SYNTHESIS AND STRUCTURE OF NORBORNANE/ENE-FUSED THIOURACILS AND THIAZINO[3,2-*a*]PYRIMIDINONES

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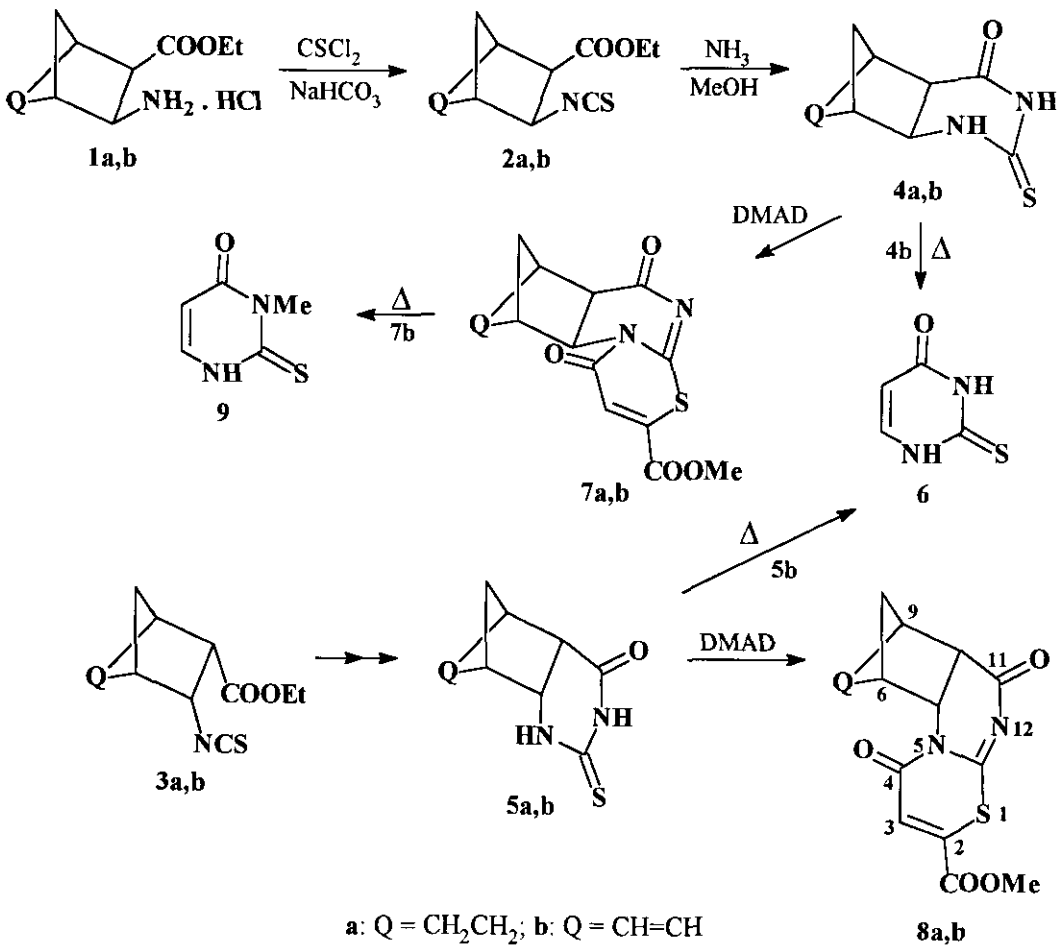
Abstract – Ethyl *diexo*-3-aminobicyclo[2.2.1]heptane- and -hept-5-ene-2-carboxylates (**1a,b**) and the *diendo* derivatives were transformed with thiophosgene to the isothiocyanates (**2a,b** and **3a,b**) and then cyclized to the norbornane/ene-condensed 2-thioxopyrimidin-4-ones (**4a,b** and **5a,b**). On heating, the norbornene compounds (**4b** and **5b**) furnished thiouracil (**6**) *via* cyclopentadiene elimination. With dimethyl acetylenedicarboxylate, the thioxopyrimidinones (**4a,b**) and (**5a,b**) form angularly-fused [1,3]thiazino[3,2-*a*]pyrimidinones (**7a,b** and **8a,b**). On heating, **7b** decomposes to give 3-methyl-2,3-dihydro-2-thioxo-4(1*H*)-pyrimidinone (**9**) in a retro Diels-Alder process by methyl migration and splitting-off of cyclopentadiene. The structures were elucidated by IR and NMR spectroscopies, with DNOE, DEPT and 2D-HSC techniques.

