Condensed Heterocycles Containing the Pyrimidine Nucleus

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Continuing earlier studies designed to obtain derivatives of 1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one and of the isomeric 7-one of pharmacological interest, some novel compounds **2** and derivatives of 6,7,8,9-tetrahydro-5*H*-1,3,4-thiadiazolo[2,3-*b*]quinazolin-5-one (**3**) were prepared. Derivatives of pyrimido[2,1-*b*]benzothiazol-2-one (**6**) and of the isomeric 4-one derivatives **8** were also synthesized. Structural identification was obtained by ^{1}H-nmr, ir and mass spectra.

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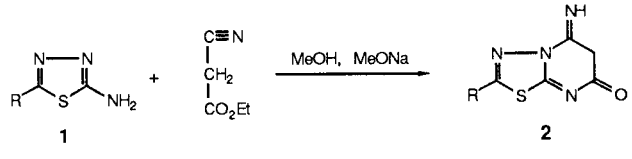
Pseudopurines have received much attention in recent years because of their interesting pharmacological properties [1-9]. Recently, we have reported the synthesis of thienothiadiazolopyrimidine derivatives with important analgesic activity [10,11]. This paper describes the synthesis and the structural characterization of derivatives of 2-substituted-5-imino-7*H*-1,3,4,-thiadiazolo[3,2-*a*]pyrimidin-7-one (**2**) and of 2-substituted-6,7,8,9-tetrahydro-5*H*-1,3,4-thiadiazolo[2,3-*b*]quinazolin-5-one (**3**). Thiadiazolopyrimidones **2** were prepared from the reaction of 5-substituted-2-amino-1,3,4-thiadiazoles (**1**) and ethyl cyanoacetate (Scheme 1).

Scheme 1



1 2

a, R = Me
b, R = Et
c, R = Ph
d, R = *o*-OEtC$_6$H$_4$
e, R = SMe

The ir and ^{1}H-nmr spectra are in accordance with the proposed imino structure (Tables 1 and 2). In particular, the methylene protons in the pyrimidine ring appeared at 30° as a very broad signal in the region of 4.00-5.00 ppm, confirming their strong acidic character. These signals were sharpened at −20, −30°. Since ir and ^{1}H-nmr data gave no informations in order to distinguish between the 7-one and 5-one structure, which may be produced in such a reaction, we felt that an investigation of the electron impact mass spectra could be of utility to gather further indications of the structure. In fact, in a previous work on some 1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-one and isomeric 5-one derivatives [12], which are structurally related to compounds 2, it has been shown that structures having a double bond in the 6,7 position in the pyrimidine ring can be differentiated from the corresponding isomers having a single bond in the same position, the latter showing in their spectra an electron impact induced retro Diels Alder (RDA) fragmentation, which does not occur in the 6,7 unsaturated compounds. According to the proposed structure for compounds **2**, which showed a single bond in position 6,7, their mass spectra should present structurally

Table 1

Analytical and IR Data for the Thiadiazolopyrimidinones **2a-e**

Compound	R	Yield (%)	Mp °C (Recrystallization solvent)	Molecular formula	Analysis % Calcd./Found C	H	N	IR (cm^{-1})
2a	Me	80	250-251 dec (EtOH-dioxane)	$C_6H_6N_4OS$	39.55 39.68	3.32 3.34	30.75 30.40	1690 (C=O) 3190 (NH)
2b	Et	85	231-233 (dioxane-DMF)	$C_7H_8N_4OS$	42.85 42.87	4.11 4.13	28.55 28.90	1700 (C=O) 3200 (NH)
2c	Ph	90	240-242 dec (EtOH-dioxane)	$C_{11}H_8N_4OS$	54.10 53.95	3.30 3.34	22.95 23.08	1700 (C=O) 3180 (NH)
2d	*o*-EtOC$_6$H$_4$	90	255-256 (dioxane)	$C_{13}H_{12}N_4O_2S$	54.15 54.30	4.20 4.25	19.43 19.55	1690 (C=O) 3190 (NH)
2e	SMe	80	235-237 (dioxane-DMF)	$C_6H_6N_4OS_2$	33.63 33.80	2.82 2.85	26.15 26.60	1695 (C=O) 3195 (NH)

Table 2

^{1}H-NMR Chemical Shifts (δ_H) and Selected Ions in the Mass Spectra for Compounds **2a-e**

