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# Synthesis of Pyrimido[2,1-b]thiazin-6-one by Retro Diels-Alder Reaction[1]

**Ferenc Fülöp, Imre Huber, Ágnes Szabó, Gábor Bernáth***

Institute of Pharmaceutical Chemistry, Albert Szent-Györgyi Medical University,
H-6701 Szeged, POB 121, Hungary,

**Pál Sohár**

Spectroscopic Department, EGIS Pharmaceuticals, H-1475 Budapest, POB 100, Hungary

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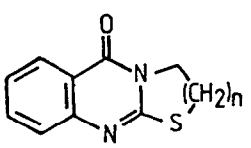
*Key Words* thiazolo[2,3-*b*]quinazolin-5-one, thiazino[2,3-*b*]quinazolin-6-one, retrodiene decomposition, thiazolo[3,2-*a*]pyrimidin-5-one, pyrimido[2,1-*b*]thiazin-6-one

*Abstract* *The first mild retrodiene processes resulting in bicyclic heterocycles are described From norbornene diexo- and diendo-β-amino acids with chloroalkyl isothiocyanates, compounds 3-6 were prepared, which, by retrodiene decomposition, furnished 7 and 8*

The substituted 2,3-dihydrothiazolo[3,2-*a*]pyrimidin-5-ones and the corresponding 3,4-dihydropyrimido [2,1-*b*]thiazin-6-ones are of current interest,[2-5] due to their pharmacological activity, and a number of different methods have been developed for their syntheses The limitations of these syntheses are illustrated by the fact that the parent pyrimido[2,1-*b*]thiazin-6-one (**8**) is unknown, while only one method[6] is at present available for the synthesis of thiazolo[3,2-*a*]pyrimidin-5-one (**7**), but this yields the 7-oxo isomer in parallel A new strategy for the synthesis of compounds **7** and **8** is described in this paper.

## SYNTHESIS

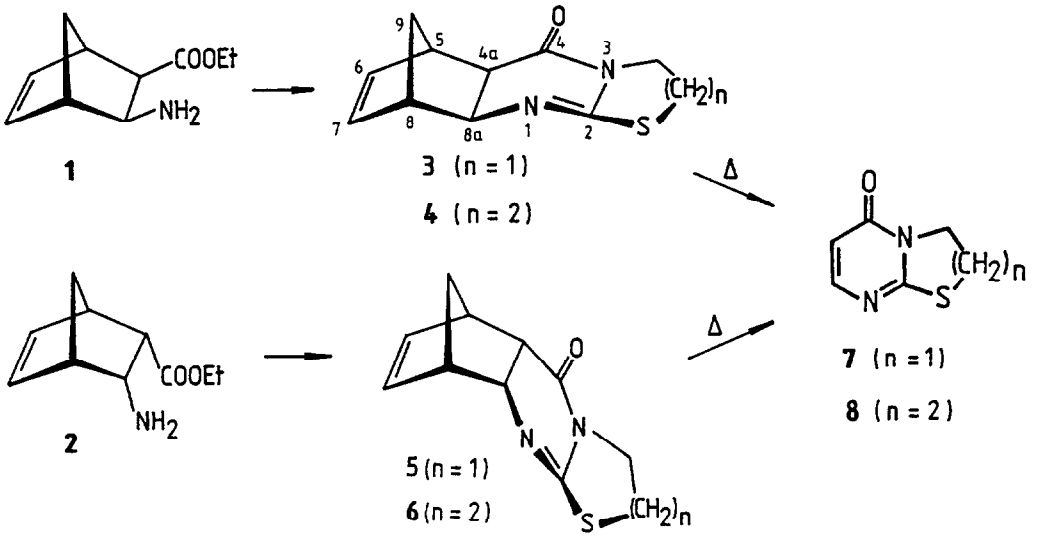


A

Although a number of papers (see *e g* refs 7-9) deal with the synthesis of thiazolo[2,3-*b*]quinazolin-5-ones (**A**, n = 1) and thiazino[2,3-*b*]quinazolin-6-ones (**A**, n = 2), the corresponding norbornene-fused derivatives **3-6** are not known The reactions of ethyl 3-*exo*-aminobicyclo[2 2 1]hept-5-ene-2-*exo*-carboxylate **1** and the *diendo* counterpart **2** with chloroethyl and chloropropyl isothiocyanates, yielded the tetracycles **3-6**

When compounds **3-6** were melted (at ~ 140 °C, for 20 minutes), bicycles **7** and **8** were formed in good yield, through the splitting-off of cyclopentadiene The *diendo* or *diexo* annelation had no significant effect on

the rates or yields of the reaction, but the decomposition of thiazolidines seemed somewhat faster than that of their six-membered homologues A mild retrodiene decomposition of norbornene-fused heterocycles was recently described[10-14] for the synthesis of monocyclic 1,3-heterocycles, *e g* pyrimidinones and oxazinones The reactions **3**, **5** → **7** and **4**, **6** → **8** described here provide the first evidence of a mild retrodiene decomposition resulting in bicyclic heteroderivatives, and the first synthesis of the parent pyrimido[2,1-*b*] thiazin-6-one **8**




