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Fused Heterocycles, VI [1]: Reactions of 3-Arylidenechromanones and -1-thiochromanones with Thiourea

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Summary. Reactions of 3-arylidenechromanones (**1** – **4**) and -1-thiochromanones (**5** – **8**) with thiourea gave thiazines (**9** – **16**) under acidic and pyrimidine derivatives (**17** – **21**) under alkaline reaction conditions

Keywords. Benzopyrano[4,3-d]pyrimidines; Benzothiopyrano[4,3-d]pyrimidines; Benzopyrano[4,3-d]-3,1-thiazines; Benzothiopyrano[4,3-d]-3,1-thiazines.

Kondensierte Heterocyclen, VI: Umsetzungen von 3-Arylidenchromanonen und -1-thiochromanonen mit Thioharnstoff

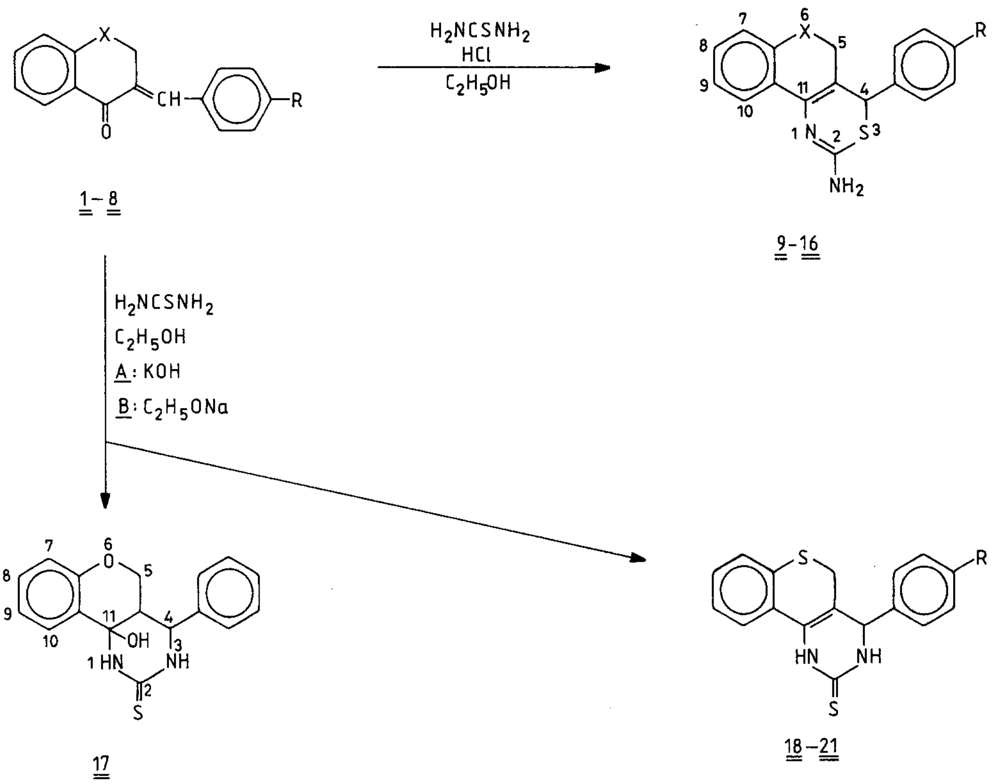
Zusammenfassung. Die Umsetzung von 3-Arylidenchromanonen **1** – **4** und -1-thiochromanonen **5** – **8** mit Thioharnstoff liefert unter sauren Bedingungen die Thiazine **9** – **16** und in basischem Milieu die Pyrimidine **17** – **21**.

Introduction

Reactions of exocyclic αβ-unsaturated ketones with thiourea have been studied by several research groups. Lóránd et al. [2, 3] investigated the reaction of 2-arylidenecyclohexanones and 2-arylidene-1-tetralones with thiourea under acidic conditions and synthesized 1,3-thiazines and 3,1-benzothiazines in this way. The 2-oxo-1,3-thiazine derivative was prepared by the acid-catalyzed reaction of chalcone and thiourea [4]. Pyrimidine derivatives were obtained by heating a mixture of 4-arylidene-2,3,4,5-tetrahydrobenzoxepin-5-ones and thiourea without solvent and catalyst [5]. Reaction of 2-arylidene-cycloalkanones, 2-arylidene-1-tetralones, and 2-arylidene-1-benzosuberones [6 – 8] with thiourea in the presence of sodium ethoxide or sodium hydroxide in ethanol gave pyrimidines. We have been engaged in the synthesis of nitrogen-containing fused heterocycles starting from 3-arylidene-chromanones and -1-thiochromanones [1, 9, 10]. In the present paper reactions of these α,β-unsaturated ketones with thiourea are reported.

