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Thieno[2,3-*d*]pyrimidines as Potential Chemotherapeutic Agents

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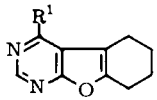
A series of new thieno[2,3-*d*]pyrimidine derivatives with a carbocyclic ring fused at positions 5 and 6 have been synthesised in order to study their pesticidal activity. Some of the compounds exhibit significant biological activity.

Thieno[2,3-d]pyrimidine als potentielle Chemotherapeutika

Eine Reihe von neuen Thieno[2,3-d]pyrimidin-derivaten mit einem in 5,6-Position ankondensierten carbozyklischem Ring wurde synthetisiert und auf pestizide Aktivität untersucht. Einige der einem Screening unterworfenen Verbindungen zeigten signifikante biologische Wirksamkeit.

Frequently, pyridine ring participates in polycyclic heterocyclic systems of biological significance. Several furo[2,3-d]pyrimidines are known[1] to exhibit relaxant properties on smooth muscles with bronchial dilation and lowering of the arterial pressure. *Schmidt*[2] et al. have described the antibacterial, antiparasitic and antimalarial activities of thieno[2,3-d]pyrimidines **2b**. *Rosowsky*[3] et al. have recently reported the antimalarial and anti-tumor activities of the title compounds. It was pertinent therefore, to synthesise several possible derivatives of ring system **2a** as bioactive substances.



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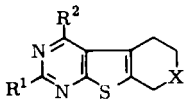

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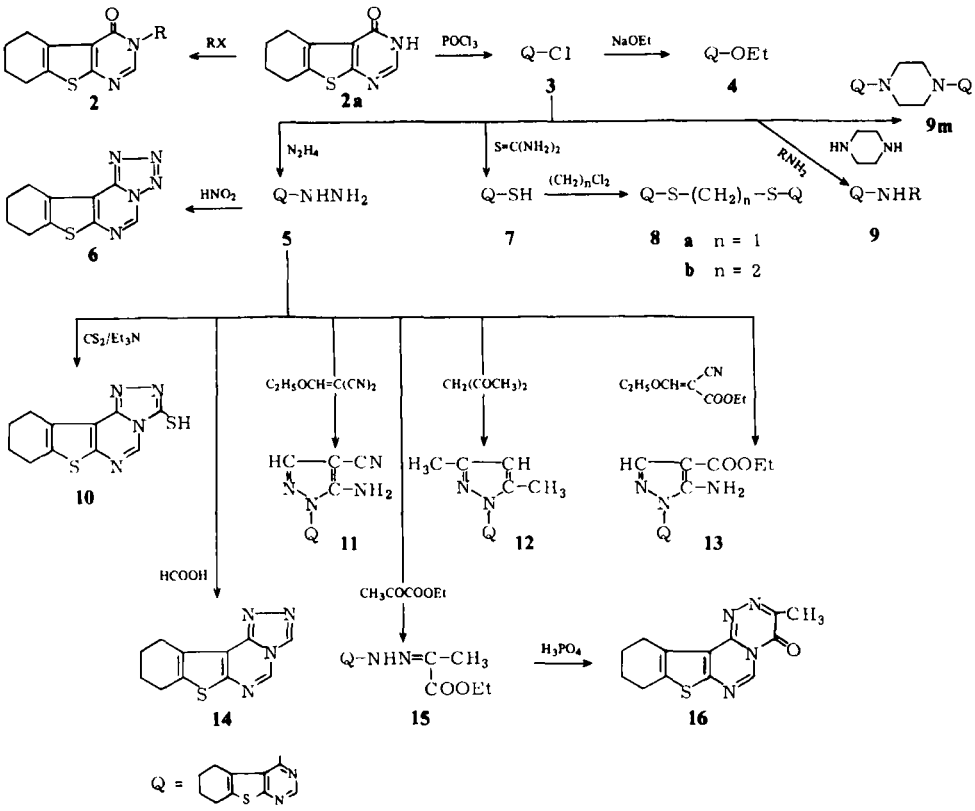
a X = CH_2; R^1 = H; R^2 = OH

b X = S or NH

Although considerable work has been done on the chemistry of various other classes of thieno[2,3-d]pyrimidines[4] but hitherto a systematic investigation of the compounds of the ring system **2a** with active moieties as pesticides has not been made. The interesting bioresponses of furo[2,3-d]pyrimidines **1** and thieno[2,3-d]pyrimidines **2** encouraged for more extensive synthetic efforts.



