ADDITION OF 2-METHYLTHIO-5-PYRIMIDINOL AND 5-METHOXY-2-PYRIMIDINETHIOL TO THE ACETYLENE TRIPLE BOND

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Reaction of 2-methylthio-5-pyrimidinol (*I*) with 2-methylthio-5-(2-propinyloxy)pyrimidine (*II*) in the presence of sodium methoxide gave *cis*-1,3-bis(2-methylthio-5-pyrimidinyloxy)-1-propene (*IIIa*) and 6-methyl-2-methylthiofuro-[3,2-*d*]pyrimidine (*IV*). On addition of *I* to 2-propinol *cis*-3-(2-methylthio-5-pyrimidinyloxy)-2-propenol (*V*) and the isomeric 2-(2-methylthio-5-pyrimidinyloxy)-2-propenol (*VI*) were formed. The latter when converted to chloro derivative *VII* was reacted with *I* to give 2,3-bis(2-methylthio-5-pyrimidinyloxy)-1-propene (*VIII*). From 1,3-dibromo-2-propanol and *I* 1,3-bis(2-methylthio-5-pyrimidinyloxy)-2-propanol (*XI*) was prepared which was converted to 1,3-bis(2-methylthio-5-pyrimidinyloxy)-2-bromopropane (*XII*) and then dehydrobrominated to a mixture of *cis*- and *trans*-1,3-bis(2-methylthio-5-pyrimidinyloxy)--1-propene (*IIIa*, *IIIb*). 5-Methoxy-2-pyrimidinethiol (*XIV*) reacts with 2-propinol similarly as *I* under formation of *cis*-3-(5-methoxy-2-pyrimidinylthio)-2-propenol (*XV*) and 2-(5-methoxy--2-pyrimidinylthio)-2-propenol (*XVI*). Compound *I* when reacting with 1-chloromethyloxirane gives both 1,2-epoxy-3-(2-methylthio-5-pyrimidinyloxy)propane (*X*) and 1-chloro-3-(2-methylthio-5-pyrimidinyloxy)-2-propanol (*XIII*), depending on reaction conditions.

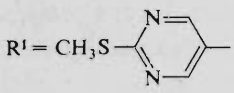
In connection with the identification of trace by-products formed during the synthesis of the fungistatic 5-(3-iodopropinyloxy)-2-methylthiopyrimidine (Jaritin SPOFA) we met with the problem of the addition of 2-methylthio-5-pyrimidinol (*I*) to the acetylenic triple bond. We were mainly interested in the reaction of phenol *I* with 2-methylthio-5-(2-propinyloxy)pyridimine (*II*). We found that on heating of these two substances in methanol at 180°C in the presence of sodium methoxide or hydroxide two substances are formed in addition to polymeric products, which we isolated by column chromatography on silica gel. On the basis of their ^{1}H-NMR spectra we identified them as *cis*-1,3-bis(2-methylthio-5-pyrimidinyloxy)-1-propene (*IIIa*) and 6-methyl-2-methylthiofuro[3,2-*d*]pyrimidine (*IV*). When using a smaller amount of alkali the amount of compound *IIIa* in the mixture decreased, while without alkali only compound *IV* was formed, which is a product of rearrangement and the cyclization of compound *II*. The formation of this compound is in agreement with the finding by Otter and coworkers[1] who described this rearrangement and the cyclization in the case of 1,3-dimethyl-5-(2-propinyloxy)uracil.

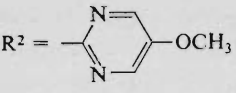
The formation of isomeric 1,2-bis(2-methylthio-5-pyrimidinyloxy)-1-propene could not be detected. Under the assumption that this could be caused by steric hindrance, we used unsubstituted 2-propinol for further experiments. The addition of phenols to acetylenic alcohols has been described in a single paper by Gelin and Makula[2] who obtained on boiling of a mixture of 2-propinol, phenol and sodium phenolate in a molar 1 : 1 : 1 ratio 3-phenoxy-2-propenol as the sole product. However, they do not mention whether it was the *cis*- or the *trans*-isomer or a mixture of both. *o*-, *m*- and *p*-Cresol and 2,4-dimethylphenol reacted in the same manner. When boiling *I* and 2-propinol with powdered potassium hydroxide in a molar 1 : 2 : 0·5 ratio for several hours we observed the formation of two substances, but the reaction rate was slow. A better result was obtained on heating this mixture at 150°C in an autoclave. Using column chromatography on silica gel we obtained from the reaction mixture the same two compounds as above, of which the first was identified on the basis of its ^{1}H-NMR spectrum as *cis*-3-(2-methylthio-5-pyrimidinyloxy)-2-propenol (*V*) and the second as 2-(2-methylthio-5-pyrimidinyloxy)--2-propenol (*VI*). The formation of the *cis*-isomer *V* is in agreement with the assumed *trans*-addition of the phenolate ion to the triple bond. 2,3-Bis(2-methylthio-5-pyrimidinyloxy)-1-propene (*VIII*) was prepared by chlorination of propenol *VI* and subsequent reaction of the propenyl chloride *VII* formed with compound *I*.