Compound	R	δ_H C(6)H_2	δ_H NH	δ_H 2-R	m/z (Relative abundance) M^+	m/z (Relative abundance) $[M-40]^+$ RDA+H
2a	Me	4.46 (s, 2 H)	9.25 (br s, 1 H)	2.59 (s, 3 H, CH_3)	182 (42)	142 (48)
2b	Et	4.45 (s, 2 H)	– – – –	1.25 (t, 3 H, 8.0 Hz, CH_2CH_3) 2.97 (q, 2 H, 8.0 Hz, CH_2CH_3)	196 (95)	156 (69)
2c	Ph	4.58 (s, 2 H)	7.06 (br s, 1 H)	7.43-8.27 (m, 5 H, C_6H_5)	244 (100)	202 (58)
2d	o-$EtOC_6H_4$	4.48 (s, 2 H)	– – – –	7.04-7.65 (4 H, m, C_6H_4OEt-o) 1.45 (t, 3 H, 7.1 Hz, $PhOCH_2CH_3$-o) 4.13 (q, 2 H, 7.1 Hz, $PhOCH_2CH_3$-o)	288 (86)	248 (100)
2e	SMe	4.48 (s, 2 H)	10.20 (br s, 1 H)	2.68 (s, 3 H, SCH_3)	214 (100)	174 (33)

diagnostic fragment ions originated in the RDA process. Inspection of the mass spectra of compounds **2** revealed however that the RDA fragment ions corresponding to m/z M-41 [M - (CH_2=C=NH)]$^+$were of low intensity, whereas were present intense ions corresponding to m/z M-40 [M - (CH_2=C=NH) + H]$^+$. This indicates that the RDA fragmentation does occur in these compounds and that it is accompanied by a concomitant hydrogen transfer to the RDA produced fragment. Hydrogen transfer accompanying the RDA fragmentation (RDA + H) is a well recognized process and it has been recently observed in several compounds [13-15] (Figure 1). In conclusion, since in an alternative isomeric structure fragment ion [M - (CH_2=C=NH) + H]$^+$ must be absent, it appears that the mass spectra of compounds **2** are consistent with the proposed structure.

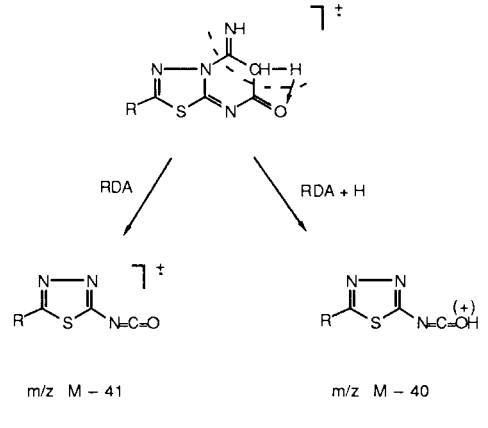


Figure 1. RDA and RDA+H fragmentation pathways for compounds **2** in the mass spectra.

The reaction of 5-substituted-2-amino-1,3,4-thiadiazoles (**1**) with ethyl 2-oxocyclohexanecarboxylate afforded the 2-substituted-6,7,8,9-tetrahydro-5*H*-1,3,4-thiadiazolo[2,3-*b*]quinazolin-5-ones (**3**) (Scheme 2). The structure of