The key intermediate for the synthesis of thieno[2,3-d]pyrimidines is 2-amino-3-carbethoxy-4,5,6,7-tetrahydrothianaphthene, readily synthesised[5] by the condensation of cyclohexanone with ethyl cyanoacetate and sulphur using morpholine as catalyst. Treatment of this compound with excess of formamide at reflux for 4 hrs afforded 4-oxo-5,6,7,8-tetrahydrothianaphtheno[2,3-d]pyrimidine (**2a**). The 3-N-methyl derivative **2** was prepared by the reaction of **2a** with methyl iodide in alkaline medium. Treatment of **2a** with $POCl_3$ yielded 4-chloro derivative **3** which served as a facile intermediate for nucleophilic substitution reactions with alcohol, hydrazine hydrate and amines. The 4-hydrazino derivative **5** was further cyclised into the higher polycyclic compounds **6**, **10**, **14** by reaction with nitrous acid, CS_2 and formic acid respectively. Reaction of **3** with thiourea yielded 4-mercapto derivative **7** which was converted into sulphides **8**,**a**,**b** by the reaction of different alkyl halides. Condensation and cyclisation of **5** with ethoxymethylenemalononitrile, acetyl acetone, ethoxymethyleneethylcyanoacetate yielded corresponding 4-pyrazolothianapththeno[2,3-d]-pyrimidines **11**, **12**, **13** resp. Ethylpyruvate condensed with **5** yielded the correspon-

ding hydrazone **15** which cyclised into triazine derivative **16** with polyphosphoric acid. NMR spectrum of this compound showed two singlets at 8.56 and 2.52 ppm due to CH and N-CH_3 protons resp. CH_2 protons of 5 and 8 positions resonate as multiplet at 2.92 and 3.28 ppm resp. as they are situated in different environments. 6 and 7 CH_2 protons appear as multiplet centered at 1.92 ppm.

NMR spectrum of s-triazoline-3'-thiono[1',5'-c]5,6,7,8-tetrahydrothianaphtheno[2,3-d]pyrimidine **(10)** showed two singlets at 7.3 and 12.1 ppm due to CH and NH protons. The latter peak disappeared on deuteration. Two multiplets at 1.53 and 2.37 ppm are attributed to 6.7 and 5.8 methylene protons resp.

4-(4'-Cyano-5'-aminopyrazolo-1'-yl)-5,6,7,8-tetrahydrothianaphtheno[2,3-d]pyrimidine **(11)** showed two singlets at 8.96 and 7.86 ppm due to CH proton of pyrimidine and pyrazole rings resp. The third singlet appeared at 7.0 ppm which was attributed to -NH_2 protons and it disappeared on deuteration. 5 and 8 CH_2 protons signals as multiplets appeared at 2.92 and 2.36 ppm resp. while 6.7-CH_2 protons resonated at 1.76 ppm as multiplet.

NMR spectral pattern of 4-(4'-carbethoxy-5'-aminopyrazolo-1'-yl)-5,6,7,8-tetrahydrothianaphtheno[2,3-d]pyrimidine **(13)** was very similar to **11** except the NH signal which appeared in low field due to intramolecular hydrogen bonding. A quartet centered at 4.29 and a triplet at 1.35 ppm are attributed to CH_2 and CH_3 protons of carbethoxy group.

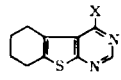
Pesticidal Activity: Compounds were assayed for herbicidal and fungicidal activities by foliage spray and soil drench methods. After 14 days phytotoxicity was rated on a scale of 0 to 11, where 0 corresponds to no injury and 11 implies death of the plants. Stunting was rated on a scale of 1(slight) to 9(severe). Compounds with phytotoxicity ratings of at least 10 or with stunt ratings of at least 8 are retested at lower concentrations.

In the pre and post emergence tests, seeds were planted and treated with test chemical. After two weeks percent control was estimated and other informations (e.g., phytotoxicity, growth regulation etc.) were noted. Compounds that showed 50% pre-emergence control and 80% post-emergence were retested at lower concentrations.