Isothiocyanates are widely used for the preparation of thioureas[1] and heterocyclic derivatives.[2] Earlier, we prepared thioureas *via* the reactions of aminocycloalkanecarboxylic esters with potassium thiocyanate, but this method was not suitable for the preparation of bicycloalkane derivatives.[3] We describe now the preparation of isothiocyanatocarboxylates (**2** and **3**) containing a norbornane/ene moiety, and a new route for the synthesis of *diexo*- and *diendo*-condensed 2-thioxopyrimidin-4-ones (**4** and **5**) from them. The norbornene derivatives (**4b**, **5b** and **7b**) are suitable starting compounds of retro Diels-Alder (RDA) reactions in which heterocycles are prepared in a convenient and simple synthetic way. Similarly to the cycloadditions of the corresponding cyclohexane, cyclohexene- and cyclopentene-fused analogues,[3] the thiouracils (**4**) and (**5**) reacted also with dimethyl acetylenedicarboxylate (DMAD). These reactions proved to differ from those of aromatic analogues, which gave thiazoloquinazolinones as the main products.[4]

Synthesis

The reactions of the ethyl *diexo*-3-aminobicyclo[2.2.1]heptane- and -hept-5-ene-2-carboxylate HCl salts[5] (**1a,b**) and the *diendo* isomers[6] with thiophosgene in $CHCl_3$–water in the presence of $NaHCO_3$ yielded *diexo* and *diendo* ethyl 3-isothiocyanobicyclo[2.2.1]heptane- and -hept-5-ene-2-carboxylates (**2a,b** and **3a,b**) in good yields (75-80%) (Scheme). The crude oily products were purified by column chromatog-

raphy and distillation. On cyclization with NH_3 in methanol, these compounds were converted in norbornane and norbornene *diexo*- and *diendo*-condensed 2-thioxotetrahydropyrimidin-4-ones (**4a,b** and **5a,b**). Earlier, the cyclopentane- and cyclohexane-condensed analogues and 3-substituted derivatives were prepared from the corresponding aminocycloalkanecarboxylates with KSCN and subsequent cyclization by boiling of the isothiocyanates in xylene,[3,7] but this method was unsuitable for the preparation of thioxopyrimidinones fused with a bicycloalkane ring.



a: Q = CH_2CH_2; **b**: Q = CH=CH

Scheme

On heating to the melting point, **4b** and **5b** undergo RDA decomposition: cyclopentadiene splits off and 2,3-dihydro-2-thioxo-4(1*H*)-pyrimidinone (**6**) is formed in good yields (over 80%). In comparison with other methods,[8] this is an easy and convenient way to prepare thiouracil. In the present case, the norborneneamino esters are transformed in two steps to the condensed thioxopyrimidinone heterocycles, and the double bond is then recovered by removing the cyclopentadiene. As the starting norborneneamino acids are prepared from cyclopentadiene, the condensed heterocycle is actually built up on this carrier, which can readily be removed on heating. A similar RDA method was earlier applied in the preparation of 3-substituted thiouracils,[7] uracils[9] and a fused tricyclic heterocycle.[10]

