Heterocylic Compounds from Malonyl Chlorides. V.* Further Investigation on Cyclization of 2-Alkylthiopyrimidones

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Malonyl chlorides with nitriles or thiocyanates give pyridines and pyrimidines.[1-3] The present work deals with further reactions of some of these products. 2-(2-Bromoethylthio)- and 2-(3-bromopropylthio)-4,5-dichloropyrimidin-6-one (*1* and *2*) have been shown to cyclize in dimethylformamide to the corresponding compounds *4* with the *ortho*-quinoid structures ($\nu_{C=O}$ 1675–1686 cm^{-1}).[4] In polar nonbasic solvents, however, they gave quaternized products which could be dehydrobrominated to compounds *5* with the *para*-quinoid structures ($\nu_{C=O}$ 1638 cm^{-1}).[4]

The utilization of a stronger base in the cyclization process would probably lead to removal of the proton before the ring closure and by-pass the quaternized intermediates. Ring closure ought to be possible also with other functional groups than bromide in the alkyl chain. When the pyrimidine *1*, *2*, or *3* was treated with diethylamine at different temperatures products were isolated according to Table 1.

The pyrimidine *3* at room temperature gave the ammonium salt *6* which must be an intermediate in the cyclization process since heating the mixture at 56 °C resulted in the pyrimidothiazine *4* ($n=3$). The reactivity was significantly increased by ionization. In most cases N(1) represented the attacking center; at 22 °C, however, the thiazolopyrimidine product appeared as a mixture of the isomeric compounds *4* and *5* in a ratio of 8:1.

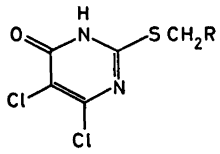
Table 1. Products from reaction of the pyrimidines *1*, *2*, and *3* in diethylamine at different temperatures.

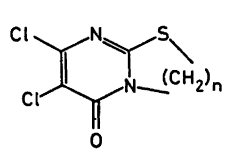
Pyrimidine	Temp. [a] °C	Products	Yields %
3	22 [b]	*6*	95
3	56 [c]	*4* ($n=3$)	60
2	0 [d]	*7*	88
2	22 and 56 [b]	*4* ($n=3$)	81
1	0 [b]	*4* ($n=2$)	90
1	22 [b]	*4* ($n=2$)	80
		5 ($n=2$)	10

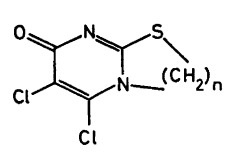
[a] Also the temperature of the reactants before mixing. [b] Instantaneous reaction. [c] Reaction time 6 h. [d] Reaction time 2 days.

The condensation to the 5-membered ring proceeded more easily than to the 6-membered ring in agreement with earlier findings.[4] At 0 °C the thiazolopyrimidine *4* ($n=2$) was formed from the pyrimidine *1* whereas no pyrimidothiazine *4* ($n=3$) was produced from compound *2* at this temperature. In the latter case reaction with the solvent gave the zwitterion *7* while at 22 and 56 °C only the pyrimidothiazine *4* ($n=3$) was formed.

Several attempts were made to cyclize the esters *8* ($n=0$, 1, and 2)[3] without success. The



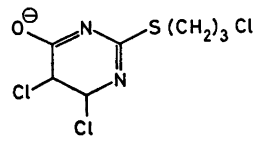


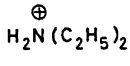


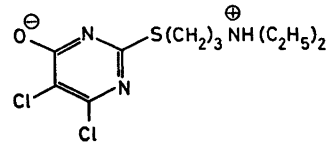
1 R = CH_2Br *8* R = $(CH_2)_nCOOC_2H_5$ *4*

2 R = $(CH_2)_2Br$ *9* R = $(CH_2)_nCOOH$

3 R = $(CH_2)_2Cl$



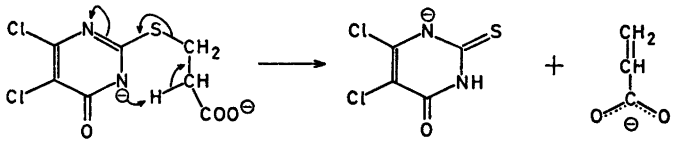




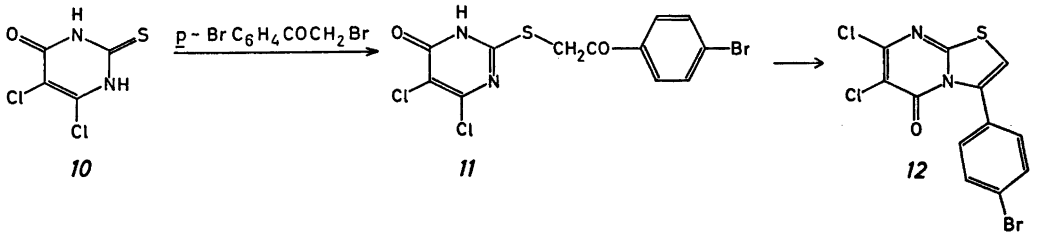
6 *7*

Scheme 1.

* Part IV: Hegrand, R., Stensrud, T. and Bernatek, E. *Medd. Norsk Farm. Selskap 32* (1971) 37.



Scheme 2.