Scheme 2

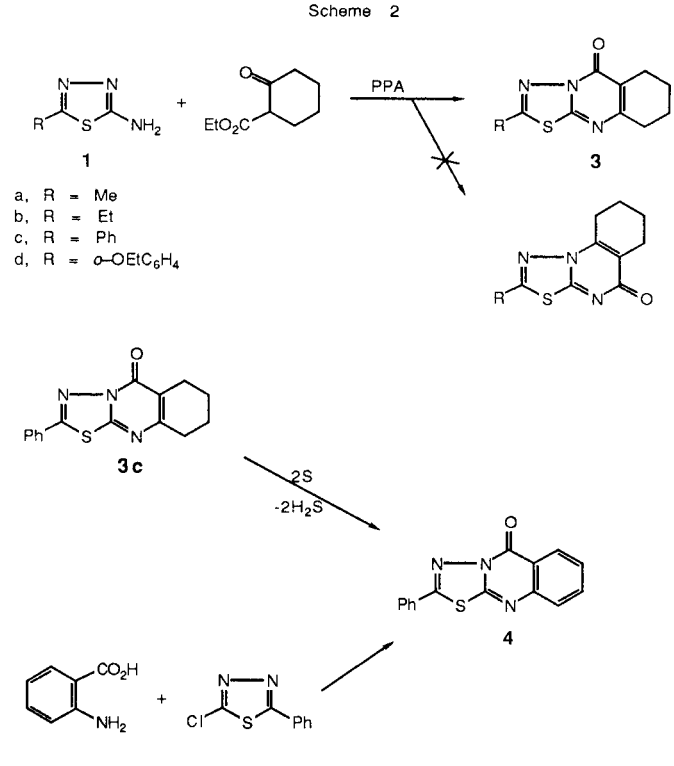
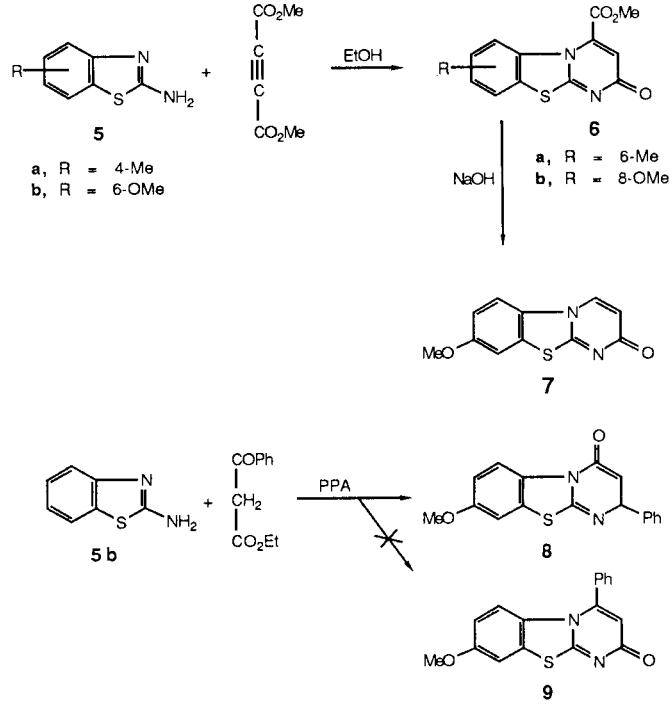


Table 3

Analytical Data for the Tetrahydrothiadiazoloquinazolinones **3a-d**

Compound	R	Yield (%)	Mp °C (Recrystallization solvent)	Molecular formula	Analysis % Calcd./Found C	H	N
3a	Me	25	169-170 (EtOH)	$C_{10}H_{11}N_3OS$	54.28 54.00	5.01 5.03	19.00 19.10
3b	Et	20	151-153 (EtOH)	$C_{11}H_{13}N_3OS$	56.15 56.17	5.57 5.70	17.86 18.12
3c	Ph	25	179-180 (EtOH)	$C_{15}H_{13}N_3OS$	63.58 63.72	4.62 4.58	14.83 14.83
3d	*o*-$EtOC_6H_4$	30	211-213 (EtOH-dioxane)	$C_{17}H_{17}N_3O_2S$	63.36 62.05	5.23 5.18	12.85 12.83

Scheme 3



2-phenyl **3c** was confirmed by dehydrogenation of cyclohexene ring. Congruously with the proposed structure for **3c**, this reaction gave compound **4**, that was identical with the compound prepared from reaction of 2-chloro-5-phenyl-1,3,4-thiadiazole with anthranilic acid [16].

Compounds **3a**, **3b** and **3d** were prepared under identical conditions of those used for compound **3c**. With the obvious differences due to the 2-substituent, they also showed ^{1}H-nmr and ir spectral data similar to those of compound **3c**. Therefore the structure assigned to **3c** is also proposed for compounds **3a**, **3b** and **3d**. Finally pyrimidobenzothiazolones **6a** and **6b** were prepared by condensing 4-methyl **5a** and 6-methoxy **5b** 2-aminobenzothiazole respectively with dimethylacetylendicarboxylate. Alkaline hydrolysis of **6b** furnished **7** that resulted to be identical with the product obtained by Dunwell *et al.* [17] (Scheme 3). The ^{1}H-nmr and ir spectra were in agreement with the proposed structures **6**. The treatment of 2-amino-6-methoxybenzothiazole (**5**) with ethyl benzoylacetate in PPA gave 2-phenyl-8-methoxy-4*H*-pyrimido[2,1-*b*]benzothiazol-4-one (**8**) (Scheme 3). The mass spectrum of this compound showed the molecular ion as the base peak and fragments of negligible intensity at m/z 102 and 206 that would have originated in a RDA process. These fragments