For bactericidal screening compounds were incorporated into a nutrient medium to produce a concentration of 64 ppm. The resulting plate was inoculated with organism and incubated for 48 hrs. Growth inhibition was rated by visual comparison with growth on untreated agar.

Only 12 compounds were screened for their pesticidal activities of which compound **3** was 100 % active against Pigweed and with 85 % formative effect against Wild mustard at 8lb/acre concentration but was inactive at lower concentration. None of the compounds exhibited viruscidal and insecticidal activities. Compounds **7**, **5**, **9h**, **9i** and **9k** showed 100 % bactericidal activity against Streptococcus faecalis at 64 ppm concentration but were inactive at lower concentration except compound **5** which was 100 % active at 32 ppm concentration. Only compounds **9g** and **9h** demonstrated fungicidal activity with phytotoxicity rating of **9i** and **9j** resp. against Pythium while latter was also active against Rhizoctonia solani with phytotoxicity of **9j**. It is evident from the screening results that compounds with a fluoro substituent at o- and m-positions exhibited pesticidal activity while p-substitution caused inactivity. An increase in the number of halogen atoms (**9e** and **9g**) enhanced the activity.

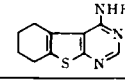
Table 1: *Pesticidal activity*



S.No.	X	Herbicidal activity (%) at 8 lb/acre concentration		Bactericidal activity (%)		Fungicidal activity at 64 ppm concentration	
		Pw	Wm	Sf 64 ppm	Sf 32 ppm	Rs	Py
3	Cl	100	85F	–	–	0	0
7	SH	0	0	100	0	0	0
5	$NHNH_2$	0	0	100	100	0	0
9e	2-Cl-$C_6H_4CH_2NH$	0	0	0	0	0	0
9g	2,4-$Cl_2C_6H_3CH_2$ NH	0	0	0	0	0	PH10
9a		0	0	0	0	0	0
9c	$HOCH_2CH_2NH$	0	0	0	0	0	0
9d	$(HOCH_2CH_2)_2N \cdot HCl$	0	0	0	0	0	0
9h	2-F-C_6H_4NH	0	0	100	0	PH11	PH11
9i	3-F-C_6H_4NH	0	0	100	0	0	0
9j	4-F-C_6H_4NH	0	0	0	0	0	0
9k	$(C_2H_5)_2NC_6H_4NH$	0	0	100	0	0	0

Pw = Pigweed, Wm = Wild mustard, Sf = Streptococcus faecalis, Rs = Rhizoctonia solani, Py = Pythium

Table 2: *4-Alkyl/arylamino-5,6,7,8-tetrahydrothianaphtheno[2,3-d]pyrimidines* 9



S.No. 9	R	Yield (%)	M. P. °C	Emperical Formula[+]
a	β-Pyrrolidinomethyl-	75	90	$C_{16}H_{22}N_4S$
b	γ-Morpholinopropyl-	93	135–136	$C_{17}H_{24}N_4OS$
c	β-Hydroxyethyl-	90	122	$C_{12}H_{15}N_3OS$
d	Bis(β-hydroxyethyl)-	85	159	$C_{14}H_{19}N_3O_2S \cdot HCl$
e	2-Chlorobenzyl-	86	190	$C_{17}H_{16}N_3ClS$
f	4-Chlorobenzyl-	82	181	$C_{17}H_{16}N_3ClS$
g	2,4-Dichlorobenzyl-	80	161	$C_{17}H_{15}N_3Cl_2S$
h	2-Fluorophenyl-	90	138	$C_{16}H_{14}FN_3S$
i	3-Fluorophenyl-	75	119	$C_{16}H_{14}FN_3S$
j	4-Fluorophenyl-	79	163	$C_{16}H_{14}FN_3S$
k	4-Diethylaminophenyl-	76	162–163	$C_{20}H_{24}N_4S$
l	NHR = Piperidino-	74	88 Rep.m.p.106	$C_{15}H_{19}N_3S$

[+] All the compounds were analysed for C, H & N satisfactorily and crystallised from ethanol and ethanol-water mixture.

Author is thankful to Prof. Dr. *W. Pfleiderer*, University of Konstanz, West Germany for NMR & mass spectra of the compounds and Prof. *R. P. Rastogi* for his encouragements. Thanks are also due to departmental colleagues für discussion and valuable suggestions.

