

## Heterocyclics from Malonyl Chlorides

## III. Cyclisation and Oxidation of Some 2-Alkylthiopyrimidones

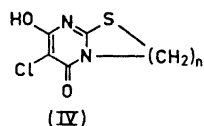
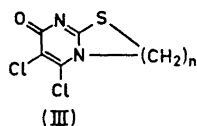
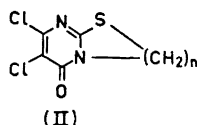
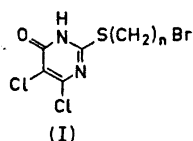
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Certain 2-alkylthiopyrimidones with a halogen atom in the alkyl group have been cyclised to thiazolopyrimidones and pyrimidothiazinones. Two 2-alkylthiopyrimidones could be oxidised to the sulphoxides.

2-Alkylthio-4,5-dichloropyrimidine-6-ones can be prepared from thiocyanates and chloromalonyl chloride.<sup>1</sup> When such pyrimidones contain a halogen atom suitably placed in the 2-alkylthio side-chain, they ought to be able to cyclise to a thiazolopyrimidone or a pyrimidothiazinone.

When I ( $n=2$ ) was heated with dimethylformamide 2,3-dihydro-6,7-dichloro-5H-thiazolo[3,2-a]pyrimidine-5-one (II) ( $n=2$ ) was formed. Heating I ( $n=2$ ) in benzene afforded the pyrimidinium bromide corresponding to II ( $n=2$ ) which could be dehydrobrominated by dimethylformamide. By heating I ( $n=2$ ) in acetone an isomeric pyrimidinium bromide was formed, which was dehydrobrominated by dimethylformamide to 2,3-dihydro-5,6-dichloro-7H-thiazolo[3,2-a]pyrimidine-7-one (III) ( $n=2$ ). II ( $n=2$ ) as well as III ( $n=2$ ) were hydrolysed by boiling water to 2,3-dihydro-6-chloro-7-hydroxy-5H-thiazolo[3,2-a]pyrimidine-5-one (IV) ( $n=2$ ).



On heating I ( $n=3$ ) with dimethylformamide 3,4-dihydro-7,8-dichloro-2H,6H-pyrimido[2,1-b]-[1,3]-thiazine-6-one (II) ( $n=3$ ) was formed. In diethyl ketone, I ( $n=3$ ) gave a pyrimidinium bromide, which was dehydrobrominated to 3,4-dihydro-6,7-dichloro-2H,8H-pyrimido[2,1-b]-[1,3]-thiazine-8-one (III) ( $n=3$ ). III ( $n=3$ ) in boiling water gave 3,4-dihydro-7-chloro-8-hydroxy-2H,6H-pyrimido[2,1-b]-[1,3]-thiazine-6-one (IV) ( $n=3$ ). II ( $n=3$ ) was resistant to hydrolysis under the applicable conditions.

Assignment of the structures II ( $n=2$ ,  $n=3$ ) and III ( $n=2$ ,  $n=3$ ) to the different substances is mainly based on the infrared spectra. Andrew and Bradsher<sup>2</sup> observed that *para*-quinoid thiazolo[3,2-a]pyrimidine-7-ones had a carbonyl absorption in the range 1600–1640  $\text{cm}^{-1}$  while *ortho*-quinoid thiazolo[3,2-a]pyrimidine-5-ones absorbed between 1680 and 1700  $\text{cm}^{-1}$ . Further they noticed that the *para*-quinoid isomers had considerably higher melting points than the *ortho*-quinoid forms. Similarly, Pashkurov<sup>3</sup> found that the *para*-quinoid 2,3-dihydro-7-methylthiazolo[3,2-a]pyrimidine-5-one (m.p. 229–230°C) absorbed at 1640  $\text{cm}^{-1}$  and that the *ortho*-quinoid, isomeric 5-methyl-7-one (m.p. 123–124°C) absorbed between 1660–1680  $\text{cm}^{-1}$ .