Table 4

^{1}H-NMR Chemical Shifts (δ_H) and IR Data for Compounds (**3a-d**)

Compound	R	δ_H C(2)R	δ_H other protons	IR (cm^{-1}) C=O
3a	Me	2.54 (s, 3 H, CH_3)	1.51-1.71 and 2.53-2.74 (m, 8 H)	1665
3b	Et	1.21 (t, 3 H, 8.0 Hz, CH_2CH_3) 2.80 (q, 2 H, 8.0 Hz, CH_2CH_3)	1.55-1.79 and 2.56-2.71 (m, 8 H)	1675
3c	Ph	7.47-7.58 and 7.93-8.06 (m, 5 H, C_6H_5)	1.57-1.64 and 2.60-2.76 (m, 8 H)	1680
3d	o-$EtOC_6H_4$	6.97-7.60 and 8.40-8.53 (m, 4 H, C_6H_4) 1.37 (t, 3 H, 7.4 Hz, $PhOCH_2CH_3$-o) 4.08 (q, 2 H, 7.4 Hz, $PhOCH_2CH_3$-o)	1.59-1.73 and 2.61-2.78 (m, 8 H)	1675

in fact are of remarkable intensities (18% and 100% respectively) in the spectrum of **9** prepared by Al-Jallo, *et al.* [18].

EXPERIMENTAL

All melting points were taken in open capillaries using a Gallemkamp melting point apparatus with digital thermometer MFB-595 and are uncorrected. The ir spectra were recorded with a Perkin-Elmer 281 spectrometer in potassium bromide disks. Elemental analyses for C, H, and N were obtained on a Carlo Erba 1106 elemental analyzer. The ^{1}H-nmr spectra were recorded in pyridine-d_5 on a Perkin-Elmer R32 spectrometer operating at 90 MHz; chemical shifts are reported in ppm from TMS as internal standard and are given in δ units. The low resolution mass spectra were recorded by direct insertion into the ion source on an LKB 9000S instrument under the following conditions: ionization energy, 70 eV; source temperature 250-270°; trap current 60 μA. The sample temperature ranged from room temperature to 250°.

Preparation of 2-Substituted-5-imino-7*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-ones (**2**). General Procedure.

To a solution of sodium (0.01 mole) in dry methanol (30 ml) 5-substituted-2-amino-1,3,4-thiadiazole (**1**) [19-23] (0.01 mole) and ethyl cyanoacetate (0.01 mole) were added and the resulting solution was refluxed for 5 hours. After cooling, the solution was diluted with water (100 ml), filtered and acidified with acetic acid. The resulting precipitate was collected, washed with water, dried and crystallized from appropriate solvent to give **2a-e** as colourless microcrystals. Analytical and spectral data are reported in Tables 1 and 2.

Preparation of 2-Substituted-6,7,8,9-tetrahydro-5*H*-1,3,4-thiadiazolo-[2,3-*b*]quinazolin-5-ones (**3**). General Procedure.

A mixture of 5-substituted-2-amino-1,3,4-thiadiazole (**1**) [19-22] (0.01 mole), ethyl 2-oxo-cyclohexanecarboxylate (0.01 mole) and PPA (polyphosforic acid) (10 g) was heated in an oil bath at 150-160° for 3 hours. The cooled reaction mixture was treated with ice water and neutralized with 10% solution of sodium hydroxide. The precipitate obtained was collected, suspended in warm ethanol and filtered. The resulting solid was washed with ethanol, dried and crystallized from appropriate solvent to give **3a-d** as colourless microcrystals. Analytical and spectral data are reported in Tables 3 and 4.

2-Phenyl-5*H*-1,3,4-thiadiazolo[2,3-*b*]quinazolin-5-one (**4**).

A mixture of **3c** (2.7 g), and of sulphur (0.7 g) in dimethyl phthalate (3 ml) was heated in an oil bath at 220° until the evolution of hydrogen sulfide was complete. After cooling, the precipitate formed was collected and crystallized from acetic acid to give **4** as white powder , mp 225-227°; ir: 1720 cm^{-1} (C=O); ^{1}H-nmr: 7.47-8.16 and 8.59-8.74 (m, 9 H, ArH).

