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THIAZOLIDINONE-ANNULATED PYRROLOBENZODIAZEPINES. SYNTHESES AND PROPERTIES OF A NEW RING SYSTEM

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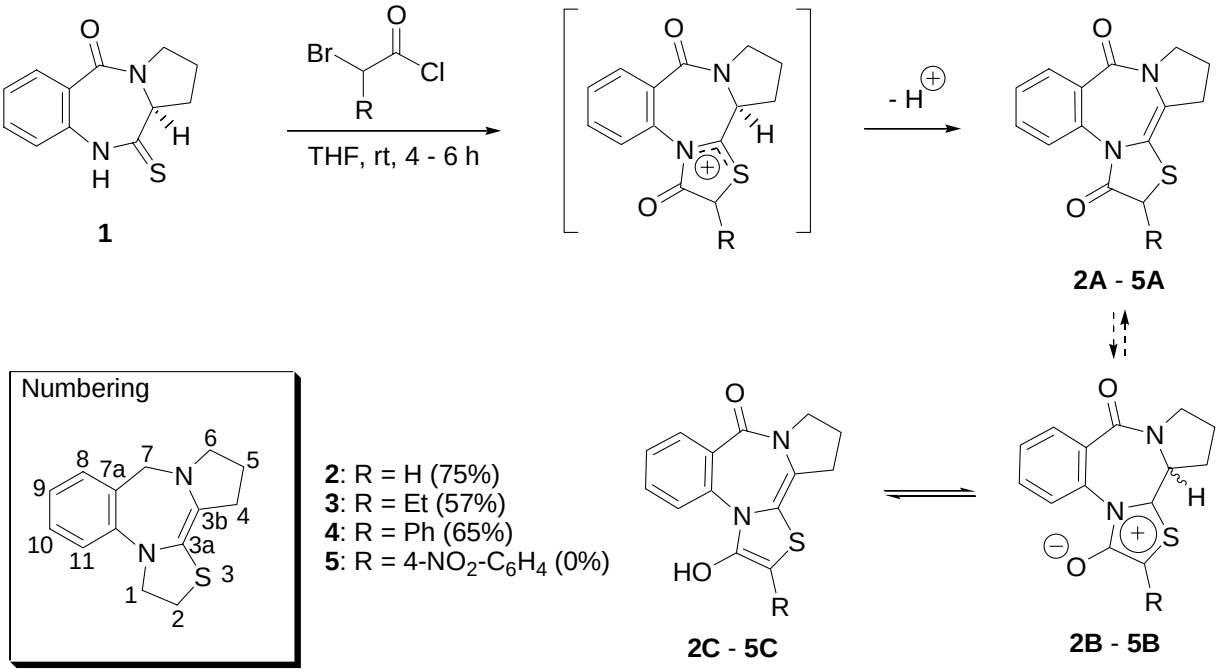
Abstract – New derivatives of pyrrolo[2,1-*c*][1,4]benzodiazepines were synthesized starting from a thiolactam and 2-bromoacetyl chlorides. Spectroscopic investigations and an X-Ray analysis are presented.

INTRODUCTION

Naturally occurring as well as synthetically prepared pyrrolo[2,1-*c*][1,4]benzodiazepines are biologically and pharmacologically highly interesting compounds as some of them recognize and bind to DNA and display cancerostatic and anti-infective properties.[1] The (*S*)-configuration of the α-C-atom of the pyrrolidine ring causes an isohelicity of this ring system with the minor groove of DNA,[2] so that tautomerism involving this position plays a crucial role for the biological activities of this class of compounds. We were interested in new derivatives of pyrrolobenzodiazepines and report here the syntheses and properties of thiazolidinone-annulated pyrrolobenzodiazepines which - to the best of our knowledge - are the first representatives of a new ring system. We focussed our attention on the potential tautomerism of the thiazole moiety, which is known to be complex[3] and strongly influenced by the nature and location of the substituents, solvents and architecture of the molecule.[4] Thus, three forms, thiazolidin-4-one, thiazol-4-ols as well as mesoionic partial structures had to be taken into consideration. The latter mentioned aromatic thioisomünchnone[5] caused an intact (*S*)-configurated pyrrolidine moiety of this biologically highly important ring system. The aromaticity indices, I_A indicate that the mesoionic forms have comparable aromaticities to the parent hydroxy thiazoles.[6]

