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PYRIMIDO [4.5 - b][1.4]THIAZINE DERIVATIVES SULFUR ISOSTERES OF DIHYDROPTERIDINES

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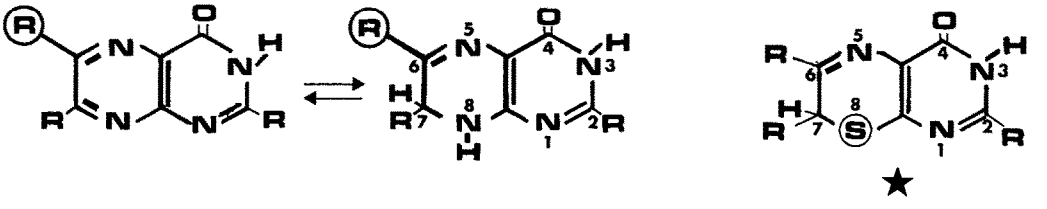
Our recent studies on pyrimido[5.4 -b][1.4]benzothiazines have shown, that these compounds can be regarded as sulfur analogs of dihydroflavines.

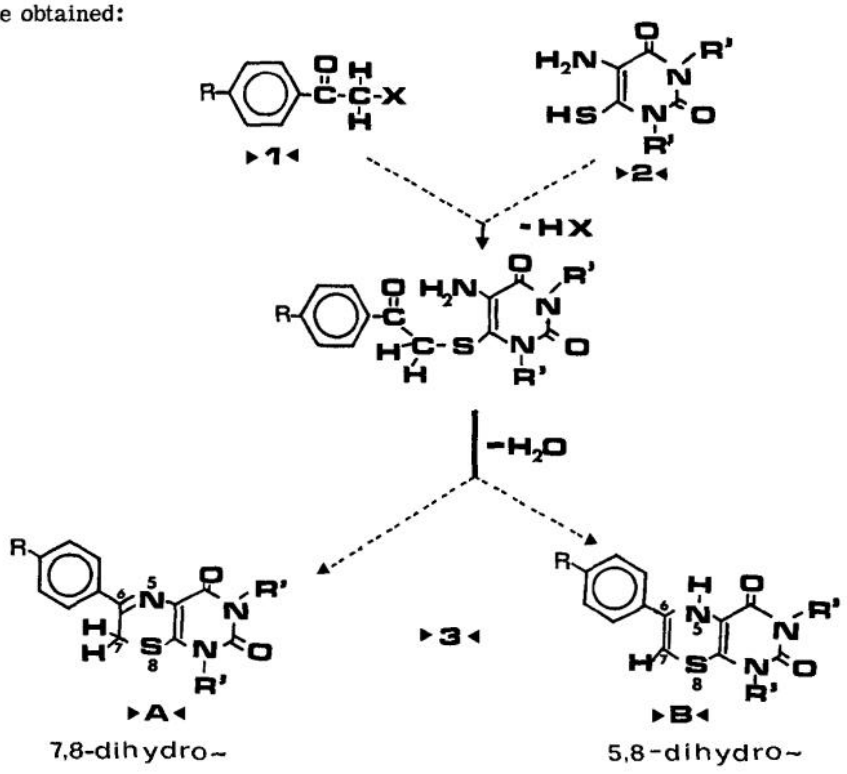
One of their most interesting properties is the formation of sulfur isosteres of flavosemiquinone radicals which we have studied by electron spin resonance. (1-3)
It appeared to be desirable to extend our studies to other sulfur analogous systems of naturally occuring dihydro-pyrimidopyrazine derivatives, especially to the isosteres of dihydropteridines. The pyrimido[4.5 -b][1.4]thiazine system (★) can be considered as a dihydropteridine system in which the nitrogen in position 8 is replaced by sulfur:



These compounds should be interesting as possible antimetabolites of dihydropteridines, the first stable intermediates in the pteridine reduction. (4)