On reaction with DMAD in methanolic solution, **4a,b** and **5a,b** yield angularly-fused tetracyclic derivatives: methano[1,3]thiazino[3,2-*a*]quinazolinones (**7a,b** and **8a,b**) in 90% yields. These compounds are similar to the earlier-prepared cycloalkane-condensed thiazino[3,2-*a*]pyrimidinones.[3] As concerns the mechanism, acylation on N^1 following addition to the sulfur and partial saturation of the triple bond is postulated. This reaction is unlike that of the aromatic 2,3-dihydro-2-thioxoquinazolin-4(1*H*)-one, which furnished three different thiazolo[3,2-*a*]quinazoline-1,2-dicarboxylates and two by-products.[4] In the formation of these, the reaction fully saturates the triple bond to yield two products, but, in one compound only partial saturation takes place. The most striking difference is that the aromatic starting compound reacts only by addition without acylation, which requires a conjugated electronic system, which is not applicable to the present compounds.

When heated to the melting point, compounds (**4b**, **5b** and **7b**) undergo decomposition and split off cyclopentadiene in an RDA process. In the reaction of **7b**, however, the substituted thiazine ring also decomposes to yield the known 3-methyl-2-thioxopyrimidin-4-one (**9**).[11] *N*-Methylation can take place either directly by thermal splitting-off of the methyl group and N^3-substitution or *via* an intramolecular process. In the latter, the thiazine ring opens and the ester group methylates the sulfur and then the N^3. The methylation and formation of **9** is an interesting reaction observed here for the first time together with the RDA process.

Structure, spectroscopy

The IR, ^{1}H- and ^{13}C-NMR spectral data (Tables 1 and 2) prove the constitutions of the new compounds.

Table 1. IR frequencies[a] and ^{1}H-NMR data[b] of compounds[c] (**4a,b**, **5a,b**, **6**, **7a,b**, **8a,b** and **9**)

Compd	νNH, νC–O[d]	νC=O (amide)	Amide[e] νC=O	CH_2 (pos. 9)[f] 2x*d* (2x1H)	CH_2, =CH (pos. 6, 7)[g] 2-3m's (4H)	H-4a[h] *d* (1H)	H-5 *s* (1H)	H-8 *s* (1H)	H-8a[h] *d* (1H)
4a	3174 3136	1711	1596	1.15 1.19[i]	1.11[k] 1.30 1.45[l]		2.47	2.29	3.45
4b	3206	1660	1582	1.20 1.35	6.30 6.08[k]	2.40	3.09	2.96	3.32
5a	3223	1666	1575	1.32 1.44[i]	1.10 1.30 1.36[l]	2.83	2.52	2.36	3.71
5b	3205	1663	1596	1.30 1.34[i]	6.14 6.9[k]	3.07	3.24	3.12	3.98
6	3300-2750	1688[n]	1567	–	–	5.78	–	–	7.37
7a	1218 1166[m]	1689[n]	1732	1.29 1.34[i]	~1.43 1.68[l]	2.76	2.84	2.74	4.10
7b	1218 1157	1689[n]	1729	1.31 1.52	6.43 6.24[k]	2.64	3.46	3.42	3.95
8a	1222 1158[m]	1700[n]	1726	1.51 1.57[i]	1.04 1.27 1.46[l]	3.00	2.83	3.03	4.33
8b	1223 1181[m]	1700[n]	1728	1.46[i] 1.60	6.26 5.96[k]	3.22	3.57	3.79	4.55
9	3300-3250	1653	1537	–	–	5.58	–	–	6.86

