Synthesis of 3-Substituted-4-phenyl-2-thioxo-1,2,3,4,5,6,7,8-octahydrobenzo[4,5]thieno[2,3-*d*]pyrimidines [1]

Salvador Vega*, Javier Alonso, Juan A. Díaz and Francisco Junquera

Instituto de Química Médica, C.S.I.C.,
Juan de la Cierva, 3, 28006-Madrid, Spain

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The reactions between 3-benzoyl-2-isothiocyanato-4,5,6,7-tetrahydrobenzo[*b*]thiophene and hydrazine or primary amines have been studied. The products obtained were identified as derivatives of 4-phenyl-2-thioxo-2,3,5,6,7,8-hexahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine. Their easy reduction with sodium borohydride provided a useful method for the synthesis of 3-substituted-4-phenyl-2-thioxo-1,2,3,4,5,6,7,8-octahydrobenzo[4,5]thieno[2,3-*d*]pyrimidines. Both kind of compounds were evaluated as potential analgesic, anti-inflammatory and anti-arthritic agents.

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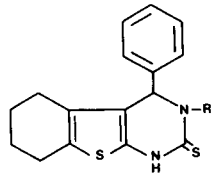
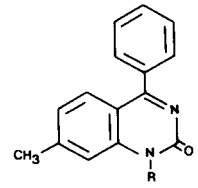
In our search for novel heterocyclic compounds with biological activity, we became interested in the synthesis of 3-substituted-4-phenyl-2-thioxo-1,2,3,4,5,6,7,8-octahydrobenzo[4,5]thieno[2,3-*d*]pyrimidines **1**, since these compounds present a great similarity with several 4-phenyl-2(1*H*)-quinazolinone derivatives **2** in which important non-steroidal anti-inflammatory activity has been found [2,3]. On the other hand, a few structural analogues of **1** have been prepared and shown to have anti-inflammatory, analgesic and antithrombosis actions [4,5].

In the present paper we describe a series of these new thieno pyrimidine derivatives **1** and the study of some intermediates involved in their synthesis.



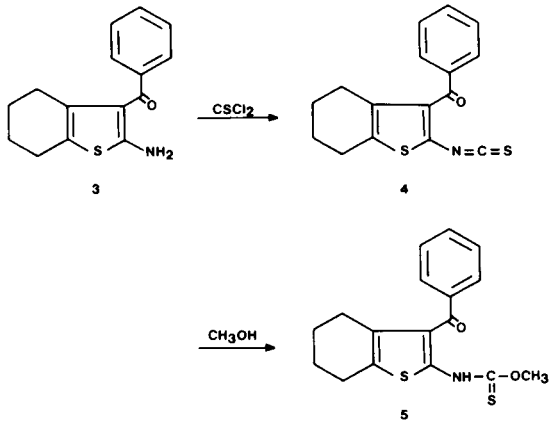
1



2

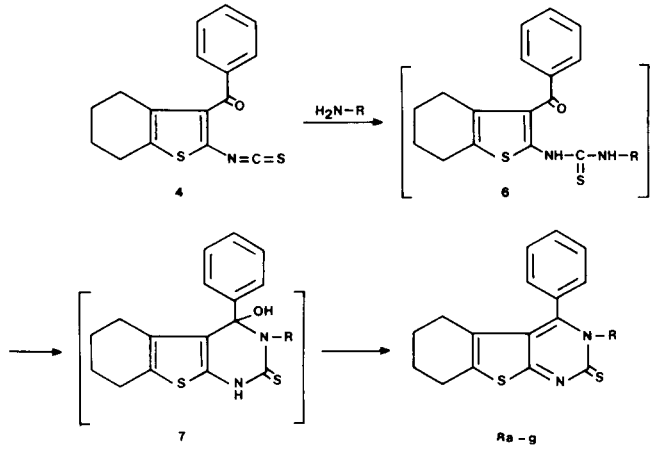
The starting material, 2-amino-3-benzoyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene **(3)** (Scheme 1), was readily prepared by the method described by Gewald [6]. Reaction of this compound with thiophosgene in chloroform, in a manner analogous to that reported for the synthesis of 2-benzoyl phenyl isothiocyanate [7], gave 3-benzoyl-2-isothiocyanato-4,5,6,7-tetrahydrobenzo[*b*]thiophene **(4)** in 80% yield [8]. Compound **4** was easily isolated from the crude reaction product by flash chromatography as a crystalline solid which turned out to be sensitive to sunlight and high temperature; this, however, did not prevent its manipulation and spectroscopic analysis. By reaction with hot methanol it was converted to thiocarbamate **5** in practical quantitative yield.