Experimental

All the m. ps. are uncorrected.

4-Oxo-5,6,7,8-tetrahydrothianaphtheno[2,3-d]pyrimidine (2a)

2-Amino-3-carbethoxy-5,6,7,8-tetrahydrothianaphthene[5] was cyclised to the title compound by the procedure reported earlier[6], yield 90 %, m. p. 255–256°, M+, 206.

3-Methyl-4-oxo-5,6,7,8-tetrahydrothianaphtheno[2,3-d]pyrimidine (2)

To a solution of 0.8 g **2a** in 5 ml 4 % sodium hydroxide, 2 ml methyl iodide was added and the mixture was stirred at room temp. for 3 hrs. A white solid separated out which was washed with water and crystallised with water-methanol mixture, yield 77.2 %, m. p. 263° Lit.[7]: 140°, M^+ 220.

4-Chloro-5,6,7,8-tetrahydrothianaphtheno[2,3-d]pyrimidine (3)

To a mixture of 6.0 g **2a** 7 ml dimethylaniline and 30 ml $POCl_3$ was added and refluxed for 4.5 hrs. Excess of $POCl_3$ and dimethylaniline were distilled under reduced pressure. The residue was poured on ice cautiously and neutralised with sodium carbonate solution. A blew-gray precipitate separated out which was washed with water and crystallised with ethanol as white shining needles, yield 3.9 g (60 %), m. p. 99–100°, M^+ 224.

4-Ethoxy-5,6,7,8-tetrahydrothianaphtheno[2,3-d]pyrimidine (4)

A solution of 0.4 g **3** in sodium ethoxide (prepared from 0.23 g Na in 30 ml of ethanol) was refluxed for 12 hrs and solvent was removed under reduced pressure. A white solid separated in quantitative yield and crystallised with water-ethanol mixture, M^+ 233, m. p. 45° lit.[7]: 109°.

4-Hydrazino-5,6,7,8-tetrahydrothianaphtheno[2,3-d]pyrimidine (5)

It was prepared by the reaction of 1.0 g **3** with 3 ml 98 % hydrazine hydrate in 30 ml ethanol by the procedure reported earlier[7] in 75.5 % yield, m. p. 184°.

Tetrazolo[1',5'-c]5,6,7,8-tetrahydrothianaphtheno[2,3-d]pyrimidine (6)

Method A: A solution of 0.63 g **5** in 10 ml 50 % acetic acid was treated with a solution of 0.5 g sodium nitrite in little water dropwise. The precipitate thus obtained was washed with water and crystallised with ethanol, yield 44.8 %, m. p. 132° lit.[7]: 138°.

Method B: The title compound was also prepared by refluxing equimolar amount of **3** with sodium azide for 12 hrs in ethanol. On cooling, a precipitate was obtained which was crystallised with ethanol. The m. p. and Rf value of the product obtained by method A or B were found to be same.

4-Mercapto-5,6,7,8-tetrahydrothianaphtheno[2,3-d]pyrimidine (7)

A mixture of 1.0 g **3** and 0.5 g thiourea in 25 ml of ethanol was refluxed for 2.5 hrs. Excess of the solvent was removed under reduced pressure and the residue was cooled and filtered. The crude product was crystallised with ethanol, yield 0.88 g, M^+ 222, m. p. 241–243°, lit.[7]: 240°.

Methylene bis[5,6,7,8-tetrahydrothianaphtheno[2,3-d]pyrimidine-4-yl]sulphide (8a)

A solution of 0.5 g 7 in 2 ml of 4 % sodium hydroxide was stirred overnight with 0.5 ml methylenechloride in presence of little ethanol and the solid which separated was washed with water and crystallised with DMF-water mixture, yield 30 %, m. p. 233°, M^+ 456.

Ethylene bis[5,6,7,8-tetrahydrothianaphtheno[2,3-d]pyrimidine-4-yl]sulphide (8b)

It was prepared as described in the preceding experiment by the reaction of 0.2 g 7 with 0.3 ml ethylenechloride, stirring for two days at room temp. The crude product was crystallised with methanol water mixture, yield 0.1 g, M^+ 470.