Further signals, ^{1}H-NMR, NCH_3 (**9**), *s* (3H); 3.31; OCH_3, *s* (3H): 3.86 (**7a**), 3.88 (**7b**), 3.84 (**8a,b**); CH (thiazinone), *s* (1H): 7.05 (**7a**), 7.09 (**7b**), 7.02 (**8a,b**); NH (Pos.1), br (1H): 9.46 (**4a**), 9.65 (**4b**), 9.42 (**5a**), ~9.50 (**5b**); NH (Pos.3), br (1H): 10.78 (**4a**), 10.95 (**4b**), 10.84 (**5a**), ~10.60 (**5b**); NH, br (2H): ~12.30 (**6**). [a]In cm^{-1} (KBr discs); [b]Chemical shifts in ppm (δ_{TMS} = 0 ppm), coupling constants in Hz, in DMSO-d_6 (**4a,b**, **5a,b** and **6**) or $CDCl_3$ solution (**7a,b**, **8a,b** and **9**), at 500.13 MHz; [c]Assignments were proved by DNOE and 2D-HSC (HMQC) measurements (except for **6** and **9**); [d]Broad (**4a,b** and **5a,b**) or diffuse νNH bands (**6**, **9**) or ν_sC–O and ν_sC–O ester bands (**7a,b**, and **8a,b**); [e]Amide (βNH-type) band of the NHCSNHCO moiety (**4a,b**, **5a,b**, **6**, and **9**) or the ester νC=O band (**7a,b**, and **8a,b**); [f]*AB*-type spectrum of bridging CH_2 (Pos.9), *J*: 10.5 (**4a** and **8a**), 9.4 (**4b** and **8b**), 10.0 (**5a** and **7b**), 8.9 (**5b**), and 11.1 (**7a**); *dd*, *J*(4a,8a): 12.0 (**5a** and **8a**), 9.8 (**5b** and **8b**), 7.5 (**9**); *J*(4a,5): 4.0 (**5a,b** and **8a,b**); *J* (8,8a): 3.6 (**5a** and **8b**), 3.2 (**5b**), 2.8 (**8a**); [g]*J* (H,NH): 5.9 (**9**); [h]*J* (H,NH): 1.3; [i]*endo* Position as proved by DNOE data; [k]Pos. 7; [l]Intensity 2H, the *exo* position for **4a** and **7a** was proved by the DNOE results; [m]Split pair of bands with the second maximum at 1153 (**7a**), 1122 (**8a**) and 1169 (**8b**); [n]The bands of the amide group are coalesced for **8a,b**, or separated, with the second maximum at 1709 (**6**) and 1697 (**7a,b**).

Comments are necessary only as regards the structures of tetracycles (**7**) and (**8**) and the annelation of the norbornane/ene moieties in **4** and **5**. The latter can be answered on the basis of the vicinal couplings H-4a,5 and H-8,8a (the two pairs of norbornane annelational hydrogens). Due to the dihedral angle of the corresponding hydrogen pairs being ~30° and 90° for *diendo* and *diexo* annelation, respectively, the values of these couplings are 3-4 or <1.5 Hz, and hence observable splits are expected only for the *diendo* compounds. In accord, signals of the H-4a and H-8a (norbornane–pyrimidine annelational hydrogens) are *d*'s in **2a,b** (*diexo*) and *dd*'s in **3a,b** (*diendo*): the coupling between them also causes splitting [*J*(H-4a,H-8a): 9.5 ± 1.6 Hz].[12] These multiplicities and, consequently the configurations in **2** and **3** remain unaltered in derivatives (**4, 5, 7** and **8**). DNOE measurements provide further proof of the *diendo* annelation in **5a,b** and **8a,b** through the interactions between the sterically closely situated H-9 (*endo*) and H-4a,8a (*exo*). The absence of such interactions in **4a,b** and **7a,b** indirectly supports the *diexo* annelation in these compounds. DNOE data were also utilized to clarify dubious assignments.

The presumed structures of **7a,b** and **8a,b** with fused dihidrothiazinone rings are obvious: a) the spectral data confirm the presence of the ester (e.g. the characteristic IR bands of ester groups and the ^{1}H- and ^{13}C-NMR lines of the methoxy group), a further amide (amide IR bands and the ^{13}C-NMR line of the carbonyl carbon) and olefinic =CH groups (singlets of this latter group in ^{1}H- and ^{13}C-NMR). b) HMBC (COLOC) measurements proved the N(1)-acylation – the ^3J(C, H) coupling of H-8a with the amide carbonyl in the thiazinone ring. c) A thiazolone ring-containing structure with a carboxymethyl-methylidene moiety on this ring can be excluded on the basis of the amide carbonyl IR frequency and the ^{13}C-NMR shifts.