Scheme 1



When **4** and hydrazine (Scheme 2) were stirred at room temperature in dioxane, work-up of the reaction mixture yielded a yellow solid (90%) which was shown not to be the expected 3-amino-4-hydroxy-4-phenyl-2-thioxo-1,2,3,4,5,6,-7,8-octohydrobenzo[4,5]thieno[2,3-*d*]pyrimidine **(7)** [8,9].

Scheme 2

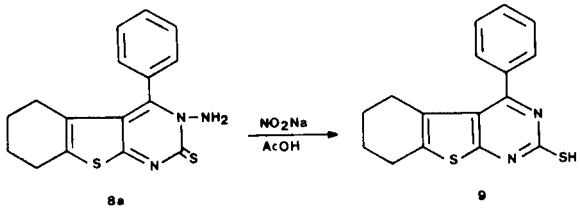


The thienopyrimidine **7** was initially ruled out as the structure of the isolated product by an infrared spectrum which indicated the absence of the hydroxyl function. However, the loss of a molecule of water, evidenced by the mass spectrum (m/z 313) and elemental analysis, and the

presence of a signal due to two NH protons at δ 6.55 in the ^{1}H nmr spectrum permitted the identification of the new product as the 3-amino-4-phenyl-2-thioxo-2,3,5,6,7,8-hexahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine (**8a**), apparently formed by dehydration of intermediate **7**. Several examples of this type of dearomatizations have been described in both benzene and thiophene series [10,5], although in these cases, the reactions were carried out under higher temperature conditions.

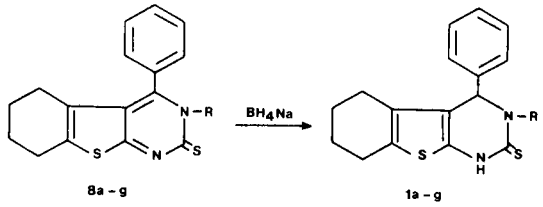
The above structural assignment was firstly confirmed by deamination of **8a** with sodium nitrite and acetic acid [11] to give 4-phenyl-2-mercapto-5,6,7,8-tetrahydrobenzo-[4,5]thieno[2,3-*d*]pyrimidine (**9**) (Scheme 3) and secondly, by its reduction to the desired 3-amino-4-phenyl-2-thioxo-1,2,3,4,5,6,7,8-octahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine (**1a**) (Scheme 4), with sodium borohydride in methanol-chloroform according to the method reported by Sternbach for the preparation of 3-substituted-2-oxo-2,3-dihydroquinazolines [10].

Scheme 3



8a 9

Scheme 4



8a-g 1a-g

The substitution of hydrazine by primary amines in the reaction of isothiocyanate **4** (Scheme 2) gave, under similar reaction conditions, the intermediate hexahydrobenzothieno[2,3-*d*]pyrimidine derivatives **8b-g** in good yields.

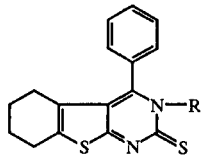
These compounds were easily converted to the final 3-substituted-4-phenyl-2-thioxo-1,2,3,4,5,6,7,8-octahydrobenzo[4,5]thieno[2,3-*d*]pyrimidines **1b-g** by reduction with sodium borohydride (Scheme 4).

The structures of these new compounds were also confirmed by elemental and spectroscopic analysis. Tables 1 and 3 list the yields and the physical and analytical data of all the products synthesized. Their main spectroscopic characteristics are summarized in Tables 2 and 4.

Compounds **1a-g** and **8a-g** were tested for their potential analgesic, anti-inflammatory and anti-arthritic activities; the pharmacological results will be published elsewhere.