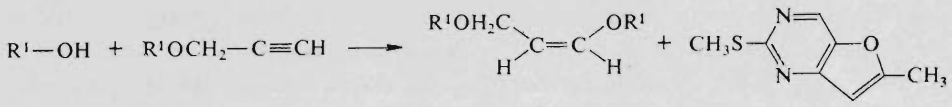
We also tried to prepare the disubstituted propene *VIII* from diethyl malonate *via* diethyl chloromalonate, from which we obtained diethyl (2-methylthio-5-pyrimidinyloxy)-malonate (*IX*) on reaction with *I*. Reduction of this ester with sodium bis-(2-methoxyethoxy)aluminum hydride to the corresponding diol was unsuccessful.

We checked the structure of compound *IIIa* by synthesis, using 1,3-dibromo-2-propanol as starting compound. This was reacted with *I* in dimethyl sulfoxide in the presence of potassium carbonate, giving rise to 1,3-bis(2-methylthio-5-pyrimidinyloxy)-2-propanol (*XI*). At 50–80°C 2,3-epoxy-1-(2-methylthio-5-pyrimidinyloxy)propane (*X*) is formed, which on elevating the temperature to 90°C reacts with another molecule of *I* under formation of propanol *XI*. On bromination with phosphorus tribromide we converted this substance to 1,3-bis(2-methylthio-5-pyrimidinyloxy)-2-bromopropane (*XII*) which on dehydrobromination with 1,8-diazabicyclo[5.4.0]undec-7-ene gave a mixture of *cis* and *trans*-1,3-bis-(2-methylthio-thio-5-pyrimidinyloxy)-1-propene (*IIIa*, *IIIb*). Epoxide *X* was also obtained on reaction of the sodium salt of phenol *I* with 1-chloromethyloxirane, while free phenol *I* reacted with 1-chloromethyloxirane in acetonitrile and in the presence of potassium carbonate under formation of 1-chloro-3-(2-methylthio-5-pyrimidinyloxy)-2-propanol (*XIII*) in addition to a small amount of epoxide *X*.

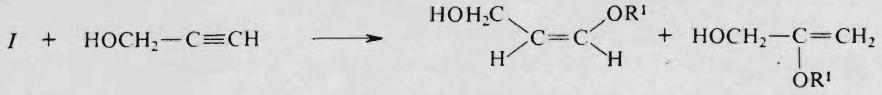
Further was studied the addition of 5-methoxy-2-pyrimidinethiol (*XIV*) to the triple bond of 2-propinol. On heating of thiophenol and 2-propinol with potassium hydroxide a mixture of *cis*-3-phenylthio-2-propenol and 2-phenylthio-2-propenol in a 3 : 2 ratio was obtained[3]. Although the predominant form of thiol *XIV* was the



