CH$_3$, 1H, 89%); 7.19 (*s*, =C*H*OCH$_2$CH$_3$, 1H, 11%); 4.40 (*q*, *J* = 7 Hz, =CHOC*H*$_2$CH$_3$, 2H); 4.13-4.27 (*m*, =OC*H*$_2$CH$_3$, 2H); 2.63-2.66 (*m*, C*H*$_2$, 2H); 2.17-2.20 (*m*, C*H*$_2$, 2H); 1.85-1.88 (*m*, C*H*$_2$, 2H); 1.63 (*s*, CC*H*$_3$, 3H); 1.39 (*t*, *J* = 7 Hz, =CHOCH$_2$C*H*$_3$, 3H); 1.23 (*m*, OCH$_2$C*H*$_3$, 3H). $^{13}$C-NMR (DEPT): 175.2 (*C*=O); 157.6 (=*C*HOEt); 158.3; 135.0; 129.7; 101.4 (thiophene); 115.1 (*C*N); 64.2 (=CHO*C*H$_2$CH$_3$); 61.4 (O*C*H$_2$CH$_3$); 44.9 (*C*CH$_3$); 35.6 (*C*H$_2$); 25.1 (*C*H$_2$); 24.5 (*C*H$_3$); 20.1 (*C*H$_2$); 14.1 (OCH$_2$*C*H$_3$); 14.0 (OCH$_2$*C*H$_3$).

**Ethyl 3-cyano-4,5,6,7-tetrahydro-2-methylaminobenzo[*b*]thiophene-4-carboxylate (5a)**
**4a** (3.06 g, 10 mmol) was dissolved in 50 mL of ethanol and sodium borohydride (0.45 g, 12 mmol) was added with stirring and ice cooling in about 10 min. The mixture was stirred at rt for 3 h and evaporated. 50 mL of water was added to the residue and the product was extracted with ethyl acetate (3 x 50 mL). The organic phase was dried ($Na_2SO_4$) and evaporated. Yield 1.55 g (59%), mp 87-88.5 °C. Anal. calcd for $C_{13}H_{16}N_2O_2S$: C, 59.06; H, 6.10; N, 10.60. Found: C, 58.81; H, 6.27; N, 10.44. IR: NH: 3310; CN: 2190; C=O: 1715. $^1$H-NMR: (DMSO-d$_6$): 7.43 (*q*, *J* = 4.7 Hz, N*H*CH$_3$, 1H); 4.12 (*q*, *J* = 7 Hz, OC*H*$_2$CH$_3$, 2H); 3.54 (*t*, *J* = 6.2 Hz, C*H*, 2H); 2.83(*d*, *J* = 4.7 Hz, NHC*H*$_3$, 3H); 2.47-2.59 (*m*, C*H*$_2$, 2H); 1.90-1.97 (*m*, C*H*$_2$, 2H); 1.73-1.77 (*m*, C*H*$_2$, 2H); 1.22 (*t*, *J* = 7.1 Hz, OCH$_2$C*H*$_3$, 3H). $^{13}$C-NMR (DMSO-d$_6$): 174.2

(*C*=O); 166.0; 130.9; 120.8; 82.8 (thiophene); 117.6 (*C*N); 62.0 ($OCH_2CH_3$); 42.0 (*C*H); 34.8 ($NHCH_3$); 27.7 ($CH_2$); 25.1 ($CH_2$); 22.0 ($CH_2$); 15.6 ($OCH_2CH_3$). MS: m/z $M^+$: 264 (38%); 100%: 191.

**Ethyl 3-cyano-4,5,6,7-tetrahydro-2-methylamino-4-methylbenzo[*b*]thiophene-4-carboxylate (5b)**
**5b** was prepared from **4b** by the method used for the preparation of **5a**. Yield 55%, mp 89-90 °C. Anal. Calcd for $C_{14}H_{18}N_2O_2S$: C, 60.40; H, 6.52; N, 10.06. Found: C, 60.57; H, 6.82; N, 10.07. IR: NH: 3250; CN: 2155; C=O: 1680. $^1$H-NMR 5.48 (br s, N*H*$CH_3$, 1H); 4.12-4.25 (*m*, $OCH_2CH_3$, 2H); 2.92 (*s*, $NHCH_3$, 3H); 2.52-2.59 (*m*, $CH_2$, 2H); 2.12-2.18 (*m*, $CH_2$, 2H); 1.80-1.86 (*m*, $CH_2$, 2H); 1.57 (*s*, $CCH_3$, 3H); 1.27 (*t*, *J* = 7 Hz,$OCH_2CH_3$, 3H). $^{13}$C-NMR (DEPT): 175.5 (*C*=O); 165.4; 134.3; 119.5; 82.3 (thiophene); 116.9 (*C*N); 61.1 ($OCH_2CH_3$); 44.8 ($CCH_3$); 35.6 ($CH_2$); 33.5 ($NHCH_3$); 24.51 ($CCH_3$); 24.48 ($CH_2$); 20.3 ($CH_2$); 14.1 ($OCH_2CH_3$). MS: m/z $M^+$: 278 (31%); 100%: 205; 164 (31%).