Table 1

Physical and Analytical Data of Compounds **8**



No.	R	Yield (%)	Mp (°C) Solvent	Formula	Analysis Calcd./Found (%) C	H	N	S
8a	Amino	90	211-213 Benzene	$C_{16}H_{15}N_3S_2$	61.34 61.38	4.79 4.60	13.41 13.04	20.45 20.99
8b	Phenyl	86	238-241 Ethanol	$C_{22}H_{18}N_2S_2$	70.58 70.28	4.81 4.97	7.48 7.78	17.13 16.97
8c	Benzyl	55	205-207 Ethanol	$C_{23}H_{20}N_2S_2$	71.13 71.06	5.15 5.25	7.21 7.30	16.49 16.39
8d	β-Phenylethyl	67	218-221 [a]	$C_{24}H_{22}N_2S_2 \cdot H_2O$	68.57 68.38	5.71 5.21	6.66 6.38	15.24 15.42
8e	Morpholinoethyl	88	208-210 Ethanol	$C_{22}H_{25}N_3OS_2$	64.23 63.93	6.08 6.23	10.21 10.01	15.57 15.36
8f	Morpholinopropyl	84	238-240 [a]	$C_{23}H_{27}N_3OS_2$	64.94 64.71	6.35 6.29	9.88 9.89	15.05 15.22
8g	Pyrrolidinoethyl	85	207-209 Ethanol	$C_{22}H_{25}N_3S_2$	66.83 66.61	6.32 6.33	10.63 10.40	16.20 16.66

[a] Purified by column chromatography on silica gel. Eluant chloroform-ethanol 9:1.

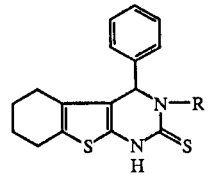
Table 2

IR and ^{1}H-NMR Data of Compounds **8**

No	√ (cm^{-1})	Solvent	∂ (ppm)
8a	1570	$CDCl_3$	1.65 (s, 6H, $3CH_2$), 2.65 (t, 2H, CH_2), 6.55 (s, 2H, NH_2), 7.60 (s, 5H, ArH)
8b	1570	$CDCl_3$	1.50 (m, 6H, $3CH_2$), 2.70 (t, 2H, CH_2), 7.20 (m, 10H, ArH)
8c	1570	$CDCl_3$	1.60 (m, 6H, $3CH_2$), 2.65 (t, 2H, CH_2), 5.90 (s, 2H, CH_2), 6.80 (m, 10H, ArH)
8d	1575	$CDCl_3$	1.50 (m, 6H, $3CH_2$), 2.65 (d, 2H, CH_2), 3.05 (t, 2H, CH_2), 4.60 (t, 2H, CH_2), 7.40-8.50 (m, 10H, ArH)
8e	1580	$CDCl_3$	1.60 (m, 6H, 3 CH_2), 2.25 (t, 4H, morpholine), 2.70 (m, 4H, $2CH_2$), 3.50 (t, 4H, morpholine), 4.60 (t, 2H, CH_2), 7.40 (m, 5H, ArH)
8f	1575	$CDCl_3$	1.00-1.60 (m, 10H, $5CH_2$), 1.75 (t, 4H, morpholine), 2.15 (t, 2H, CH_2), 3.00 (t, 4H, morpholine), 2.15 (t, 2H, CH_2), 3.00 (t, 4H, morpholine), 4.00 (t, 2H, CH_2), 7.00 (m, 5H, ArH)
8g	1575	$CDCl_3$	1.55 (m, 10H, $5CH_2$), 2.35 (m, 4H, $2CH_2$), 2.65 (t, 2H, CH_2), 2.85 (t, 2H, CH_2), 4.60 (t, 2H, CH_2), 7.45 (m, 5H, ArH)