4-Morpholino-5,6,7,8-tetrahydrothianaphtheno[2,3-d]pyrimidine

To a solution of 0.2 g 3 in 10 ml absol. ethanol 0.12 g morpholine were added. The mixture was refluxed for 18 hrs. The excess of solvent was removed under reduced pressure and a brown solid separated, which was washed with water and crystallised with water-ethanol mixture, yield 0.18 g, M^+ 275, m. p. 99–100°, lit.[7]: 128°.

Other compounds in this series are prepared by a similar procedure and are listed in table 2.

Bis[5,6,7,8-tetrahydrothianaphtheno[2,3-d]pyrimidine-4-yl]piperazine (9m)

A solution of 2.0 g 3 in 15 ml absol. ethanol was treated with 0.08 g piperazine and the resulting mixture was refluxed for 12 hrs. The white precipitate thus obtained was washed with water and crystallised with water-formamide mixture, yield 0.15 g, M^+ 462, m. p. 98°.

s-Triazoline-3-thiono[1',5'-c]5,6,7,8-tetrahydrothianaphtheno[2,3-d]pyrimidine (10)

A mixture of 0.33 g 5 and 1.1 ml carbondisulphide and 0.1 ml triethylamine in 6 ml n-butanol was refluxed for 16 hrs and then cooled. An yellow crystalline solid separated out. The filtrate on further concentration afforded an additional amount. The crude product was extracted with ether, dried and filtered. The ether was distilled and the solid thus obtained was analytically pure, M^+ 262, m. p. 275–277°, yield 60 mg (15 %).

4-[4'-Cyano-5'-aminopyrazol-1'-yl]-5,6,7,8-tetrahydrothianaphtheno[2,3-d]pyrimidine (11)

A mixture of 0.66 g 5 and 0.37 g ethoxymethylenemalononitrile in 25 ml ethanol was refluxed for 14 hrs. At the end of reaction, ethanol was removed under reduced pressure. A grayish solid separated out which was washed with water and crystallised with methanol, yield 0.3 g (33 %). M^+ 296, m. p. 185°.

4-[4'-Carbethoxy-5'-aminopyrazolo-1'-yl]-5,6,7,8-tetrahydrothianaphtheno[2,3-d]pyrimidine (13)

It was prepared from 0.44 g 5 and 0.34 g ethoxymethylene ethylcyanoacetate following the procedure described in the earlier experiment, yield 0.33 g (45 %), M^+ 343, m. p. 96°.

4-[3',5'-Dimethylpyrazol-1'-yl]-5,6,7,8-tetrahydrothianaphtheno[2,3-d]pyrimidine (12)

To a solution of 0.2 g 5 in 15 ml glacial acetic acid, 0.5 ml acetyl acetone was added. The resulting mixture was refluxed for 12 hrs and the excess of the acid removed under reduced pressure. The precipitate was crystallised with alcohol, yield 0.1 g, M^+ 284, m. p. 152°.

s-Triazolo[1',5'-c]-5,6,7,8-tetrahydrothianaphtheno[2,3-d]pyrimidine (**14**)

A mixture of 0.6 g **5** in 15 ml of formic acid was refluxed for 2 hrs and the excess of acid was removed under reduced pressure. The white solid which separated was washed with methanol. The crude product was extracted with ether which gave a white solid on removal of the excess of the solvent. The product was then crystallised with methanol, yield 0.26 g (44.7 %), m. p. 129°, lit.[7]: 300°.

4-Ethylpyruvatehydrazono-5,6,7,8-tetrahydrothianaphtheno-[2,3-d]pyrimidine (**15**)

0.11 g Ethylpyruvate and 0.22 g **5** in 10 ml acetic acid were heated for a few minutes, stirred overnight and placed in a refrigerator. The yellow solid thus separated was crystallised with water-DMF mixture, yield 0.25 g, M^+ 318, m. p. 97°.

6'-Methyl-5'-oxo-1',2',4' triazino[1',6'-c]5,6,7,8-tetrahydrothianaphtheno[2,3-d]pyrimidine (**16**)

0.27 g **15** were suspended in 0.5 g polyphosphoric acid and heated for an hour at 145° C. The reaction mixture was poured on ice and the solution was neutralised with sodium hydrogencarbonate up to pH 4. The brown solid thus obtained was washed with water. The crude product was crystallised with ethanol, yield 20 mg, M^+ 272, m. p. 245°, IR.: 1635 cm^{-1} (C=O).

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