**Ethyl 2-amino-3-carbamoyl-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-4-carboxylate (6a)**
**2** (n = 1, $R^1$ = H) was dissolved in 10 mL of conc. sulfuric acid and left to stand at rt for 3 days. The mixture was then poured onto 80 g ice and the product was extracted with chloroform (3 x 50 mL). The organic phase was dried ($Na_2SO_4$) and evaporated. Yield 1.12 g (56%), mp 129.5-131 °C (ethanol). Anal. Calcd for $C_{11}H_{14}N_2O_3S$: C, 51.95; H, 5.55; N, 11.02. Found: C, 52.24; H, 5.78;, N, 10.96. IR: NH: 3480, 3375, 3265, 3150; ester C=O: 1715; amide C=O: 1655. $^1$H-NMR 6.35 (s, N$H_2$, CON$H_2$, 4H); 4.09-4.23 (*m*, $OCH_2CH_3$, 2H); 3.93 (*m*, C*H*, 1H); 2.98-3.06 (*m*, $CH_2$, 1H); 2.65-2.73 (*m*, $CH_2$ 2H); 2.48-2.58 (*m*, $CH_2$, 1H); 1.25 (*t*, *J* = 7 Hz, $OCH_2CH_3$, 3H). $^{13}$C-NMR 174.4 (ester *C*=O); 168.3 (amide *C*=O); 166.0; 136.5; 125.4; 104.1 (thiophene); 61.5 ($OCH_2CH_3$); 48.4 (*C*H); 33.4 ($CH_2$); 28.2 ($CH_2$); 14.1 ($OCH_2CH_3$).

**Ethyl 2-amino-3-carbamoyl-5,6-dihydro-4-methyl-4*H*-cyclopenta[*b*]thiophene-4-carboxylate (6b)**
**6b** was prepared from **2** (n = 1, $R^1$ = Me) by the method used for the preparation of **6a**. Yield 56%, mp 162-164 °C (solvent). Anal. Calcd for $C_{12}H_{16}N_2O_3S$: C, 53.71; H, 6.01; N, 10.44. Found: C, 53.91; H, 5.88; N, 10.38. IR: NH: 3480, 3375, 3265, 3150; ester C=O: 1675; amide C=O: 1650. $^1$H-NMR 6.42 (*s*, CON$H_2$, 2H); 5.20 (*s*, N$H_2$, 2H); 4.14-4.22 (*m*, $OCH_2CH_3$, 2H); 2.83-2.96 (*m*, $CH_2$, 2H); 2.67-2.74 (*m*, $CH_2$, 1H); 2.18-2.25 (*m*, $CH_2$, 1H); 1.59 (*s*, $CH_3$, 3H); 1.26 (*t*, *J* = 7 Hz, $OCH_2CH_3$, 3H). $^{13}$C-NMR (DEPT): 178.2 (ester *C*=O); 168.3 (amide *C*=O); 165.1; 141.1; 125.4; 105.3 (thiophene); 61.8 ($OCH_2CH_3$); 54.1 ($CCH_3$); 43.3 ($CH_2$); 27.6 ($CH_2$); 24.2 ($CH_3$); 14.2 ($OCH_2CH_3$). MS: m/z $M^+$: 268 (39%); 100%: 178.

**2-Amino-6,7-dimethylene-3,4-dihydro-7*H*-thieno[4,3-*c*]pyridine-3,5-dione (7a)**
**7a** was prepared from **2** (n = 1, $R^1$ = Me) by the method used for the preparation of **6a.** The reaction time was 12 days. Yield 64%, mp 283-286 °C, with decomposition (dimethylformamide—ethanol). Anal. Calcd for $C_9H_8N_2O_2S$: C, 51.91; H, 3.87; N, 13.46. Found: C, 51.66; H, 4.03; N, 13.39. $^1$H- NMR (DMSO-$d_6$); 9.89 (*s*, CON*H*CO, 1H); 9.39 (*s*, N$H_2$, 1H); 8.51 (*s*, N$H_2$, 1H); 4.90-4.95 (*m*, C*H*, 1H); 2.62-2.76 (*m*, $CH_2$, 2H); 1.99-2.09 (*m*, $CH_2$, 2H). $^{13}$C-NMR (DMSO-$d_6$): 177.2 (*C*=O); 172.9 (*C*=O); 163.3; 161.5; 111.8; 95.2 (thiophene); 53.3 (*C*H); 37.8 ($CH_2$); 30.9 ($CH_2$). MS: m/z $M^+$: 208 (100%); 175 (82%).