Table 3

Physical and Analytical Data of Compounds **1**



No.	R	Yield (%)	Mp (°C) Solvent	Formula	Analysis Cacld./Found (%) C	H	N	S
1a	Amino	85	211-214 Ethanol	$C_{16}H_{17}N_3S_2$	60.95 60.88	5.39 5.47	13.33 13.38	20.31 20.27
1b	Phenyl	84	~ 252 dec Dioxane	$C_{22}H_{20}N_2S_2$	70.21 70.01	5.31 5.42	7.44 7.40	17.02 17.17
1c	Benzyl	82	224-226 Acetonitrile	$C_{23}H_{22}N_2S_2$	70.76 70.91	5.64 5.69	7.17 7.15	16.43 16.25
1d	β-Phenylethyl	75	232-234 Ethanol	$C_{24}H_{24}N_2S_2$	71.28 71.50	5.94 5.89	6.93 7.05	15.84 15.56
1e	Morpholinoethyl	92	202-204 Ethanol	$C_{22}H_{27}N_3OS_2$	63.92 64.04	6.53 6.72	10.16 9.91	15.49 15.10
1f	Morpholinopropyl	90	215-217 Ethanol	$C_{23}H_{29}N_3OS_2$	64.63 64.82	6.79 6.74	9.83 9.82	14.98 15.00
1g	Pyrrolidinoethyl	92	198-200 Acetonitrile	$C_{22}H_{27}N_3S_2$	66.49 66.53	6.80 7.00	10.57 10.81	16.14 15.66

Table 4

IR and ^{1}H-NMR Data of Compounds **1**

No	√ (cm^{-1})	Solvent	δ (ppm)
1a	3150	DMSO-d_6	1.60 (m, 6H, $3CH_2$), 2.40 (m, 2H, CH_2), 5.25 (s, 2H, NH_2), 5.75 (s, 1H, CH) , 7.30 (d, 5H, ArH), 11.00 (s, 1H, NH)
1b	3140	DMSO-d_6	1.55 (m, 6H, $3CH_2$), 2.40 (m, 2H, CH_2), 5.75 (s, 1H, CH), 7.10 (m, 10H, ArH), 11.20 (s, 1H, NH)
1c	3300	$CDCl_3$	1.60 (m, 6H, $3CH_2$), 2.50 (t, 2H, CH_2), 3.90 (d, 1H, CH_2), 5.30 (s, 1H, CH), 6.35 (d, 1H, CH), 7.30 (d, 10H, ArH), 9.70 (s, 1H, NH)
1d	3150	$CDCl_3$	1.65 (m, 6H, $3CH_2$), 2.50 (m, 2H, CH_2), 3.25 (m, 2H, CH_2), 4.50 (m, 2H, CH_2), 5.00 (s, 1H, CH), 7.20 (d, 10H, ArH), 9.15 (s, 1H, NH)
1e	3120	$CDCl_3$	1.65 (s, 6H, $3CH_2$), 2.15-3.05 (m, 8H, 4CH2), 3.35 (m, 1H, CH), 3.70 (t, 4H, $2CH_2$), 4.40 (m, 1H, CH), 5.65 (s, 1H, CH), 7.30 (s, 5H, ArH), 9.35 (s, 1H, NH)
1f	3145	$CDCl_3$	1.60 (m, 6H, $3CH_2$), 1.90-2.70 (m, 8H, 4CH2), 3.25 (m, 1H, CH), 3.65 (t, 4H, 2CH2), 4.25 (m, 1H, CH), 5.50 (s, 1H, CH), 7.30 (s, 5H, ArH), 9.15 (s, 1H, NH)
1g	3100	$CDCl_3$	1.40-4.65 (m, 20H, $10CH_2$), 5.60 (s,1H, CH), 7.25 (s, 5H, ArH), 9.50 (s, 1H, NH)

EXPERIMENTAL

All melting points (uncorrected) were determined using a Gallenkamp capillary apparatus. The ir spectra were recorded on a Perkin Elmer 257 instrument. The ^{1}H nmr spectra were measured with a Varian EM-390 and a Bruker AM-200 spectrometers using TMS as internal standard. The purity of compounds was verified by thin-layer chromatography (tlc) which was run on silica gel GF_{254} (Merck) with cyclohexane-ethyl acetate mixtures (2:1 and 1:1, v/v respectively) as eluents.

3-Benzoyl-2-isothiocyanato-4,5,6,7-tetrahydrobenzo[*b*]thiophene (**4**).