Results and Discussion

Reaction of 3-arylidenechromanones **1** – **4** and -1-thiochromanones **5** – **8** have been studied both under acidic and alkaline reaction conditions as described for similar exocyclic α,β-unsaturated ketones [2 – 8].



1, **9**, **17**: X = O, R = H
2, **10**: X = O, R = Cl
3, **11**: X = O, R = CH_3
4, **12**: X = O, R = $CH(CH_3)_2$
5, **13**, **18**: X = S, R = H
6, **14**, **19**: X = S, R = CH_3
7, **15**, **20**: X = S, R = $CH(CH_3)_2$
8, **16**, **21**: X = S, R = OCH_3

When compounds **1** – **8** were allowed to react with thiourea in hot ethanol in the presence of concentrated hydrochloric acid 2-amino-4-aryl-4,5-dihydro[1]-benzopyrano[4,3-d]-3,1-thiazines **9** – **12** and -[1]benzothiopyrano[4,3-d]-3,1-thiazines **13** – **16** were obtained as the only products. In the IR spectra of these compounds characteristic νC = N and νNH_2 bands have been assigned (Table 1). The ^{1}H-NMR spectra measured in $CDCl_3$ corroborated the fused thiazine structure as well (Table 2).

Substances **1** – **8** have also been allowed to react with thiourea in boiling ethanol in the presence of potassium hydroxide (Method A) or C_2H_5ONa (Method B). Under such reaction conditions compound **1** afforded 11-hydroxy-4-phenyl-3,4,4 a,5,11-pentahydro[1]benzopyrano[4,3-d]pyrimidine-2(1*H*)-thione (**17**). In

Table 1. Physical constants and IR spectroscopic data of compounds **9**–**21**

Compound	M.p. °C	Yield %		Molecular formula[c]	IR cm^{-1} ν_{CSNH}	 $\nu_{C=N}$
9	147–148	55.2		$C_{17}H_{14}N_2OS$	–	1612
10	193–194	42.7		$C_{17}H_{13}ClN_2OS$	–	1610
11	147–148	53.3		$C_{18}H_{16}N_2OS$	–	1608
12	155–156	66.2		$C_{20}H_{20}N_2OS$	–	1608
13	149–150	77.4		$C_{17}H_{14}N_2S_2$	–	1620
14	153–154	80.2		$C_{18}H_{16}N_2S_2$	–	1614
15	152–153	62.5		$C_{20}H_{20}N_2S_2$	–	1606
16	130–131	82.3		$C_{18}H_{16}N_2OS_2$	–	1614
17	256–258	51.3[a]	56.2[b]	$C_{17}H_{16}N_2O_2S$	1204	–
18	224–225	48.4[a]	77.4[b]	$C_{17}H_{14}N_2S_2$	1212	–
19	228–229	67.9[a]	68.7[b]	$C_{18}H_{16}N_2S_2$	1214	–
20	237–238	68.2[a]	79.5[b]	$C_{20}H_{20}N_2S_2$	1213	–
21	177–178	58.8[a]	64.7[b]	$C_{18}H_{16}N_2OS_2$	1236	–

[a] Method A

[b] Method B

[c] Elemental analyses (C, H) were in good agreement with the calculated values

the case of other 3-arylidenechromanones (**2**–**4**) strong decomposition reactions took place in alkaline solution and no pyrimidine derivative could be isolated. However, the 3-arylidene-1-thiochromanones **5**–**8** yielded the 4-aryl-3,4,5-trihydro-[1]benzothiopyrano[4,3-d]pyrimidine-2(1*H*)-thiones **18**–**21** by both methods. The structures of compounds **17**–**21** were elucidated by IR and ^{1}H-NMR spectroscopy (Tables 1 and 2). On the basis of these results it can be established that the reactions of 3-arylidenechromanones and -1-thiochromanones with thiourea are similar to those of other exocyclic α,β-unsaturated ketones yielding thiazines under acidic and pyrimidine derivatives under alkaline reaction conditions.

Experimental Part

The ^{1}H-NMR spectra were recorded on a Bruker WP 200 SY spectrometer at 200 MHz in $CDCl_3$ or *DMSO-d$_6$* (internal standard *TMS*). IR spectra were measured for KBr discs with a Perkin-Elmer 283 B instrument.

TLC was performed on Kieselgel 60 F_{254} (Merck) layer using hexane : acetone (7 : 3 *v*/*v*) as eluant. Starting materials **1**–**8** were synthesized as described earlier [11].

2-Amino-4-aryl-4,5-dihydro[1]benzopyrano[4,3-d]-3,1-thiazines (**9**–**12**) *and -benzothiopyrano[4,3-d]-3,1-thiazines* (**13**–**16**)

A mixture of compounds **1**–**8** (5.0 mmol), thiourea (10.0 mmol), ethanol (50.0 ml), and concentrated HCl (10.0 ml) was refluxed for 24 h, then alkalized with NH_4OH, the precipitate filtered off, washed with water, and crystallized from methanol to yield compounds **9**–**16** (Tables 1 and 2).