**2-Amino-3,4,6,7,8,8a-hexahydro-5*H*-thieno[4,3,2-*d,e*]isoquinoline-3,5-dione (7b)**
**7b** was prepared from **2** (n = 2, $R^1$ = Me) by the method used for the preparation of **6a.** The reaction time was 3 days. Yield 79%, mp 312-317 °C (dimethylformamide—ethanol). Anal. Calcd for $C_{10}H_{10}N_2O_2S$: C, 54.03; H, 4.54; N, 12.61. Found: C, 54.10; H, 4.44; N, 12.56. $^1$H-NMR (DMSO-$d_6$): 10.34 (*s*, CON*H*CO, 1H); 9.35 (*s*, N$H_2$, 1H); 8.66 (*s*, N$H_2$, 1H); 4.72-4.75 (*m*, C*H*, 1H); 2.28-2.33 (*m*, $CH_2$, 2H); 2.15-2.24 (m, $CH_2$, 1H); 2.03-2.08 (*m*, $CH_2$, 1H); 1.72-1.78 (*m*, $CH_2$, 1H); 1.51-1.61 (m, $CH_2$, 1H). $^{13}$C-NMR (DMSO-

$d_6$, JMODXH); 174.9 (*C*=O); 166.8 (*C*=O); 162.6; 168.8; 110.7; 99.4 (thiophene); 50.6 (*C*H); 28.5 ($CH_2$); 23.4 ($CH_2$); 21.3 ($CH_2$). MS: m/z $M^+$: 222 (100%); 194 (89%).

**2-Amino-6,7-tetramethylene-3,4-dihydro-7*H*-thieno[4,3-*c*]pyridine-3,5-dione (7c)**
**7c** was prepared from **2** (n = 3, $R^1$ = H) by the method used for the preparation of **6a.** The reaction time was 3 days. Yield 74%, mp 310 °C (decomp) (dimethylformamide—ethanol). Anal. Calcd for $C_{11}H_{12}N_2O_2S$: C, 55.91; H, 5.12; N, 11.86. Found: C, 56.08; H, 5.31; N, 11.78. $^1$H-NMR (DMSO-$d_6$): 10.46 (*s*, CON*H*CO, 1H); 9.40 (*s*, N$H_2$, 1H); 8.93 (*s*, N$H_2$, 1H); 4.90 (*d*, *J* = 10.6 Hz, C*H*, 1H); 3.03-3.08 (*m*, C$H_2$, 1H); 2.15 (*d*, *J* = 4.3 Hz, C$H_2$, 1H); 2.01 (*t*, *J* = 10.6 Hz, C$H_2$, 2H); 1.82 (*t*, *J* = 9.8 Hz, C$H_2$, 1H); 1.72 (*t*, *J* = 11.2 Hz, C$H_2$, 1H); 1.58 (*q*, *J* = 10.6 Hz, C$H_2$, 1H); 1.08-1.22 (*m*, C$H_2$, 1H). $^{13}$C-NMR (DMSO-$d_6$, JMODXH): 175.7 (*C*=O); 166.8 (*C*=O); 162.5; 161.6; 116.0; 99.7 (thiophene); 54.6 (*C*H); 36.1 ($CH_2$); 32.9 ($CH_2$); 29.7 ($CH_2$) 26.0 ($CH_2$). MS: m/z $M^+$: 268 (39%); 100%: 178.

**2-Methylamino-3,4,6,7,8,8a-hexahydro-5*H*-thieno[4,3,2-*d,e*]isoquinoline-3,5-dione (7d)**
**7d** was prepared from **5a** by the method used for the preparation of **6a.** The reaction time was 3 days. Yield 62%, mp 335-343 °C (sublimation) (dimethylformamide—ethanol). Anal. Calcd for $C_{11}H_{12}N_2O_2S$: C, 55.91; H, 5.12; N, 11.86. Found: C, 55.78; H, 4.93; N, 11.72. $^1$H-NMR (DMSO-$d_6$): 10.33 (*s*, CON*H*CO, 1H); 9.23 (*s*, N*H*$CH_3$, 1H); 4.75 (*d*, *J* = 11.9 Hz, C*H*, 1H); 3.05 (*s*, NHC$H_3$, 3H); 2.32-2.36 (*m*, C$H_2$, 1H); 2.23-2.29 (*m*, C$H_2$, 1H); 2.16-2.22 (*m*, C$H_2$, 1H); 2.01-2.07 (*m*, C$H_2$, 1H); 1.71-1.76 (*m*, C$H_2$, 1H); 1.52-1.60 (*m*, C$H_2$, 1H). MS: m/z $M^+$: 268 (39%); 100%: 178.