Anal. Calcd. for $C_{15}H_9N_3OS$: C, 64.51; H, 3.22; N, 15.05. Found: C, 64.40; H, 3.35; N, 14.90.

A mixture melting point with a sample prepared by Russo *et al.* [16] was not depressed. The two samples exhibited identical ^{1}H-nmr and ir spectra.

Methyl 2-Oxo-6-methyl-2*H*-pyrimido[2,1-*b*]benzothiazole-4-carboxylate (**6a**) and Methyl 2-Oxo-8-methoxy-2*H*-pyrimido[2,1-*b*]benzothiazole-4-carboxylate (**6b**).

A solution of 2-amino-4-methylbenzothiazole (**5a**) [24] (0.01 mole) or of 2-amino-6-methoxybenzothiazole (**5b**) [25] (0.01 mole) and of dimethyl acetylendicarboxylate (0.012 mole) in absolute ethanol (50 ml) was refluxed for 6 hours. After cooling, the precipitate formed was collected and crystallized from appropriate solvent to give **6a** or **6b**.

Compound **6a** was obtained in 35% yield, mp 206-208° (from dioxane-ethanol) yellow microplates; ir: 1655 (C=O) and 1735 cm^{-1} (C=O); ^{1}H-nmr: 2.25 (s, 3 H, CH_3) 3.87 (s, 3 H, $COOCH_3$), 6.94 (s, 1 H, 3-H) and 7.12-7.67 (m, 3 H, Ar-H).

Anal. Calcd. for $C_{13}H_{10}N_2O_3S$: C, 56.93; H, 3.67; N, 10.21. Found: C, 56.66; H, 3.63; N, 10.20.

Compound **6b** was obtained in 40% yield, mp 204-206° (from DMF), yellow powder; ir: 1669 (C=O) and 1735 cm^{-1} (C=O); ^{1}H-nmr: 3.75 (s, 3 H, $COOCH_3$), 4.01 (s, 3 H, OCH_3), 6.94 (s, 1 H, 3-H) and 6.94-7.72 (m, 3 H, ArH).

Anal. Calcd. for $C_{13}H_{10}N_2O_4S$: C, 53.80; H, 3.46; N, 9.65. Found: C, 54.11; H, 3.37; N, 10.06.

Hydrolysis of **6b**.

A suspension of **6b** (0.01 mole) in a solution of sodium hydroxide (0.05 mole) in methanol (50 ml) and water (10 ml) was refluxed under stirring for 0.5 hour. After cooling, by dilution with water (50 ml) and acidifica-

tion with concentrated hydrochloric acid a solid separated. This solid was collected, washed with water and dried to give **7**, mp 300° (from DMF); ir: 1630 cm^{-1} (C=O).

Anal. Calcd. for $C_{11}H_8N_2O_2S$: C, 56.90; H, 3.45; N, 12.06. Found: C, 57.14; H, 3.45; N, 12.13.

A mixture melting point of **7** with 8-methoxy-2*H*-pyrimido[2,1-*b*]-benzothiazol-2-one, prepared by Dunwell and Evans [17] was not depressed. The two compounds exhibited identical ir spectra.

2-Phenyl-8-methoxy-4*H*-pyrimido[2,1-*b*]benzothiazol-2-one (**8**).

A mixture of 2-amino-6-methoxybenzothiazole (**5b**) [25] (0.01 mole), ethyl benzoylacetate (0.015 mole) and PPA (12 g) was heated in an oil bath at 150-160° for 1 hour. After cooling the reaction mixture was treated with ice water and neutralized with 10% solution of sodium hydroxide. The precipitate formed was suspended in warm ethanol, collected, washed with water, dried (20%) and crystallized from ethanol-dioxane to give **8** as yellow solid, mp 226-228°; ir: 1670 cm^{-1} (C=O); ^{1}H-nmr: 4.03 (s, 3 H, 8-OCH_3), 6.90 (s, 1 H, 3-H) and 6.91-7.72 (m, 8 H, Ar-H); ms: m/e 292 (M^+).

Anal. Calcd. for $C_{17}H_{12}N_2O_2S$: C, 66.21; H, 3.92; N, 9.08. Found: C, 65.80; H, 3.87; N, 9.36.

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