RESULTS AND DISCUSSION

2-Bromoacetyl chloride and its 2-ethyl- and 2-phenyl-substituted derivatives converted the monothiolactam (**1**)[7] at room temperature in THF into the 5,6-dihydro-4*H*-3-thia-6a,11b-diazabenzo[*g*]cyclopenta[*e*]-azulene-1,7-diones (**2**) – (**4**). This reaction typically proceeds *via* intermediary iminium salts which can sometimes be trapped and used for heterocyclic synthesis.[5] The treatment of the thiolactam (**1**) with 2-(4-nitrophenyl)-2-bromoacetyl chloride, however, resulted in the formation of a complex mixture of compounds from which no nitro derivative (**5**) could be isolated (Scheme 1). The formations of the thiazolidinones (**2A**) – (**4A**) in $CDCl_3$ and DMSO-d_6, respectively, were unambiguously proved by the existence of only three CH_2-groups (4-*H*, 5-*H*, 6-*H*) of the pyrrolidine ring, and one additional sp^3-hybridized carbon atom which couples with the ethyl (**3A**) and phenyl (**4A**) group, respectively. In the 2-unsubstituted compound (**2A**), this CH_2-group forms a singlet at δ = 3.83 ppm in $CDCl_3$. In contrast to thiazol-4(5*H*)-ones,[4,8] neither the tautomeric thioisomünchnones (**2B**) – (**4B**), nor hydroxy isomers (**2C**) – (**4C**) were detectable by NMR spectroscopy, regardless of the solvent used. The C(2)-*H* protons are acidic and can be exchanged by deuterium on addition of D_2O to the solutions, respectively.



Scheme 1

As remarkable differences in the tautomerisations of thiazols and its reduced derivatives exist in the solid state and in solution,[3] we performed an X-Ray analysis.[9] Suitable single crystals of the 2-phenyl derivative (**4**) were obtained by slow evaporation of a concentrated solution in 2-propanol. The compound crystallized

monoclinic. The molecular structure and the crystallographic numbering are shown in Figure 1. The 6:7:5 pyrrolobenzodiazepine ring system adopts a twisted conformation. The C6-C7 bond distance (crystallographic numbering) is 132.21(17) pm which corresponds to a $C(sp^2)=C(sp^2)$ double bond. This C=C-bond is twisted due to the helicity of the 6:7:5 ring system, so that the dihedral angles C5-C6-C7-N11 and N2-C6-C7-S8 are –173.40(12)° and 172.06(9)°, respectively. The thiazolidine ring adopts an envelope conformation. The sulfur atom is located above a plane defined by C9-C10-N11-C7, the dihedral angle of which is 1.44(15)°. The dihedral angles N11-C7-S8-C9 and S8-C9-C10-N11 were determined to be 31.81(9)° and 21.43(12°), respectively. The phenyl ring is twisted by approximately 51° around the C9-C91-bond. Thus, (**4**) displays a different behaviour than thiazol-4-ones, the 4-hydroxy isomers of which predominate in the solid state.[3,12] One hydrogen bonding is found between the CH-acidic C9-H and the C1=O carbonyl group of a neighbouring molecule. The elemental cell is presented in Figure 2.