Table 2. ^{13}C-NMR chemical shifts[a] of compounds[b] (**4a,b**, **5a,b**, **6**, **7a,b**, **8a,b** and **9**)

Compd	C–2	C=O (4)	C–4a	C–5	C–6	C–7	C–8	C–8a	CH_2(9)
4a	176.9	168.0	45.59	43.4	29.3	25.3	45.63	59.3	34.4
4b	176.9	168.0	41.1	48.9	139.7	135.7	51.7	56.0	44.5
5a	177.5	168.7	40.7	42.0	25.1	21.3	43.6	56.0	36.8
5b	177.0	168.3	41.5	48.6	137.3	136.0	49.6	55.9	46.7
6	177.0	161.8	106.1	142.9	–	–	–	–	–
7a	170.2	175.8	46.1	43.6	28.9	26.2	44.2	59.7	35.0
7b	169.8	176.1	40.7	49.3	140.0	135.3	49.8	56.0	44.6
8a	169.0	176.3	41.01[c]	42.0	25.0	21.0	41.04[c]	55.7	36.0
8b	169.1	175.7	41.0	48.9	139.0	133.1	46.9	55.6	46.4
9	177.6	161.3	104.4	139.8	–	–	–	–	–

Further signals: OCH_3: 53.4 (**7a,b**), 52.9 (**8a,b**); NCH_3 (**9**): 33.5; Thiazinone ring (**7a,b** and **8a,b**), CH: 120.6 and 120.0, SC(quat., sp^2): 138.6 and 138.0, C=O(ester): 166.2 and 165.7, C=O(amide): 164.5 and 163.9. [a]In ppm (δ_{TMS} = 0 ppm) at 125.76 MHz in DMSO-d_6 (**4a,b**, **5a,b** and **6**), or $CDCl_3$ (**7a,b**, **8a,b** and **9**); [b]The assignments were supported by DNOE, DEPT and 2D-HSC measurements (except for **6** and **9**) and for **5b**, **7b**, **8a,b** and **9** also by 2D-HMBC (≡ COLOC) experiments; [c]Interchangeable assignments.

EXPERIMENTAL

IR spectra were run in KBr discs on a Bruker IFS-55 FT-spectrometer controlled by Opus 2.0 software. The ^{1}H- and ^{13}C-NMR spectra were recorded in DMSO-d_6 or $CDCl_3$ solution in 5 mm tubes at room temperature, on a Bruker DRX-500 spectrometer at 500.13 (^{1}H) and 125.76 (^{13}C) MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. For DNOE measurements,[13,14] the standard Bruker microprogram DNOEMULT.AU to generate NOE[15] was used, with a selective pre-

irradiation time. DEPT spectra[16] were run in a standard manner,[17] using only the $\theta = 135°$ pulse to separate the CH/CH_3 and CH_2 lines phased "up" and "down", respectively. The 2D-HSC spectra[18] were obtained by using the standard Bruker pulse program HXCO.AU.

Preparation of isothiocyanates (2a,b) and (3a,b)

To a stirred mixture of chloroform (20 mL), water (10 mL), thiophosgene (1.15 g, 0.01 mol) and $NaHCO_3$ (2.52 g, 0.03 mol), a solution of the ethyl 3-aminobicyclo[2.2.1]heptane- or -hept-5-ene-1-carboxylate HCl salt[5,6] (2.2 g **1a** or **1b**, 0.01 mol) in water (20 mL) was added dropwise during a period of 40 min. After stirring for 3 h at 40 °C, the chloroform layer was separated, dried ($MgSO_4$) and transferred to a silica gel column (0.060-0.200 mm) and the eluate was evaporated. Physical data on compounds (**2a,b**) and (**3a,b**) are listed in Table 3.