Scheme 3.

three esters were therefore hydrolyzed under basic conditions. Hydrolysis of the ester *8* ($n=1$) with 1.5 – 2 equiv. of sodium hydroxide gave the acid *9* ($n=1$) as the sole product; with 2.25 – 3 equiv. the product was a mixture of the acid and 5,6-dichloro-2-thiouracil (*10*); larger quantities of sodium hydroxide gave the thiouracil *10* exclusively. The acid *9* ($n=1$) treated as the ester *8* ($n=1$) gave the same amount of the thiouracil *10*. The base abstracts both the carboxylic and the ring proton which leaves the nitrogens with higher electron density. The thione is formed with elimination of acrylic acid which is found in the filtrate.

The hydrolysis of the esters *8* ($n=0$ and 2) stopped at the acid stage even with a large excess of the hydroxide. In these cases no conjugative stabilized species such as acrylic acid could be eliminated. No cyclization of the acids *9* ($n=0$, 1, and 2) was observed with dicyclohexylcarbodiimide, acetic anhydride, or thionyl chloride.

p-Bromophenacyl bromide reacted with the thiouracil *10* to the pyrimidine *11*. This was cyclized in concentrated sulfuric acid to 3-*p*-bromophenyl-6,7-dichloro-5*H*-thiazolo[3,2-*a*]-pyrimidin-5-one (*12*).

Experimental. Melting points were determined on a micro hot-stage. IR spectra were recorded on a Perkin-Elmer 457 Grating Infrared Spectrophotometer (in KBr), NMR spectra on Varian A-60 A and HA 100 Spectrometers in DMSO-d_6 with TMS as an internal standard and the mass spectra on an AEI/EC MS 902 instrument. Elemental analyses were performed by I. Beetz, West Germany and were correct within 0.5 %.

Reaction of the pyrimidines 1, 2, *and* 3 *in diethylamine. (Table 1). General procedure.* The pyrimidine (0.5 g) was dissolved in diethylamine (10 ml) at the reaction temperature. Compound *5* ($n=2$) was insoluble in diethylamine and was separated from the isomeric compound *4* ($n=2$) by filtration. The compounds *4* ($n=2$ and 3) and *5* ($n=2$) were identified by comparison with authentic samples,[4] mixed m.p. and IR spectra.

4,5-Dichloro-2-(3-diethylaminopropylthio)-pyrimidin-6-one (7). M.p. 207 – 208 °C (from dioxane), NMR (TFA): δ 1.46 (t, J 7 Hz, CH_3), 2.20 – 2.55 and 3.06 – 3.78 (m, CH_2). The IR spectrum had no absorption due to carbonyl and the X-ray diffraction pattern revealed the zwitterion structure.[5]

5,6-Dichloro-2-thiouracil (10). The ester *8* ($n=1$) (3.0 g, 10 mmol) was refluxed in sodium hydroxide solution (40 ml, 10 %) for 1 h, acidified to pH = 1 and cooled. The product *10* (1.8 g, 90 %) was filtered off, m.p. 236 – 238 °C. (The filtrate was kept). IR: 3500, 3390, 1670 cm^{-1}. MS: *m/e* 196 (M^+) with two chlorine atoms.

Acrylic acid was isolated from the filtrate from above and identified by comparison with an authentic sample, mixed m.p. and IR spectrum.

2-(2-Carboxylethylthio)-4,5-dichloropyrimidin-6-one (9, n = *1).* The ester *8* ($n=1$) (3.0 g, 10 mmol) was refluxed in sodium hydroxide solution (15 ml, 4 %) for 1 h, acidified to pH = 1, cooled and filtered to give compound *9* ($n=1$) (1.9 g, 70 %), m.p. 205 – 207 °C (from acetic acid/water). NMR: δ 2.70 (t), 3.28 (t); J 6.5 Hz. IR: 1705 and 1650 cm^{-1}. MS: *m/e* 268 (M^+) with two chlorine atoms.

2-(p-Bromophenacylthio)-4,5-dichloropyrimidin-6-one (11). A solution of the thiouracil *10* (1.0 g, 5 mmol) and *p*-bromophenacyl bromide (1.4 g, 5 mmol) in acetone (50 ml) was refluxed for 3 h. The acetone was removed to give compound *11* (1.2 g, 60 %) m.p. 232 – 235 °C (from acetic acid/water), sublimation started at 210 °C. NMR: δ 4.80 (s, CH_2), 7.44 (d) and 7.96

(d, J 8.5 Hz, aromatic H). IR: 1690 and 1655 cm^{-1}. MS: m/e 392 (M^+) with one bromine and two chlorine atoms.

3-p-Bromophenyl-6,7-dichloro-5H-thiazolo-[3,2-a]pyrimidin-5-one (12). A solution of the pyrimidine *11* (0.5 g) in concentrated sulfuric acid (7.5 ml) was kept at room temperature for 20 min and then cautiously poured into ether (10 ml). Solid sodium bicarbonate was added together with some water until pH = 6 – 7. The separated compound *12* was filtered off (0.35 g, 72 %) m.p. 204 – 206 °C (from acetic acid/water). NMR: δ 7.51 (s, ethylenic H), 7.30 (d) and 7.55 (d, J 8.5 Hz, aromatic H). IR: 1691 cm^{-1}. MS: m/e 374 (M^+) with one bromine and two chlorine atoms.

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