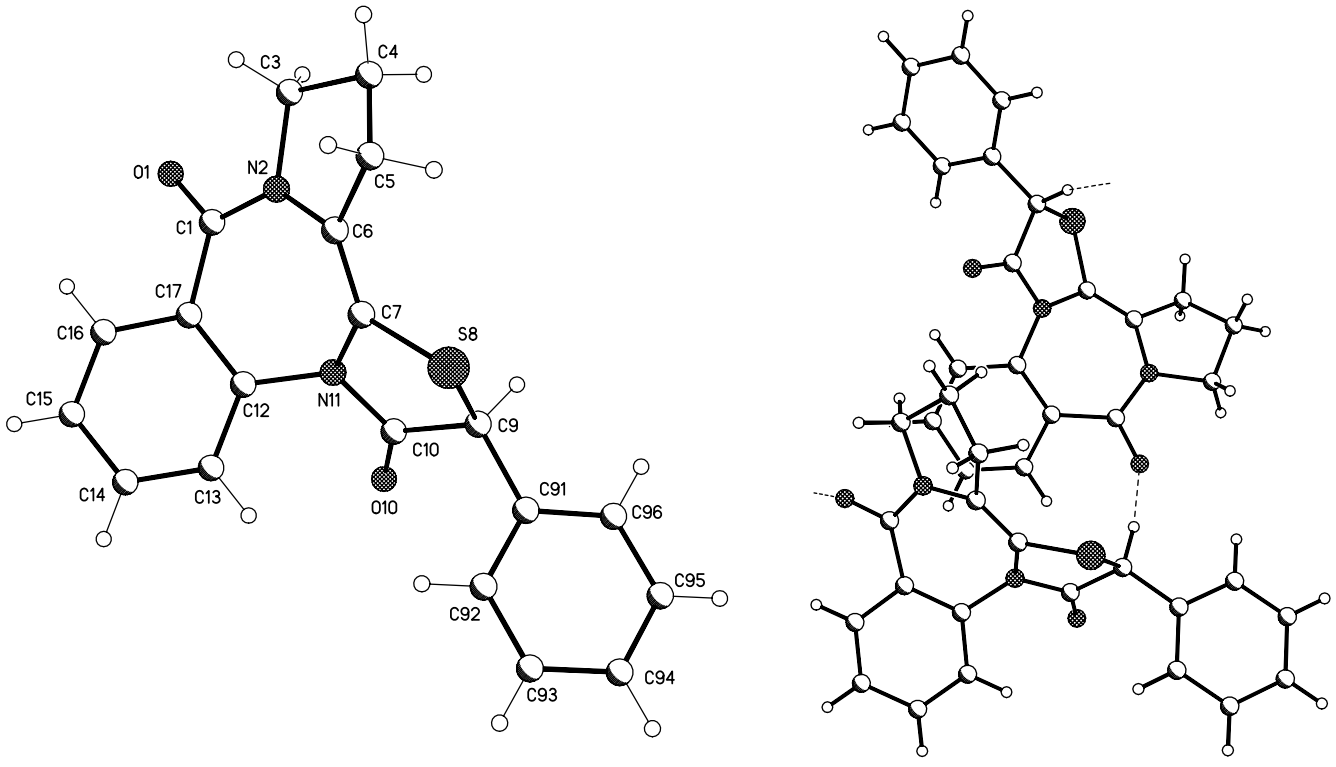


Figure 1. Molecular drawing of **4A** (left); hydrogen bonding between two molecules (right).

