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Pyrimido[4,5—*e*] (1,2,4)-triazolo[3,4—*b*] (1,3,4)-thiadiazine-7,9(6*H*,8*H*)-diones

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Some 5*H*-pyrimido[4,5—*e*](1,2,4)-triazolo[3,4—*b*](1,3,4)-thiadiazine-7,9-(6*H*,8*H*)-diones (**4 a–d**) have been synthesised by the condensation of 3-alkyl-4-amino-5-mercapto-(1,2,4)-triazoles (**1 a–d**) with 5-bromobarbituric acid (**2 a**). Similarly some 9a-nitro-5*H*-pyrimido[4,5—*e*](1,2,4)-triazolo[3,4—*b*](1,3,4)-thiadiazine-7,9(8*H*,9a*H*)-diones (**5 a–d**) have been obtained by the condensation of **1 a–d** with 5-bromo-5-nitrobarbituric acid (**2 b**) and final cyclisation with *PPA*. The structures have been confirmed by PMR spectra and analytical results.

(Keywords: Heterocyclic compounds)

Pyrimido[4,5—e](1,2,4)-triazolo[3,4—b](1,3,4)-thiadiazin-7,9(6H,8H)-dione

Es wurden einige 5*H*-pyrimido[4,5—*e*](1,2,4)-triazolo[3,4—*b*](1,3,4)-thiadiazin-7,9(6H,8H)-dione (**4 a—d**) mittels Kondensation von 3-Alkyl-4-amino-5-mercapto-(1,2,4)-triazolen (**1 a—d**) mit 5-Brombarbitursäure (**2 a**) dargestellt. Des weiteren wurden einige 9a-Nitro-5*H*-pyrimido[4,5—*e*](1,2,4)-triazolo-[3,4—*b*](1,3,4)-thiadiazin-7,9(8*H*,9a*H*)-dione (**5 a—d**) über die Kondensation von **1 a—d** mit 5-Brom-5-nitrobarbitursäure (**2 b**) und anschließender Cyclisierung mit *PPA* synthetisiert. Die angeführten Strukturen wurden mittels PMR-Spektren und analytischen Daten abgesichert.

Introduction

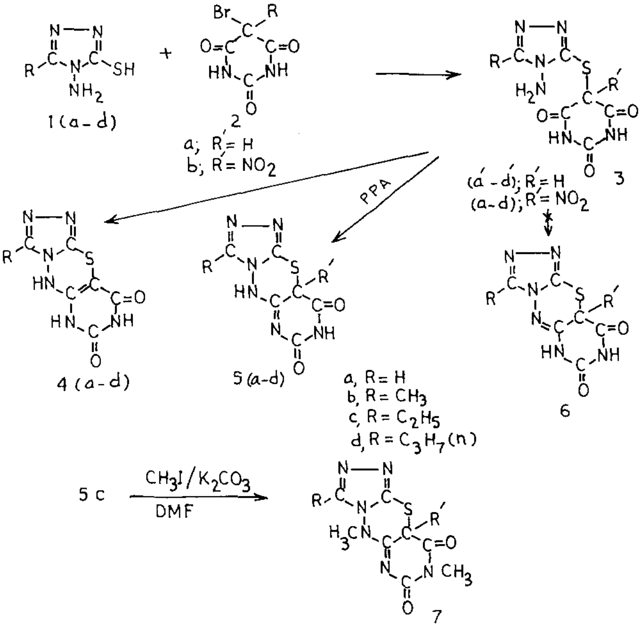
Some triazolothiadiazines have been reported[1—7] to possess antibacterial and antifungal activity. Therefore it seemed to be of interest to introduce another pyrimidine ring. We now report the synthesis of another new system, namely 5*H*-pyrimido[4,5—*e*](1,2,4)-triazolo-[3,4—*b*](1,3,4)-thiadiazines.

Results and Discussion

We started with 3-alkyl-4-amino-5-mercapto(1,2,4)-triazoles (**1**) which in turn were accessible by the treatment of hydrazine hydrate with carbondisulphide followed by reaction with various carboxylic acids.

The 3-alkyl-4-amino-5-mercapto(1,2,4)-triazoles (**1 a**—**d**) thus formed were reacted with 5-bromobarbituric acid (**2 a**) to give the required 3-alkyl-5*H*-pyrimido[4,5—*e*](1,2,4)-triazolo[3,4—*b*](1,3,4)-thiadiazine-7,9(6*H*,8*H*)-diones (**4 a**—**d**) via the intermediate **3 a′**—**d′** (*R*=H) which could not be isolated. Structures **4 a**—**d** are supported by analytical results, by PMR spectra and their insolubility in sodium hydroxide solution.

In its PMR-spectrum (chemical shifts in δ/ppm) in $CDCl_3$ + *TFA* **4 c** exhibited a quartet (2H) at 3.17 and a triplet (3H) at 1.50 assignable to two and three protons respectively of the ethyl group at position 3. The signal for the proton at 9a did not appear excluding therefore the possibility of structures **5** or **6**.



Similarly (**1 a**—**d**) on condensation with 5-bromo-5-nitrobarbituric acid (**2 b**) gave rise to **3 a**—**d** ($R'=NO_2$) which on cyclodehydration with *PPA* could give **5** or **6**. These two structures differ only in the position of the C=N double bond. However, we have assigned structure **5** to the cyclised product on the basis of its greater stability because of the conjugation of the carbonyl group with the —C=N bond.

In its PMR-spectrum ($CDCl_3$ + *TFA*) **5 c** displayed a quartet (2H) at 3.34 and a triplet (3H) at 1.48 assignable to two and three protons, respectively of the ethyl group at position 3.

Compound **5 c** was methylated with CH_3I in the presence of K_2CO_3 to give **7**. The PMR spectrum of **7** could not be recorded because of its insolubility.