To a stirred mixture of thiophosgene (10.0 g, 0.087 mole), chloroform (20 ml), water (40 ml) and calcium carbonate (12.5 g) a solution of 2-amino-3-benzoyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene (**3**) (15.4 g, 0.060 mole) in chloroform (70 ml) was added dropwise at 10-15° over a one hour period. After stirring the mixture at this temperature for 4 hours it was filtered and the filtrate was separated. The organic layer was washed with water, dried (magnesium sulfate) and evaporated. The residue was purified by flash chromatography on silica gel 60 using chloroform as eluent to give **4** (14.4 g, 80%) as a yellow oil which crystallized on standing, mp 59-61°; ir (nujol): 2100 (-N=C=S), 1650 (C=O); ms: m/z 299 (M^+); ^{1}H nmr (deuteriochloroform): δ 1.80 (m, 4H), 2.55 (m, 4H), 7.35-8.00 (m, 5H).

3-Amino-4-phenyl-2-thioxo-2,3,5,6,7,8-hexahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine (**8a**).

To a stirred mixture of aqueous hydrazine-hydrate (80%) (8.75 g, 0.17 mole) and dioxane (70 ml) a solution of isothiocyanate **4** (9.00 g, 0.03 mole) in dioxane (30 ml) was added at 10° during 30 minutes. The reaction mixture was stirred at this temperature for 30 minutes and then it was poured onto cold water (250 ml). The yellow precipitate formed was collected by filtration, washed with water and dried to yield 8.5 g (90%) of 3-amino-4-phenyl-2-thioxo-2,3,5,6,7,8-hexahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine (**8a**). For analytical and spectroscopic data see Tables 1 and 2.

4-Phenyl-2-mercapto-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]-pyrimidine (**9**).

The above compound **8a** (3.1 g, 0.01 mole) was suspended in glacial acetic acid (30 ml) and sodium nitrite (0.7 g, 0.01 mole) in water (10 ml) was added. The reaction mixture was stirred at room temperature for 20 hours and the yellow crystalline solid formed was filtered, washed with water and dried to give 2.1 g (71%) of **9**, mp 215-217° (chloroform-hexane); ^{1}H nmr (deuteriochloroform): 1.40-2.20 (m, 6H), 2.80 (t, 2H), 7.40 (s, 5H).

Anal. Calcd. for $C_{16}H_{14}N_2S_2$: C, 64.42; H, 4.69; N, 9.39; S, 21.47. Found: C, 64.75; H, 4.46; N, 9.43; S, 21.13.

4-Phenyl-2-thioxo-2,3,5,6,7,8-hexahydrobenzo[4,5]thieno[2,3-*d*]-pyrimidines **8b-g**.

General Method.

To a stirred solution of isothiocyanate **4** (2.00 g, 6.68 mmoles) in dioxane (20 ml) a solution of the corresponding amine (0.014 mole) in dioxane (15 ml) was added dropwise at 10°. After stirring for one hour at room temperature, the mixture was poured onto cold water and the precipitate formed was filtered, washed with water and dried. All the pyrimidine derivatives **8b-g** were solid compounds which were recrystallized from the apropriate solvent or chromatographed on silica gel using a mixture of chloroform-ethanol 9:1. Their physical, analytical and spectroscopic data are listed in Tables 1 and 2.

4-Phenyl-2-thioxo-1,2,3,4,5,6,7,8-octahydrobenzo[4,5]thieno-[2,3-*d*]pyrimidines **1a-g**.

General Method.

To a stirred suspension of the corresponding 3-substituted-hexahydrothieno[2,3-*d*]pyrimidine **8a-g** (2.4 mmoles) in a mixture of methanol-chloroform 1:1 (5 ml) sodium borohydride (90 mg, 2.4

mmoles) was added. The mixture was stirred at room temperature for 45 minutes and poured onto water. The crystalline solid was collected by filtration, washed with water and dried. Recrystallization from the appropriate solvent gave pure thieno[2,3-*d*]-pyrimidines **1a-g**, Tables 3 and 4.

Acknowledgements.

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