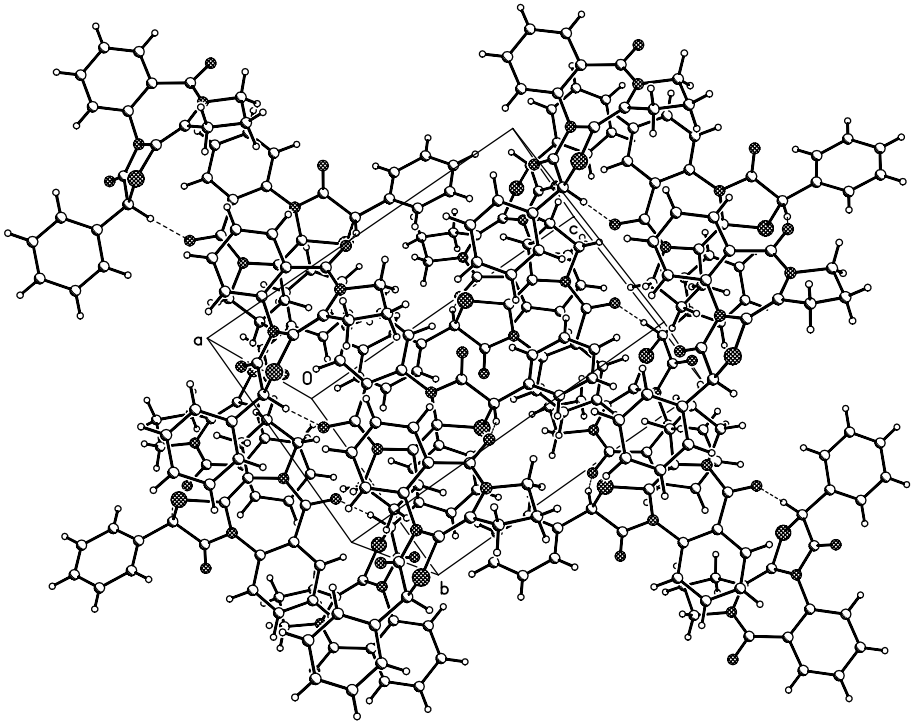


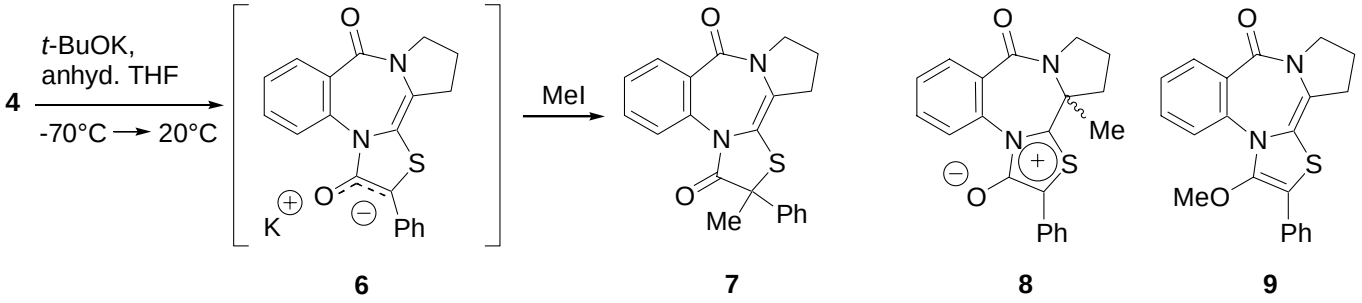
Figure 2. Elemental cell of **4A**.

Table 1. Atom Nos. / Selected bond lengths [pm], bond angles [°], and torsion angles [°] of (**4A**) (crystallographic numbering)

C1-N2	136.07(17)	O1-C1-N2	119.10(12)	C17-C1-N2-C6	0.6(2)
N2-C6	141.88(16)	C1-N2-C6	131.21(11)	C17-C1-N2-C3	-172.40(11)
C7-N11	142.54(15)	C7-C6-N2	125.22(12)	C1-N2-C3-C4	179.60(11)
N11-C12	143.74(15)	C6-C7-N11	124.81(12)	N2-C3-C4-C5	-24.96(14)
C7-S8	176.26(13)	N11-C7-S8	109.37(9)	C1-N2-C6-C7	29.9(2)
S8-C9	183.66(14)	C7-S8-C9	88.49(6)	N2-C6-C7-N11	-0.7(2)
C9-C10	153.15(17)	C10-C9-S8	105.02(8)	C5-C6-C7-N11	-173.40(12)
C10-N11	138.16(16)	C96-C91-C9	119.64(11)	N2-C6-C7-S8	172.06(9)
C10-O10	121.02(15)	O10-C10-N11	124.87(12)	C10-N11-C12-C13	33.23(17)
C9-C91	150.25(18)	C10-N11-C7	113.99(10)	C10-C9-C91-C92	-50.98(16)