Pyrimido[4.5 -b][1.4]thiazines have been described by Rose (5) and other authors (6-9), but the synthesis of a pyrimidothiazine system analogous to dihydropteridines - dihydropterins or dihydrolumazines - has not been described since now. We assumed that some reactions known from the pteridin series might be applied. We studied the reactions of a number of different α-halogeno-ketones and α-halogeno-aldehydes with 5-amino-6-mercapto-pyrimidines. (10)

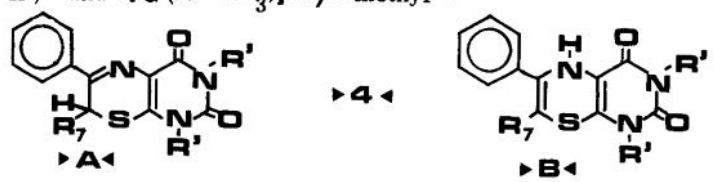
By heating α-chloroacetophenone (**1**, R=H) or p-bromo-phenacylbromide (**1**, R=Br) with 6-thiouramil (**2**, R'=H) or 1.3-dimethyl-6-thiouramil (**2**, R'=CH_3) in EtOH/water mixtures in the presence of Na-acetate under nitrogen the 6-phenyl-pyrimido[4.5-b][1.4] thiazines **3a** (R=H, R'=H), **3b** (R=H, R'=CH_3), **3c** (R=Br, R'=H) and **3d** (R=Br, R'=CH_3) were obtained:



Under similar conditions some 6,7-disubstituted pyrimido[4.5-b][1.4]thiazines could be prepared from α-halogeno-ketones, in which the α-carbon carries a single hydrogen, e.g.,

desylchloride (α-chloro-α-phenyl-acetophenone) formed 6,7-diphenyl-pyrimido[4.5-b][1.4]thiazines: **4a** (R'=H) and **4b** (R'= CH_3), R_7 = phenyl ;

α-chloro-propiophenone formed 6-phenyl-7-methyl-pyrimido[4.5-b][1.4]thiazines: **4c** (R = H) and **4d** (R = CH_3), R_7 = methyl :



▸A◂ ▸4◂ ▸B◂

These reactions made evident that the formation of pyrimidothiazines involves nucleophilic attack by the mercaptopyrimidines with subsequent cyclisation to the enamine-structure ▸B◂ or the tautomeric imine-structure ▸A◂ . The nmr data allow a more precise characterization of these tautomeric forms: (cf. table 1) showing that the 7,8 - dihydro-structure is preferred by all compounds described in this paper.

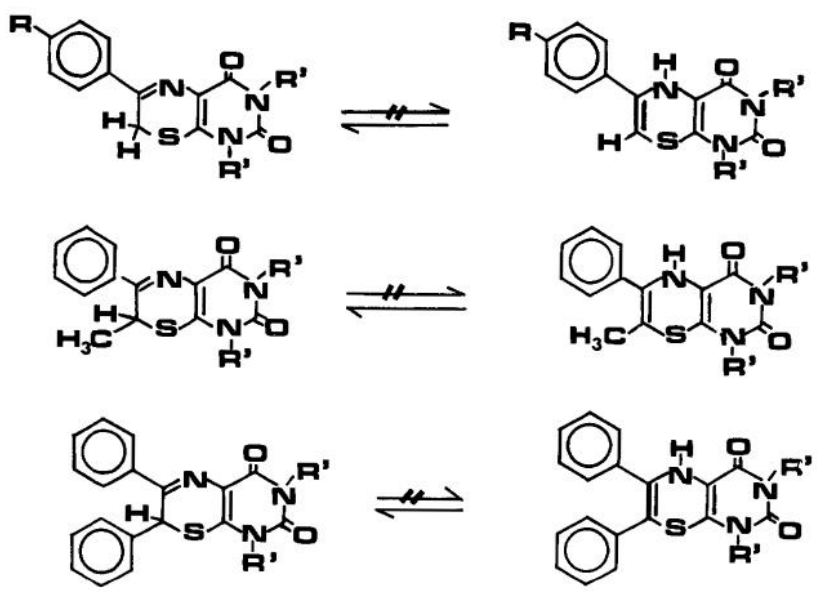


TABLE I: (nmr data & values)