**2-Amino-5a-methyl-3,4,5a,6,7,8a-hexahydro-5*H*-thieno[4,3,2-*d,e*]isoquinoline-3,5-dione (8a)**
**8a** was prepared from **2** ($R^1$ = Me, n = 2) by the method used for the preparation of **6a**. The reaction time was 3 days. Yield 88%, mp 270-271 °C (ethanol). Anal. Calcd for $C_{11}H_{12}N_2O_2S$: C, 55.91; H, 5.12; N, 11.86. Found: C, 55.87; H, 5.33; N, 11.78. $^1$H-NMR (DMSO-$d_6$): 10.24 (*s*, CON*H*CO, 1H); 7.31 (*s*, N$H_2$, 2H); 2.37-2.45 (*m*, C$H_2$, 1H); 1.95-2.01 (*m*, C$H_2$, 1H); 1.90 (*t*, *J* = 6.2 Hz, C$H_2$, 1H); 1.87 (*m*, C$H_2$, 1H); 1.54-1.61 (*m*, C$H_2$, 2H); 1.36 (*s*, C$H_3$, 3H). $^{13}$C-NMR (DMSO-$d_6$, DEPT): 178.1 (*C*=O); 162.2 (*C*=O); 161.9; 133.8; 115.1; 99.9 (thiophene); 41.6 (*C*$CH_3$); 28.5 ($CH_2$); 28.2 (*C*$H_3$); 22.0 ($CH_2$); 18.5 ($CH_2$). MS: m/z $M^+$: 236 (100%); 208 (50%).

**2-Amino-5a-ethyl-3,4,5a,6,7,8a-hexahydro-5*H*-thieno[4,3,2-*d,e*]isoquinoline-3,5-dione (8b)**
**8b** was prepared from **2** ($R^1$ = Et, n = 2) by the method used for the preparation of **6a.** The reaction time was 3 days. Yield 63%, mp 212-218 °C (ethanol). Anal. Calcd for $C_{12}H_{14}N_2O_2S$ C, 55.67; H, 5.52; N, 11.81. Found: C, 55.87; H, 5.73; N, 11.68. $^1$H-NMR (DMSO-$d_6$): 10.20 (*s*, CON*H*CO, 1H); 7.25 (*s*, N$H_2$, 2H); 2.38-2.47 (*m*, C$H_2$, 1H); 1.99-2.04 (*m*, C$H_2$, 1H); 1.90-1.95 (*m*, C$H_2$, 2H); 1.65-1.76 (*m*, C$H_2$, 2H); 1.43-1.50 (*m*, C$H_2$, 2H); 0.79 (*t*, *J* = 7 Hz, $CH_2CH_3$, 3H). $^{13}$C-NMR (DMSO-$d_6$, DEPT): 176.6 (*C*=O); 162.2 (*C*=O); 161.8; 133.7; 115.2; 100.6 (thiophene); 45.4 (*C*H); 33.5 ($CH_2$); 25.3 ($CH_2$); 21.9 ($CH_2$); 18.1 ($CH_2$); 8.8 ($CH_2CH_3$). MS: m/z $M^+$: 268 (39%); 100%: 178.

**5a-Methyl-2-methylamino-3,4,5a,6,7,8a-hexahydro-5*H*-thieno[4,3,2-*d,e*]isoquinoline-3,5-dione (8c)**
**8c** was prepared from **5b** by the method used for the preparation of **6a.** The reaction time was 3 days. Yield 87%, mp 285-287 °C (sublimation) (dimethylformamide—ethanol). Anal. Calcd for $C_{12}H_{14}N_2O_2S$: C, 57.58; H, 5.64; N, 11.19. Found: C, 57.75; H, 5.78; N, 11.20. $^1$H-NMR (DMSO-$d_6$): 10.23 (s, CON*H*CO, 1H); 7.52 (*s*, N*H*$CH_3$, 1H); 2.87 (*d*, *J* = 4.8 Hz, NHC$H_3$, 3H); 2.58-2.63 (*m*, C$H_2$, 2H); 1.94-2.01 (*m*, C$H_2$, 1H); 1.91 (*t*, *J* = 8.4 Hz, C$H_2$, 1H); 1.88 (*t*, *J* = 7.9 Hz, C$H_2$, 1H); 1.54-1.62 (*m*, C$H_2$, 1H); 1.37 (*s*, C$H_3$, 3H). $^{13}$C-NMR (DMSO-$d_6$, DEPT): 176.7 (*C*=O); 163.0 (*C*=O); 160.5; 134.0; 114.0; 97.4 (thiophene); 40.3 (*C*$CH_3$); 32.2 (NH*C*$H_3$); 27.4 ($CH_2$); 26.9 ($CH_2$); 21.0 ($CH_2$); 17.3 (*C*$H_3$). MS: m/z $M^+$: 250 (100%).