It is known that aromatizations of thiazolidines can be accomplished by addition to exocyclic double bonds.[4] We therefore studied the behaviour of the new ring system towards acids, bases, and alkylating agents. The non-nucleophilic base 1,8-dimethylaminonaphthalene (proton sponge®) induced an immediate decomposition of **4** in THF to a complex mixture, whereas 4-dimethylaminopyridine (DMAP) and triethylamine, respectively, were not able to deprotonate this compound. On addition of $NaOD/D_2O$ to a DMSO-d_6-solution of **4**, the resoncance frequencies shift considerably upfield due to the formation of the

enolate (**6**). Thus, the proton in the *para*-position of the phenyl ring, which is overlapped in DMSO-d_6 by other signals at approximately δ = 7.39 ppm, shifts to δ = 6.53 ppm on addition of the base. The signal of C(2)-H at δ = 5.59 ppm disappears in parallel with a shifting of the resonance frequency of C(2) at δ = 52.6 ppm to δ = 72.6 ppm in the ^{13}C NMR spectra on addition of the base (for numbering, *cf*. Scheme 1). Potassium *tert*-butoxide proved to be the most suited base to deprotonate the phenyl derivative (**4**) at C(2) in THF at –70 °C to the corresponding enolate on a preparative scale. The enolate could be trapped by methyl iodide to form the 2-methyl-2-phenyl-substituted pyrrolobenzodiazepine (**7**) in 82% yield. HMBC-NMR spectroscopic experiments proved the couplings of the methyl protons with C(2), C(1)=O, and the phenyl group. Neither mesoion (**8**), which - in contrast to (**7**) - contained two aromatic rings, nor the *O*-methylated enol (**9**) were detected. Accordingly, no changes were moreover observable in the NMR spectra on addition of DCl, so that a protonation of the C(3a)=C(3b)-double bond could be excluded from consideration under these conditions.



6 **7** **8** **9**

Scheme 2.

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EXPERIMENTAL

General methods: The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX-400 and DPX-200 in DMSO-d_6 and $CDCl_3$ (400 and 200 MHz for ^{1}H NMR), respectively. The chemical shifts are reported in ppm relative to internal tetramethylsilane (δ = 0.00 ppm). FT-IR spectra were obtained on a Bruker Vektor 22 in the range of 400 to 4000 cm^{-1} (2.5 % pellets in KBr). The GC-MS spectra were recorded on a GC Hewlett-Packard 5980, Serie II in combination with a MS Hewlett-Packard 5989 B, and on a Varian GC3900 with SAT2100T mass spectrometer. Solvents and reagents were obtained from commercial sources and used as received without further purification.

General procedure for the preparation of the benzocyclopentaazulene-1,7-diones (2 - 4). To a solution containing 0.232 g (1.0 mmol) of the monothiolactam (**1**) in 30 mL of anhydrous THF was added 1.2 mmol of the corresponding freshly distilled acetyl chloride. The mixture was stirred for 4 - 6 hours at rt under nitrogen and then quenched by addition of 20 mL of saturated $NaHCO_3$ solution. After extraction with 2 × 20 mL of chloroform, the combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude residue was subjected to flash silica gel column chromatography using ethyl acetate / petroleum ether (1:4) as eluent to give yellow solids.