Table 3. Physical and analytical data on compounds (**2-9**)

Compd	Mp. °C	Yield %	Formula	Analysis Calcd % C	H	N	Found % C	H	N
2a	120-123[a]	78	$C_{11}H_{15}NO_2S$	58.64	6.71	6.22	58.41	6.63	6.34
2b	102-105[b]	85	$C_{11}H_{13}NO_2S$	59.17	5.87	6.27	59.01	6.02	6.39
3a	125-128[c]	80	$C_{11}H_{15}NO_2S$	58.64	6.71	6.22	58.67	6.53	6.30
3b	128-130[d]	80	$C_{11}H_{13}NO_2S$	59.17	5.87	6.27	58.97	5.66	6.21
4a	249-251[e]	80	$C_9H_{12}N_2OS$	55.08	6.13	14.27	54.89	5.97	14.30
4b	321-323[e]	87	$C_9H_{10}N_2OS$	55.65	5.19	14.42	55.50	5.26	14.52
5a	223-225[e]	85	$C_9H_{12}N_2OS$	55.08	6.16	14.27	55.09	6.19	14.04
5b	325-327[f]	90	$C_9H_{10}N_2OS$	55.65	5.19	14.42	55.41	5.35	14.46
6	329-331[g,h]	70	$C_4H_4N_2OS$						
7a	240-242[e]	88	$C_{14}H_{14}N_2O_4S$	54.89	4.61	9.14	55.05	4.72	9.27
7b	234-235[e]	92	$C_{14}H_{12}N_2O_4S$	55.26	3.97	9.20	55.37	4.11	9.26
8a	191-193[e]	91	$C_{14}H_{14}N_2O_4S$	54.89	4.61	9.14	54.71	4.69	9.29
8b	193-195[e]	95	$C_{14}H_{12}N_2O_4S$	55.26	3.97	9.20	55.38	4.17	8.98
9	289-291[i]	35	$C_5H_6N_2OS$						

[a-e]Bp. 800 Pa; [a]n_D^{20}: 1.5307; [b]$n_D^{22.5}$: 1.5387; [c]n_D^{25}: 1.5348; [d]n_D^{22}: 1.5423; [e]From EtOH; [f]From dioxane; [g]From AcOH; [h]lit.,[8] mp. 304 ° (decomp); [i]lit.,[11] mp. 292-294 °C.

5,8-Methano-2-thioxo-1,4,4a,5,6,7,8,8a-octahydro- (4a and 5a) and 1,4,4a,5,8,8a-hexahydroquinazolin-4-ones (4b and 5b)

A mixture of isotiocyanates (**2a,b**) and (**3a,b**) (0.9 g, 4 mmol) with an excess of ammonia in MeOH (25%, 5 mL) was left to stand overnight at ambient temperature. After evaporation to dryness, the residue was crystallized.

2,3-Dihydro-2-thioxopyrimidin-4(1*H*)-one (6)

4b or **5b** (1.9 g, 0.01 mol) was heated in a metallic bath (Wood alloy) at 320 °C for 10 min. The product was transferred to an Al_2O_3 column (Aluminium oxide, basic, Acros, 50-200 μ) and eluted with hot EtOH; the residue was crystallized.

6,9-Methano-2-methoxycarbonyl-5a,6,7,8,9,9a-hexahydro- (7a and 8a) and 5a,6,9,9a-tetrahydro-[1,3]thiazino[3,2-*a*]quinazoline-4,11-diones (7b and 8b)

DMAD (2.13 g, 15 mmol) in MeOH (20 mL) was added dropwise with stirring to a solution of thioxoquinazolinones (**4a** and **5a**: 1.96 g, **4b** and **5b**: 1.94 g, 0.01 mol) in MeOH (20 mL). After refluxing of the mixture for 15 min, the solid product was separated by suction and crystallized.

3-Methyl-2-thioxo-4(1*H*)-pyrimidinone (9)

7b (3.0 g, 0.01 mol) was heated in an oil bath at 235 °C for 20 min. The product was transferred to an Al_2O_3 column (Aluminium oxide, acidic, Acros, 50-200 μ) and eluted with EtOAc. After evaporation, the residue was crystallized.

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