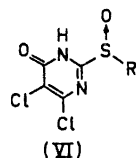
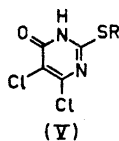
II ( $n=2$ ) had  $\nu_{\text{C=O}}$  at 1675  $\text{cm}^{-1}$  (m.p. 168–172°C), while III ( $n=2$ ) had  $\nu_{\text{C=O}}$  at 1638  $\text{cm}^{-1}$  (m.p. 194–202°C).

The carbonyl absorption is expected to follow the same pattern for *para*-quinoid and *ortho*-quinoid pyrimido[2,1-b]-[1,3]-thiazinones. Pashkurov<sup>3</sup> records a  $\nu_{\text{C=O}}$  at 1650  $\text{cm}^{-1}$  for the *ortho*-quinoid 3,4-dihydro-8-methyl-2H,6H-pyrimido[2,1-b]-[1,3]-thiazine-6-one.

II ( $n=3$ ) had  $\nu_{\text{C=O}}$  at 1686  $\text{cm}^{-1}$  (m.p. 133–134°C), while III ( $n=3$ ) has  $\nu_{\text{C=O}}$  at 1638  $\text{cm}^{-1}$  (m.p. 234–235°C).

The hydrolysis products IV ( $n=2$  and  $n=3$ ) had carbonyl absorptions at 1685–1675  $\text{cm}^{-1}$  and 1685  $\text{cm}^{-1}$ , respectively, which is highly suggestive of an *ortho*-quinoid monocarbonyl form. From the ultraviolet spectra (see Experimental) the same conclusion can be drawn. Also in the starting material for the cyclisation I ( $n=2$  and  $n=3$ ) with  $\nu_{\text{C=O}}$  1665  $\text{cm}^{-1}$  and  $\nu_{\text{C=O}}$  1655  $\text{cm}^{-1}$ , respectively, the *ortho*-quinoid tautomer probably predominates. This is supported by the ultraviolet spectra.

In the mass spectrum of I ( $n=2$ ) occurred a minor peak at  $m/e$  346, the fragment containing one chlorine and two bromine atoms. This must be due to a contamination of I ( $n=2$ ) with a compound where one of the two chlorine atoms in the ring has been substituted with bromine. In I ( $n=3$ ) no such phenomenon was visible, however, in this case the molecular ion was barely discernible. The cyclised products II ( $n=2$  and 3) and III ( $n=2$  and 3) gave mass spectra where peaks occurred at  $m/e$  266 ( $n=2$ ) and  $m/e$  280 ( $n=3$ ), the fragments containing one chlorine and one bromine atom. Mass spectra of the hydrolysed products IV ( $n=2$  and 3) showed peaks at  $m/e$  248 and 262, respectively, containing one bromine atom each. Since the chlorine in 4-position is known to have been removed by hydrolysis, the bromine in all the mentioned fragments most likely occupies the 5-position. The exchange of chlorine with bromine must have taken place before the pyrimidine ring was formed from chloromalonyl chloride and the bromoalkylthiocyanate.<sup>1</sup> Probably



the exchange occurred between these starting materials with the formation of bromomalonyl chloride.

The substances mentioned in Part II of this series<sup>1</sup> were prepared also with consideration of their possible biological activity. For this reason, it was of interest to oxidise some of them to the corresponding sulphoxides and sulphones. With peracetic acid, V ( $R = C_6H_5CH_2$ ) gave a sulphoxide VI ( $R = C_6H_5CH_2$ ).

Since the sulphur atom had become chiral, the benzyl methylene singlet in the NMR spectrum of the starting material ( $\tau$  5.58) occurred as two doublets in the oxidised product ( $\tau$  5.66, 5.52;  $J_{AB}$  12.5 cps). With performic acid, V ( $R = CH_3CH_2$ ) gave in poor yield a sulphoxide VI ( $R = CH_3CH_2$ ). In this case the original methylene quartet ( $\tau$  6.88) became a diffuse multiplet centered around  $\tau$  6.85 in the oxidised product. The  $\beta$ -methyl protons were displaced 0.1 unit towards higher field ( $\tau$  8.69 to 8.80). Usually such protons do not change their chemical shifts on oxidation of the sulphur atom.<sup>4</sup> V ( $R = CH_3$ ,  $C_2H_5$ , and  $C_3H_7$ ) on oxidation with peracetic acid gave, in addition to some unreacted substance, about 50 % yield at 5,6-dichlorouracil. In these cases the oxidation evidently has gone very far and it has not been possible to stop the reaction at the sulphoxide stage.