5,6-Dihydro-4*H*-3-thia-6a,11b-diazabenzo[*g*]cyclopenta[*e*]azulene-1,7-dione (2).
α-Bromoacetyl chloride (0.19 g, 1.2 mmol) was used, yield 0.20 g (75%), mp 165 - 167 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ = 8.00 (dd, *J* = 7.95/1.59 Hz, 1H, 8-H), 7.51 - 7.55 (m, 1H, 9-H), 7.44 (dd, *J* = 8.19/0.98 Hz, 1H, 11-H), 7.28 - 7.32 (m, 1H, 10-H), 3.90 - 3.94 (m, 2H, 6-H), 3.83 (s, 2H, 2-H), 2.67 (t, *J* = 7.95 Hz, 2H, 4-H), 1.98 – 2.05 (m, 2H, 5-H); ^{13}C NMR ($CDCl_3$): δ = 20.8 (CH_2), 31.1 (CH_2), 35.8 (CH_2), 50.1 (CH_2), 115.5, 124.3, 124.9, 127.2, 128.5, 133.3, 133.6, 138.9, 165.4 (CO), 172.7 (CO); IR (KBr) 3074, 2983, 2934, 1721, 1700, 1625, 1528, 1489, 1451, 1393, 1325, 1242, 1209 cm^{-1}; MS *m/z* (rel. int.) 272 (M^+, 100), 230 (9), 201 (11), 76 (12), 50 (13); Anal. Calcd for $C_{14}H_{12}N_2O_2S$: C, 61.75; H, 4.44; N, 10.29. Found: C, 61.44; H, 4.43; N, 10.24.

2-Ethyl-5,6-dihydro-4*H*-3-thia-6a,11b-diazabenzo[*g*]cyclopenta[*e*]azulene-1,7-dione (3).
α-Bromoethylacetyl chloride (0.22 g, 1.2 mmol) was used, yield 0.17 g (57%), mp 131 - 132 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ = 7.99 (dd, *J* = 7.89/1.58 Hz, 1H, 8-H), 7.47 - 7.56 (m, 1H, 9-H), 7.40 (dd, *J* = 8.21/1.14 Hz, 1H, 11-H), 7.24 - 7.32 (m, 1H, 10-H), 4.03 (dd, *J* = 8.72/4.29 Hz, 1H, 2-H), 3.88 - 3.95 (m, 2H, 6-H), 2.64 - 2.72 (m, 2H, 4-H), 2.11 - 2.32 (m, 1H, 5-H), 1.86 - 2.08 (m, 2H), 1.10 (t, *J* = 7.33 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ = 11.6 (CH_3), 20.5 (CH_2), 25.8 (CH_2), 30.8 (CH_2), 49.7 (CH_2), 52.1 (CH), 114.3, 123.9, 124.3, 126.6, 128.0, 132.8, 133.0, 138.6, 165.0 (CO), 174.4 (CO); IR (KBr) 2966, 2874, 1724, 1703, 1628, 1451, 1393, 1319, 1199 cm^{-1}; MS *m/z* (rel. Int.) 300 (M^+, 100), 195 (10); Anal. Calcd for $C_{16}H_{16}N_2O_2S$: C, 63.98; H, 5.37; N, 9.33. Found: C, 63.79; H, 5.32; N, 9.35.

2-Phenyl-5,6-dihydro-4*H*-3-thia-6a,11b-diazabenzo[*g*]cyclopenta[*e*]azulene-1,7-dione (4).
α-Bromophenylacetyl chloride (0.28 g, 1.2 mmol) was used, yield 0.26 g (65%), mp 193-195 °C (2-propanol); ^{1}H NMR ($CDCl_3$): δ = 8.02 (dd, *J* = 7.95/1.47 Hz, 1H, 8-H), 7.51 - 7.56 (m, 1H, 9-H), 7.36 - 7.48 (m, 6H), 7.29 - 7.33 (m, 1H), 5.15 (s, 1H, 2-H), 3.90 - 4.00 (m, 2H, 6-H), 2.65 - 2.77 (m, 2H, 4-H), 1.96 - 2.07 (m, 2H, 5-H); ^{13}C NMR ($CDCl_3$): δ = 21.0 (CH_2), 31.3 (CH_2), 50.2 (CH_2), 54.3 (CH), 114.3, 124.4, 125.6, 127.2, 128.5, 128.8, 129.1, 129.5, 133.3, 133.6, 136.6, 139.1, 165.5 (CO), 173.3 (CO); IR

(KBr) 3057, 2896, 1719, 1699, 1625, 1574, 1489, 1451, 1394, 1328, 1242, 1201 cm^{-1}; MS *m/z* (rel. Int.) 348 (M^+, 100), 320 (6), 199 (7), 90 (8); Anal. Calcd for $C_{20}H_{16}N_2O_2S$: C, 68.94; H, 4.63; N, 8.04. Found: C, 69.09; H, 4.72; N, 7.87.