## STRUCTURE CONFIRMATION BY NMR

The spectral data shown in Tables 1 and 2 are self-explanatory and only a few comments are necessary The doublet splits of the H-4a,8a signals of **3** and **4** are characteristic of *diexo*-annelated fused norbornenes[15] and prove the unaltered C-4a,8a configurations in the tetracyclic products from the starting compound **1** Due to the ca 90° dihedral angles of bonds C(4a)-H and C(8a)-H with the CH bonds at positions 5 and 8, respectively, no significant splitting corresponding to these couplings is observable, while in the case of *diendo* annelation (**2**, **5**, **6**), the double doublet splitting of the H-4a,8a signals appears as a result of these vicinal H,H interactions Similarly, the downfield shifts of these signals in case of **5** and **6** as compared to the shifts measured for **3** and **4** are indicative of a change in the positions of these hydrogens from *endo* to *exo*

The $^{1}H$ and $^{13}C$ chemical shifts of the $NCH_2$ and $SCH_2$ groups are characteristically different for thiazolidines (**3**, **5** and **7**) and thiazines (**4**, **6** and **8**) In the spectra of **7** and **8**, of course, all the signals on the H and C atoms in positions 5-9 are missing The chemical shifts of "H-4a,8a" and "C-4a,8a" are characteristic of unsaturated compounds, and the carbonyl line in the $^{13}C$-NMR spectrum of **8** is upfield-shifted by ca 7 ppm as compared with the values measured for **3-6** Similarly, the shift of the $^{13}C$-NMR line of C-2 is indicative both of the size of the S-containing ring and of the saturation of the "C(4a) C(8a)" bond

Table 1 $^1$H-NMR Chemical Shifts ($\delta_{TMS}$ = 0 ppm) of Compounds **3-6**, **7** and **8**

| Compound | δH-4a *d*[a](1H) | δH-5 (1H)[b] | δH-6 d*d*[c](1H) | δH-7 d*d*[c](1H) | δH-8 (1H)[b] | δH-8a *d*/d*d*[a](1H) | δCH$_2$(9) 2x*d*[d](2H) | δSCH$_2$ *m*/*t*[e](2H) | δNCH$_2$ *m*(2H) | δCH$_2$ *m*(2H) |
|---|---|---|---|---|---|---|---|---|---|---|
| **3** | 2 31 | 3 30 | 6 19 | 6 30 | 3 12 | 3.78 | 1 38, 1 46 | 3 20 | 4.10 | - |
| **4** | 2.43 | 3 28 | 6 18 | 6 30 | 3 14 | 3 65 | 1.40 | 3 06 | 3 86 | 2 14 |
| **5** | 2 86 | 3.46 | 6 15 | | 3 38 | 4 39 | 1 35, 1.47 | 3 10 | 4 00 | - |
| **6** | ~3 0[f] | 3.46 | 6 10 | 6 26 | 3 39 | 4 22 | 1.32, 1.42 | ~3.0[f] | 3.73 | 2 06 |
| **7** | 6 14 | - | - | - | - | 7 72 | - | 3 45 | 4 49 | - |
| **8** | 6 18 | - | - | - | - | 7 68 | - | 3 20 | 4 10 | 2.30 |

[a]Doublet for **3**, **4**, **7** and **8** (*J* 8 3, 8 6, 6,6 and 6 5 Hz), double doublet for **5** (*J* 9 4 and 4 0 Hz), and **6** (*J* 9 7 and 3 9 Hz) [b]Broadened singlet-like signal [c]*J*(H-6,H-7) 5 6 Hz, *J*(H-5,H-6)~*J*(H-7,H-8) 3 0 Hz, coalesced lines for **5** [d]AB-type spectrum For **4** near to the A$_2$-limiting case *J*(A,B) 9 3 (3), 8 8 (5) and ~ 9 Hz (6) [e]Triplet for **4** and **5** (*J* 6 2 and 7 0 Hz) [f]Overlapping signals

Table 2 $^{13}$C-NMR Chemical Shifts ($\delta_{TMS}$ = 0 ppm) of Compounds **3-6**, **7** and **8**

| Compound | C(2) | C=O (4) | CH (4a) | CH (5) | CH (6) | CH (7) | CH (8) | CH (8a) | CH$_2$ (9) | SCH$_2$ | NCH$_2$ | CH$_2$[a] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **3**[b] | 154 0 | 167 9 | 41 3 | 48 6 | 138 8 | 136 2 | 52 1 | 63 1 | 44.4 | 25 1 | 46 6 | - |
| **4** | 147 8 | 168 7 | 43 0 | 49 4 | 138 7 | 136 3 | 52 4 | 59 6 | 44 3 | 28 3 | 40 9 | 24 3 |
| **5** | 153 4 | 168 2 | 41 9 | 48 8[c] | 136 4 | 135 0 | 49 9[c] | 63 6 | 46 3[d] | 24 7 | 46 2[d] | - |
| **6**[b] | 147 2 | 168 8 | 43 4 | 49 4 | 136 5 | 134 8 | 50 1 | 60 1 | 45 8 | 28 1 | 40 1 | 24.1 |
| **7** | 165 6 | 160 9 | 110 4 | - | - | - | - | 152 1 | - | 26 2 | 48 5 | - |
| **8** | 160 3 | 161 4 | 109 8 | - | - | - | - | 153 9 | - | 27 8 | 41 4 | 22 6 |