### EXPERIMENTAL

Melting points were determined on a micro hot-stage. UV-spectra were recorded on a Perkin-Elmer 137UV Ultraviolet-Visible Spectrophotometer, infra-red spectra on a Perkin-Elmer 457 Grating Infrared Spectrophotometer (in KBr), NMR spectra on a Varian A-60 A Spectrometer and the mass spectra on an AEI/EC MS 902 instrument. Elemental analyses were performed by I. Beetz, West Germany.

*2,3-Dihydro-6,7-dichloro-5H-thiazolo[3,2-*a*]pyrimidine-5-one (II) ( $n = 2$ ).* 2-(2-Bromoethylthio)-4,5-dichloropyrimidine-6-one (I) ( $n = 2$ ) (2 g) was heated in dimethylformamide (30 ml) on a steam-bath for 1 h. After removing most of the solvent, the remaining dark liquid was purified with charcoal, and the crystalline product recrystallised twice from water. M.p. 168–172°C. Yield 40 mg, 4 %. The mass spectrum showed the molecular ion at  $m/e$  222. High resolution:  $m/e$  221.9430. Calc. for  $C_6H_4N_2OSCl_2$ : 221.9421. I ( $n = 2$ ) (2.5 g) was refluxed in benzene (20 ml) for 2 h. Some unreacted material separated and was removed. The filtrate was concentrated and a solid substance remained. Yield 1.7 g. This was evidently a hydrobromide as it immediately gave a copious precipitate of AgBr with  $AgNO_3$ . The hydrobromide was heated in dimethylformamide (40 ml) on a steam-bath for 1 h. The product was isolated and purified as before. Yield 50 mg, 4 %. M.p. 168–172°C. Identical with the product in the first experiment by mixed m.p. and IR-spectra.

*2,3-Dihydro-5,6-dichloro-7H-thiazolo[3,2-*a*]pyrimidine-7-one (III) ( $n = 2$ ).* 2-(2-Bromoethylthio)-4,5-dichloropyrimidine-6-one (I) ( $n = 2$ ) (2 g) was refluxed in acetone (20 ml) for 3 h. The precipitate (1 g) was thoroughly washed with hot acetone and consisted of a hydrobromide as it gave an immediate precipitate with  $AgNO_3$ . It was heated in dimethylformamide (40 ml) on a steam-bath for 1 h. After removal of the solvent the oily residue was treated with charcoal in water. The solid product was recrystallised

thrice from water. Yield 40 mg. M.p. 194–202°C. In the mass spectrum the molecular ion appeared at  $m/e$  222 (two chlorine atoms). High resolution:  $m/e$  221.9423. Calc. for  $C_6H_5N_2OSCl_2$ : 221.9421.

*2,3-Dihydro-6-chloro-7-hydroxy-5H-thiazolo[2,3-a]pyrimidine-5-one (IV) (n=2)*. During the recrystallisation from hot water of the two compounds II ( $n=2$ ) and III ( $n=2$ ) white insoluble products were formed which were shown to be identical. M.p. 310–320°C. Identical IR-spectra. In both mass spectra the molecular ion appeared at  $m/e$  204 (one chlorine atom).

*3,4-Dihydro-7,8-dichloro-2H,6H-pyrimido[2,1-b]-[1,3]-thiazine-6-one (II) (n=3)*. 2-(3-Bromopropylthio)-4,5-dichloropyrimidine-6-one (I) ( $n=3$ ) (1 g) was refluxed in dimethylformamide (20 ml) for 1 h. The solvent was evaporated and the product recrystallised from water. Yield 150 mg. M.p. 133–134°C. Molecular ion at  $m/e$  236 with two chlorine atoms. Elemental analysis correct for  $C_7H_8N_2OSCl_2$ .