2-Methyl-2-phenyl-5,6-dihydro-4*H*-3-thia-6a,11b-diazabenzo[*g*]cyclopenta[*e*]azulene-1,7-dione (7). To a solution of 0.174 g (0.50 mmol) of phenylthiazolidinone (**4**) in anhydrous THF (10 mL) was added 0.068 g (0.6 mmol) of potassium *tert*-butoxide portionwise at –70 °C under nitrogen. The resulting mixture was stirred for additional 10 min at the same temperature. Methyl iodide (0.3 mL) was then added at –70 ° C, and the mixture was warmed to rt over a period of 10 min. Stirring was then continued for additional 30 min at rt. Then, the reaction was cautiously quenched with 10 mL of saturated NH_4Cl solution and extracted with 2 × 20 mL of chloroform. The combined organic layers were dried over Na_2SO_4, and concentrated in *vacuo*. Purification by flash chromatography using ethyl acetate / petroleum ether (1:3) as eluent gave product (**7**) as a pale-yellow solid (0.148 g, 82%), mp 230 - 232 °C (acetonitrile); ^1H NMR ($CDCl_3$): δ = 7.97 - 8.02 (m, 1H, 8-H), 7.50 - 7.60 (m, 4H), 7.28 - 7.42 (m, 4H), 3.83 - 3.90 (m, 2H, 6-H), 2.52 - 2.78 (m, 2H, 4-H), 2.03 (s, 3H, CH_3), 1.74 - 1.99 (m, 2H, 5-H); ^{13}C NMR ($CDCl_3$): δ = 20.6 (CH_2), 26.4 (CH_3), 31.1 (CH_2), 49.7 (CH_2), 60.4, 123.9, 126.1, 126.7, 127.9, 128.0, 128.6, 132.7, 133.1, 138.7, 140.5, 165.2 (CO), 175.4 (CO); IR (KBr) 3070, 2965, 1715, 1690, 1630, 1489, 1454, 1389, 1328, 1197 cm^{-1}; MS *m/z* (rel. Int.) 363 (M^++1, 100), 333 (25), 301 (18), 226 (37), 195 (29), 159 (14), 104 (20), 79 (8); Anal. Calcd for $C_{21}H_{18}N_2O_2S$: C, 69.59; H, 5.01; N, 7.73. Found: C, 69.44; H, 4.98; N, 7.79.

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9. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-249826. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk). Some crystal data of **4**: $C_{20}H_{16}N_2O_2S$; M = 348.41; space group $P2_1/n$ (no. 14); dimensions 0.50 x 0.30 x 0.15 mm, a = 13.4178(3), b = 9.1816(2), c = 13.4360(4) Å; β = 100.102(1)°; V = 1629.61(7) $Å^3$, D_c = 1.420 Mg m^{-3}, Z = 4, μ(MoKα) = 0.215 mm^{-1}; T = 123(2) K; F(000) = 728, 15182 reflections were collected in a Nonius KappaCD diffractometer ($2\Theta_{max.}$ = 55°, $-17 \le h \le 15$, $-9 \le k \le 9$, $-16 \le l \le 16$), 3629 symmetry independent reflections (R_{int} = 0.0347) were used for the structure solution (direct methods)[10] and refinement (full-matrix least-squares on F^2,[11] 226 parameters), non-hydrogen atoms were refined anisotropically, H atoms localized by difference electron density, and were defined using a riding model; wR2 (all data) = 0.0890 [R1 = 0.0329 for 2900 $I>2\sigma(I)$].
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