[a]Thiazine ring [b]Assignments were proved by DEPT and for **6** also by DNOE (differential nuclear Overhauser effect) and 2D-HSC (2 dimensional heteronuclear shift correlation) measurements [c,d]Interchangeable assignments

## EXPERIMENTAL

Ethyl *exo*-aminobicyclo[2 2 1]hept-5-ene-2-*exo*-carboxylate (**1**) was prepared by cycloaddition of norbornadiene and chlorosulphonyl isocyanate followed by sodium sulphite reduction, ring opening with hydrochloric acid and esterification [12] Ethyl *endo*-aminobicyclo[2 2 1]hept-5-ene-2-*endo*-carboxylate (**2**) was prepared by ammonolysis and Hofmann degradation of the Diels-Alder adduct of cyclopentadiene and maleic anhydride, followed by esterification [17] Chloroethyl and chloropropyl isothiocyanates were prepared according to the literature [18] The yields, physical properties and analytical data on the prepared compounds are given in Table 3 The IR spectra of compounds in KBr pellets were measured with an Aspect 2000 computer-controlled Bruker IFS-113v FT spectrometer $^1$H- and $^{13}$C-NMR spectra were recorded at room temperature in $CDCl_3$ solution on a Bruker WM 250 ($^1$H,$^{13}$C) or on an AM-80 and a WP-80 SY ($^{13}$C, for compounds **4** and **8**) spectrometer – controlled by an Aspect 2000 computer – at 250 ($^1$H) and 64 or 20 ($^{13}$C) MHz, respectively, using the deuterium signal of the solvent as the lock and TMS as internal standard The experimental details have been given earlier [13]

*General procedure for preparation of tetracycles* **3-6** To a solution of 5 mmol **1** or **2** in ethanol (10 ml), 15 mmol triethylamine was added, and to this mixture 5 mmol isothiocyanate in ethanol (10 ml) was added

dropwise in one hour under ice cooling and stirring. After 24 h, the solvent was evaporated off, and tetracycles **3-6** were separated by means of chloroform/water extraction. The combined chloroform extracts were dried ($Na_2SO_4$) and evaporated. The oily residue was transformed to the hydrochloride with ethanolic hydrogen chloride, and recrystallized from an ethanol/ether mixture.

Table 3 Physical and Analytical Data on Compounds Prepared

| Compound | M.p (°C) | Yield (%) | Found C | H | N | Formula | Calculated % C | H | N | IR $\nu_{C=O}$ ($cm^{-1}$) |
|---|---|---|---|---|---|---|---|---|---|---|
| **3**[a] | 210-213 | 61 | 51.5 | 5 2 | 11.0 | $C_{11}H_{13}ClN_2OS$ | 51 5 | 5.1 | 10.9 | 1660 |
| **4**[a] | 194-196 | 57 | 53.4 | 5 7 | 10 4 | $C_{12}H_{15}ClN_2OS$ | 53.2 | 5 6 | 10.4 | 1680 |
| **5**[a] | 203-207 | 55 | 51 5 | 5 3 | 10.8 | $C_{11}H_{13}ClN_2OS$ | 51 5 | 5.1 | 10.9 | 1670 |
| **6**[a] | 176-178 | 57 | 53 2 | 5.7 | 10 3 | $C_{12}H_{15}ClN_2OS$ | 53 2 | 5.6 | 10 4 | 1685 |
| **7** | 109-110[b] | c | 46.8 | 4.1 | 18 4 | $C_6H_6N_2OS$ | 46 7 | 3 9 | 18 2 | 1678 |
| **8** | 133-134 | d | 50.1 | 4 9 | 16 7 | $C_7H_8N_2OS$ | 50 0 | 4.8 | 16 7 | 1673 |

[a]HCl salt [b]Lit [6] mp 107-109 °C c From **3** 80, from **5** 70% d From **4** 83, from **6** 75%

*Retrodiene decomposition of tetracycles* **3-6** The free bases were liberated from the corresponding hydrochlorides with $Na_2CO_3$ in chloroform/water system, and submitted to the following retrodiene reaction without isolation. The bases of compounds **3-6** (5 mmol) were heated on an oil bath (140 °C) for 20 minutes, respectively The crude brown product crystallized after cooling to room temperature. This was dissolved in benzene (70 ml), silica gel (5 g) was added and the resulting slurry was stirred for 5 minutes The silica gel was filtered off and washed with benzene After removal of benzene the residue was recrystallized from ethyl acetate, furnishing products **7** and **8**.

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