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Experimental

Melting points were determined in open glass capillaries using liquid paraffin bath and are uncorrected. IR spectra were recorded in nujol on a Perkin Elmer 337 and PMR on a Varian EM 390 90 MHz spectrometer using *TMS* as the internal reference. The analytical values (C, H, N) agree with the proposed structures **3 a—d**, **4 a—d**, and **5 a—d**.

3-Ethyl-5H-pyrimido[4,5—e](1,2,4)-triazolo[3,4—b](1,3,4)-thiadiazine-7,9(6H,8H)-dione (**4 c**, $R = C_2H_5$)

A solution of 4-amino-3-ethyl-5-mercepto(1,2,4)-triazole (**1**)[8,9] (1.44 g, 0.01 mol) in ethanol (40 ml) was added to an ethanolic solution (300 ml) of 5-bromobarbituric acid (**2 a**) (2.07 g, 0.01 mol) dropwise with continuous stirring at room temperature. There was immediate separation of a new solid which increased as the addition progressed. The contents were stirred at room temperature for 2 h and then refluxed on a steam bath for 0.5 h. After cooling, the solid product was collected under suction, washed with a dilute solution of sodium carbonate and finally with water. Recrystallisation from glacial acetic acid gave colourless needles.

Other 3-alkyl-4-amino-5-mercepto(1,2,4)-triazoles were also condensed with 5-bromobarbituric acid under identical conditions. The data regarding these compounds are collected in Table 1.

Table 1. *3-alkyl-5 H-pyrimido[4,5—e] (1,2,4)-triazolo[3,4—b] (1.3.4)-thiadiazine-7,9 (6 H,8 H)-diones* **4 a–d**

No.	*R*=	Yield %	M.P.* °C	Molecular Formula
4 a	H	85	257	$C_6H_6N_6O_3S$
4 b	CH_3	90	254	$C_7H_8N_6O_3S$
4 c	C_2H_5	93	235	$C_8H_{10}N_6O_3S$
4 d	n-C_3H_7	60	242	$C_9H_{12}N_6O_3S$

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* **4 a** and **4 b** were crystallised from ethanol while **4 c** and **4 d** were crystallised from glacial acetic acid. All compounds crystallise with one molecule of water.

5-[(4-Amino-5-ethyl-4H-1,2,4-triazol-3-yl)thio]-barbituric acid (**3c**, $R = C_2H_5$, $R' = NO_2$)

To a solution of 5-bromo-5-nitrobarbituric acid (**2**, 2.52 g, 0.01 mol) in absolute ethanol (300 ml) was added an ethanolic solution (40 ml) of 4-amino-3-ethyl-5-mercepto(1,2,4)-triazole (**1c**, 1.44 g, 0.01 mol) dropwise with constant stirring at room temperature when the intermediate **3c** separated out immediately. It was collected under suction, washed with a diluted solution of sodium carbonate and finally with cold water.

Other 3-alkyl-4-amino-5-mercepto-(1,2,4)-triazoles were condensed with 5-bromo-5-nitrobarbituric acid under identical conditions. Corresponding data are collected in Table 2.

Table 2. *5-[(4-Amino-5-alkyl-4H-1,2,4-triazol-3-yl)thio]-barbituric acid* **3a–d**

No.	$R=$	Yield %	M.P.* °C	Molecular Formula
3a	H	53	155	$C_6H_7N_7O_6S$
3b	CH_3	48	188 (d)	$C_7H_9N_7O_6S$
3c	C_2H_5	42	260	$C_8H_{11}N_7O_6S$
3d	n-C_3H_7	45	280	$C_9H_{13}N_7O_6S$

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* All these compounds were crystallised from water and include one molecule of water.

3-Ethyl-9a-nitro-5H-pyrimido[4,5—e](1,2,4)-triazolo[3,4—b](1,3,4)-thiadiazine-7,9(8H,9aH)-dione (**5c**)

Intermediate **3c** (1.00 g) was mixed with a freshly prepared solution of polyphosphoric acid [by mixing phosphorous pentoxide (4 g) and orthophosphoric acid (3 ml)]. The contents were heated on an oil bath at 120–130° for 3 h. It was cooled to room temperature and basified with 10% potassium carbonate solution. The solution was concentrated to 10 ml and the solid thus separated was collected under suction. After washing it with ice-cold water (5 ml), it was crystallised from ethanol.

Other intermediates were also cyclised in a similar fashion. For corresponding data see Table 3.

5,8-Dimethyl-9a-nitro-5H-pyrimido[4,5—e](1,2,4)-triazolo[3,4—b](1,3,4)-thiadiazine-7,9(8H,9aH)-dione (**7**)

A mixture of **5c** (0.315 g, 0.001 ml) methyl iodide (0.170 g, 0.0012 mol) and K_2CO_3 (0.069 g, 0.0005 mol) in *DMF* (5 ml) was stirred at 120° for 2 h. The contents were evaporated to dryness and the residue treated with water. The product thus separated was crystallised from ethanol m.p. > 360°.

Table 3. *3-Alkyl-9a-nitro-5H-pyrimido[4,5—e](1,2,4)-triazolo[3,4—b](1,3,4)-thiadiazine-7,9(8H,9aH)diones* **5a–d**

No.	*R*=	Yield %	M.P.* °C	Molecular formula
5a	H	53	268	$C_6H_5N_7O_5S$
5b	CH_3	48	>360	$C_7H_7N_7O_5S$
5c	C_2H_5	42	>360	$C_8H_9N_7O_5S$
5d	*n*-C_3H_7	45	>360	$C_9H_{11}N_7O_5S$

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* All these compounds were crystallised from ethanol and include one molecule of water.

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