3a: yellow needles, m.p. 305° ,	nmr:(DMSO)	11.0 (N-H), 10.6(N-H), 7.2-7.5 ($5H_{arom.}$)
$C_{12}H_9N_3O_2S$, mass:259 M^+		3.8 (CH_2)
3b: yellow needles, m.p. 241° ,	nmr: ($CDCl_3$)	7.2-7.6 ($5H_{arom.}$) , 3.52 ($N-CH_3$),
$C_{14}H_{13}N_3O_2S$, mass:305 M^+		3.46 ($N-CH_3$), 3.8 (CH_2)
3c: yellow needles , m.p. 310° ,	nmr: (DMSO)	11.5(N-H), 11.1(N-H), 7.8 ($4H_{arom.}$),
$C_{12}H_8N_3O_2SBr$, mass:338 M^+		3.8 (CH_2)
3d: yellow needles, m.p. 217° ,	nmr: ($CDCl_3$)	7.8 ($4H_{arom.}$) , 3.52 ($N-CH_3$), 3.46 ($N-CH_3$),
$C_{14}H_{12}N_3O_2S$ Br , mass:366 M^+		3.75 (CH_2)
4a: yellow needles , m.p. 212°,	nmr: (DMSO)	11.5 (N-H), 11.2(N-H), 7.3-7.9 ($10H_{arom.}$)
$C_{18}H_{13}N_3O_2S$, mass: 335 M^+		6.0 (C-H)
4b: yellow needles , m.p. 265°,	nmr:($CDCl_3$)	7.0 - 7.6 (10 $H_{arom.}$), 5.5 (C-H) , 3.5($N-CH_3$),
$C_{20}H_{17}N_3O_2S$, mass: 363 M^+		3.4 ($N-CH_3$)
4c: yellow needles , m.p. 272°,	nmr:(DMSO)	11.5(N-H), 11.2(N-H), 7.5-8.3 ($5H_{arom.}$) ,
$C_{13}H_{11}N_3O_2S$, mass:273 M^+		4.8 (C-H, q), 1.36 (CH_3, d)
4d: yellow needles , m.p. 195° ,	nmr:($CDCl_3$)	7.4-8.1 ($5H_{arom}$), 3.55($N-CH_3$), 3.46($N-CH_3$),
$C_{15}H_{15}N_3O_2S$, mass: 301 M^+		4.45 (C-H, q), 1.4 (CH_3, d)

We are currently investigating the redox reactions of these compounds for further elucidation of their properties as sulfur analogs of dihydropteridines. We have studied the formation of pyrimido[4.5-b][1.4]thiazine radicals by electron spin resonance. The structure of these radicals will be discussed in another paper.[11]

REFERENCES:

1) H. Fenner : Arzneimittel-Forsch. 20, 1815 (1970)
2) H. Fenner : Tetrahedron Letters 1970, 617
3) H. Fenner, S. Ghisla and P. Hemmerich : unpublished results
4) A. Ehrenberg, P. Hemmerich, F. Müller and W. Pfleiderer:Eur. J. Biochem. 16, 584 (1970)
5) F. L. Rose :J. Chem. Soc. 1952 , 3448
6) M. Ishidate and H. Yuki : Chem. and Pharm. Bull. (Japan) 1960 , 131
7) E. C. Taylor and E. E, Garcia : J. Org. Chem. 29 , 2121 (1964)
8) T. S. Safonova and M. P. Nemeryuk :Khim. geterotsikl. Soed. 1, 149 (1965)
9) M. P. Nemeryuk and T. S. Safonova : ibid. 3 , 470 (1966)
10) parts of this paper have been presented to the "Third Intern. Congr. of Heterocycl. Chem.", Sendai/Japan - Aug. 23-27 , 1971
11) H. Fenner, H. Motschall, S. Ghisla and P. Hemmerich:Helv. chim. Acta , in prep.