**Crystal data on 7b.** $C_{10}H_{11}N_2O_{2.5}S$, $M_r$ = 231.27, triclinic, space group P-1 (No 2), lattice parameters: a = 9.2218(10), b = 14.6154(17), c = 8.0569(10) Å, α = 103.94(1), β = 107.78(1), γ = 87.63(1)°, Z = 4, V =

1002.9(2) Å$^3$, $D_c$ = 1.532 g/cm$^3$, m($MoK_a$) = 0.309 mm$^{-1}$, F(000) = 484, T = 294 K; yellow plates, crystal dimensions 0.12 x 0.28 x 0.38 mm.

**Crystal data on 8a.** $C_{11}H_{12}N_2O_2S$, $M_r$ = 236.29, triclinic, space group P-1 (No 2), lattice parameters: a = 7.6927(8), b = 10.448(2), c = 7.0587(8) Å, α = 95.993(14), ß = 107.959(9)°, γ = 80.214(12), Z = 2, V = 531.00(14) Å$^3$. $D_c$ = 1.478 g/cm$^3$, m($MoK_a$) = 0.290 mm$^{-1}$, F(000) = 248, T = 294 K; colourless prisms, crystal dimensions 0.10 x 0.12 x 0.20 mm.

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## REFERENCES

1. J. Fröhlich, F. Sauter, A. Z. M. S. Chowdhury, and C. Hametner, *Sci. Pharm.*, 1997, **65**, 83.
2. J. Santagati, S. Longmore, T. Guccione, E. Langer, M. Tonnel, M. Modica, M. Santagati, L. Monsu-Scolaro, and F. Rosso, *Eur. J. Med. Chem.*, 1997, **32**, 973.; M. Santagati, M. Modica, A. Santagati, F. Russo, and S. Spampinato, *Pharmazie*, 1966, **51**, 7; A. Santagati, M. Santagi, and M. Modica, *Heterocycles*, 1993, **36**, 1315.
3. U. Urleb, B. Stanovnik, and M. Tisler, *J. Heterocycl. Chem.*, 1990, **27**, 407.
4. S. Guccione, M. Modica, J. Longmore, D. Shaw, G. U. Barretta, A. Santagi, M. Santagi, and F. Russo, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 59.
5. M. Gutschow and U. Neumann, *J. Med. Chem.*,1998, **41**, 1729.
6. F. Fülöp, H. Wamhoff, and P. Sohár, *Synthesis,* **1995**, 863.
7. K. Gewald, E. Schinke, and H. Böttcher, *Chem. Ber.*, 1966, **99**, 94.
8. K. Gewald, *Lect. Heterocycl. Chem.*, 1982, **6**, 121; K. Gewald, *Chimia*, 1980, **34**, 101.
9. H. Wamhoff, *Adv. Heterocycl. Chem.*, 1985, **38**, 299; H. Wamhoff, *Adv. Heterocycl. Chem.*, 1992, **55**, 129.
10. B. Naumann, R. Böhm, F. Fülöp, and G. Bernáth, *Pharmazie*, 1996, **51**, 1.
11. A. Miyashita, K. Fujimoto, T. Okada, and T. Higashino, *Heterocycles*, 1996, **42**, 691.
12. R. A. Crochet and C. D. Blanton, *Synthesis*, **1974**, 55.
13. R. Neidlein, and M. H. Salzl, *Chemik.-Ztg.* 1977, **101**, 357.
14. A. Altomare, M. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla,G. Polidori, and M. Camalli, *J. Appl. Cryst.*, 1994, **27**, 435.
15. G. M. Sheldrick, SHELXL-97, University of Göttingen, Germany, *1997.*
16. Molecular Structure Corporation, teXsan for Windows. Single Crystal Structure Analysis Software. Version 1.01. MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA.1997.
17. L. J. Farrugia, *J. Appl. Cryst.*, 1997, **30**, 565.

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