*3,4-Dihydro-6,7-dichloro-2H,8H-pyrimido[2,1-b]-[1,3]-thiazine-8-one (III) (n=3)*. I ( $n=3$ ) (2 g) was refluxed for 24 h in diethyl ketone (8 ml). The precipitate was washed with hot diethyl ketone. Yield 0.8 g. The product gave an immediate precipitate with  $AgNO_3$ . It was heated in dimethylformamide (30 ml) on a steam-bath for 30 min. After removal of the solvent the residue was heated with charcoal in water and the product recrystallised twice from water. M.p. 234–235°C. Molecular ion at  $m/e$  236 with two chlorine atoms. High resolution:  $m/e$  235.9580. Calc. for  $C_7H_8N_2OSCl_2$ : 235.9578.

*3,4-Dihydro-7-chloro-8-hydroxy-2H,6H-pyrimido[2,1-b]-[1,3]-thiazine-6-one (IV) (n=3)*. During recrystallisation of III ( $n=3$ ) from hot water a white insoluble substance was formed. Subl. 320°C. Molecular ion at  $m/e$  218 with one chlorine atom.

Table 1. UV-spectra of the compounds I–IV in ethanol.

Compound	$\lambda_{max}$ (m $\mu$ )	log $\epsilon$	$\lambda_{max}$ (m $\mu$ )	log $\epsilon$	$\lambda_{max}$ (m $\mu$ )	log $\epsilon$
I ( $n=2$ )	230	3.8	245	3.6	293	3.6
I ( $n=3$ )	228	4.0	250	3.8	300	3.9
II ( $n=2$ )	230	3.8	246	3.5	305	3.7
II ( $n=3$ )	230	4.0	256	3.8	312	3.8
III ( $n=2$ )	237	4.0				
III ( $n=3$ )	237	4.0				
IV ( $n=2$ )	228	4.0			297	3.5
IV ( $n=3$ )	227	3.9			300	3.5

*2-Benzylsulphinyl-4,5-dichloropyrimidine-6-one (IV) (R=C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>)*. 2-Benzylthio-4,5-dichloropyrimidine-6-one (V) (R=C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>) (2.9 g) was dissolved in glacial acetic acid (500 ml) and hydrogen peroxide (1.1 ml, 30%) was added. The mixture was kept at room temperature for two weeks, evaporated and the residue recrystallised thrice from water. Yield 2.0 g. M.p. 165–166°C.  $\nu_{S \rightarrow O}$  1030  $cm^{-1}$ . Molecular ion at  $m/e$  302 with two chlorine atoms. Elemental analysis correct for  $C_{11}H_8N_2O_2S_2Cl_2$ .

*4,5-Dichloro-2-ethylsulphinylpyrimidine-6-one (VI) (R=C<sub>2</sub>H<sub>5</sub>)*. 4,5-Dichloro-2-ethylthiopyrimidine-6-one (V) (R=C<sub>2</sub>H<sub>5</sub>) (3 g) in formic acid (800 ml) to which was added hydrogen peroxide (1.5 ml, 30%) was kept at room temperature for five days. After evaporation the residue was recrystallised from water and consisted then obviously of two substances. The crystals were separated mechanically and the smaller part (100 mg) recrystallised again from water. M.p. 137.5–140.5°C.  $\nu_{S \rightarrow O}$  1045  $cm^{-1}$ . Elemental analysis correct for  $C_6H_8N_2O_2S_2Cl_2$ . The main product of the oxidation had m.p. 302–305°C and a molecular ion at  $m/e$  180 with two chlorine atoms. Elemental analysis correct for  $C_4H_8N_2O_2Cl_2 \cdot \frac{1}{2}H_2O$ . The substance was 5,6-dichlorouracil. The same substance was identified by oxidation of V (R=CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, and C<sub>3</sub>H<sub>7</sub>) with hydrogen peroxide in glacial acetic acid.

## REFERENCES

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