Table 2. ^{1}H-NMR spectroscopic data of compounds **9** – **21**

Compound	Solvent[a]	δ (ppm)
9	A	4.52 (s, 1 H), 4.62 (d, 1 H), 4.88 (d, 1 H), 4.96 (br, NH_2), 6.90 – 7.92 (m, 9 aromatic protons)
10	A	4.50 (s, 1 H), 4.68 (d, 1 H), 4.86 (d, 1 H), 5.02 (br, NH_2), 6.86 – 7.72 (m, 8 aromatic protons)
11	A	2.34 (s, 3 H), 4.50 (s, 1 H), 4.64 (d, 1 H), 4.81 (d, 1 H), 4.98 (br, NH_2), 6.78 – 7.76 (m, 8 aromatic protons)
12	A	1.26 (d, 6 H), 2.86 (m, 1 H), 4.52 (s, 1 H), 4.66 (d, 1 H), 4.82 (d, 1 H), 5.04 (br, NH_2), 6.78 – 7.72 (m, 8 aromatic protons)
13	A	3.32 (d, 1 H), 3.60 (d, 1 H), 4.64 (s, 1 H), 4.86 (br, NH_2), 7.10 – 7.92 (m, 9 aromatic protons)
14	A	2.34 (s, 3 H), 3.30 (d, 1 H), 3.62 (d, 1 H), 4.64 (s, 1 H), 4.76 (br, NH_2), 7.06 – 7.94 (m, 8 aromatic protons)
15	A	1.24 (d, 6 H), 2.88 (m, 1 H), 3.34 (d, 1 H), 3.60 (d, 1 H), 4.64 (s, 1 H), 4.90 (br, NH_2), 7.14 – 7.92 (m, 8 aromatic protons)
16	A	3.30 (d, 1 H), 3.64 (d, 1 H), 3.73 (s, 3 H), 4.64 (s, 1 H), 4.95(br, NH_2), 6.84 – 7.92 (m, 8 aromatic protons)
17	B	3.06 (dd, 1 H), 3.40 (dd, 1 H), 3.94 (m, 1 H), 4.76 (dd, 1 H), 6.78 – 7.74 (m, 9 aromatic protons), 8.14 (NH), 8.36 (NH)
18	B	3.02 (d, 1 H), 3.54 (d, 1 H), 5.04 (d, 1 H), 7.20 – 7.56 (m, 9 aromatic protons), 9.26 (NH), 9.82 (NH)
19	B	2.30 (s, 3 H), 2.96 (d, 1 H), 3.52 (d, 1 H), 4.94 (d, 1 H), 7.18 – 7.70 (m, 8 aromatic protons), 9.21 (NH), 9.80 (NH)
20	B	1.20 (d, 6 H), 2.88 (m, 1 H), 3.02 (d, 1 H), 3.54 (d, 1 H), 4.96 (d, 1 H), 7.20 – 7.68 (m, 8 aromatic protons), 9.20 (NH), 9.82 (NH)
21	B	3.02 (d, 1 H), 3.34 (s, 3 H), 3.52 (d, 1 H), 4.98 (d, 1 H), 6.92 – 7.62 (m, 8 aromatic protons), 9.16 (NH), 9.76 (NH)

[a] $CDCl_3$ (A), *DMSO-d_6* (B)

11-Hydroxy-4-phenyl-3,4,4a,5,11-pentahydro[1]benzopyrano[4,3-d]pyrimidine-2(1H)-thione (**17**)

Method A. A mixture of compound **1** (10.0 mmol), thiourea (20.0 mmol), KOH (50.0 mmol), ethanol (50.0 ml) and water (3.0 ml) was refluxed for 6 h, then acidified with dilute HCl, the precipitate filtered off, washed free of acid, and crystallized from acetone to afford compound **17**.

Method B. A mixture of **1** (10.0 mmol), thiourea (20.0 mmol), C_2H_5ONa (60.0 mmol), and anhydrous ethanol (50.0 ml) was refluxed for 3 h, then worked up as described for Method A to obtain compound **17** (Tables 1 and 2).

4-Aryl-3,4,5-trihydro[1]benzothiopyrano[4,3-d]pyrimidine-2(1H)-thiones (**18** – **21**)

Method A. A mixture of **5** – **8** (5.0 mmol), thiourea (10.0 mmol), KOH (25.0 mmol), ethanol (30.0 ml), and water (2.0 ml) was allowed to react as described for compound **17** (Method A) to yield compounds **18** – **21**.

Method B. A mixture of **5**–**8** (5.0 mmol), thiourea (10.0 mmol), C_2H_5ONa (30.0 mmol), and anhydrous ethanol (30.0 ml) was allowed to react in the above-described reaction conditions (Method B) to afford compounds **18**–**21** (Tables 1 and 2).

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