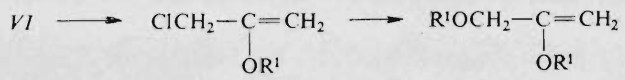




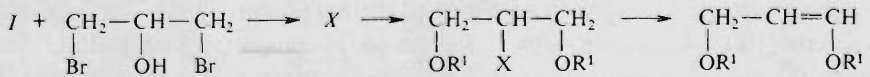
I *II* *IIIa* *IV*



V *VI*

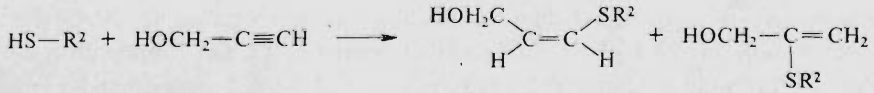


VII *VIII*

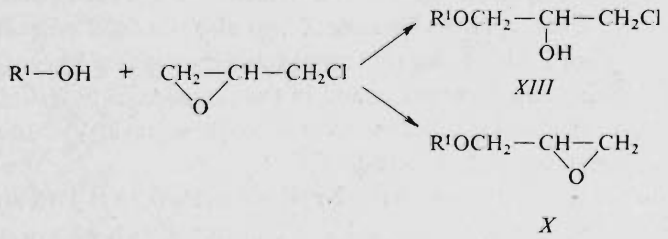


XI, X = OH
XII, X = Br

IIIa = *cis*-
IIIb = *trans*-



XIV *XV* *XVI*



XIII

X

tautomeric thioxo-form in our case, the addition to the triple bond had an analogous course. We obtained *cis*-3-(5-methoxy-2-pyrimidinylthio)-2-propenol (*XV*) and 2-(5-methoxy-2-pyrimidinylthio)-2-propenol (*XVI*) in a 3 : 1·75 ratio.

The nucleophilic additions of both hydroxypyrimidine *I* and the mercaptopyrimidine *XIV* proceeded by a *trans*-mechanism and both of them aim simultaneously at $C_{(2)}$ and $C_{(3)}$ of 2-propinol, while the addition to $C_{(3)}$ predominates.

EXPERIMENTAL

The melting points were determined on a Mettler FP 2 apparatus. The ^{1}H-NMR spectra were measured on a Varian XL-200 spectrometer (200 MHz) in the FT mode in deuteriochloroform, using tetramethylsilane as internal reference. The chemical shifts are given in δ-scale and the coupling constants in Hz.

In the case of hydroxy derivatives *in situ* acylation of the hydroxy group with trichloroacetyl isocyanate (TAI) was carried out after the measurement of the spectra[4,5]. In all instances the reaction took place practically immediately and the ^{1}H-NMR data of the trichloroacetylcarbamoyl derivatives formed are mentioned below as ^{1}H-NMR ($CHCl_3$ + TAI). The signal of the NH proton of the product and the characteristic acylation shifts of the hydrogens in the neighbourhood of the hydroxy group were used in the structure determination of hydroxy derivatives.

2-Methylthio-5-(2-propinyloxy)pyrimidine (*II*)

This compound was prepared by us earlier[6,7] and now we describe a modified procedure. Anhydrous potassium carbonate (1·445 g, 0·105 mol) and propinyl chloride (8·19 g, 0·11 mol) were added to a solution of *I* (14·2 g, 0·1 mol) in dimethyl sulfoxide (100 ml) under stirring and the mixture was heated at 50°C for 4 h. After cooling to 30—35°C it was poured into water (350 ml), the precipitated product was filtered off under suction and washed with water. Yield: 14·5 g (80·5%), m.p. 81—85°C. The m.p. of an analytical sample was 85·8—86·6°C (tetrachloromethane); b.p. 109—110°C/57 Pa. ^{1}H-NMR spectrum: 2·56 s, 3 H (CH_3S); 2·60 t, J = 2·5, 1 H (C≡CH); 4·74 d, J = 2·5, 2 H (OCH_2); 8·36 s, 2 H (arom. H).

cis-1,3-Bis(2-methylthio-5-pyrimidinyloxy)-1-propene (*IIIa*) and 2-Methylthio-6-methylfuro[3,2-*d*]pyrimidine (*IV*)

A mixture of *I* (2·8 g; 20 mmol), *II* (3·6 g; 20 mmol), 1M-NaOH (10 ml; 10 mmol) and methanol (40 ml) was heated in an autoclave at 160—180°C for 2 h and then neutralized with 5M-HCl and evaporated under reduced pressure. The residue was triturated with 1M-NaOH (10 ml) and extracted with benzene (5 × 25 ml). The combined benzene extracts were freed of the residues of *I* by washing with 1M-NaOH (10 ml) and water, then dried over magnesium sulfate and evaporated under reduced pressure. The residue (3·1 g) was dissolved in benzene and put on a silica gel column (120 g, Lachema L 100/160). Elution with benzene was monitored by TLC on Silufol, (using tetrachloromethane–ethyl acetate 2 : 1 for development). Unreacted compound *I* was eluted first (1·40 g), followed by *IV*: 0·34 g (9·4%), m.p. 75·5—76·6°C (tetrachloromethane), R_F 0·63 (DC-Fertigplatte, Merck, tetrachloromethane–ethyl acetate 2 : 1). For $C_8H_8N_2OS$ (180·2) calculated: 53·32% C, 4·47% H, 15·54% N, 17·79% S; found: 53·24% C, 4·54% H, 15·94% N, 16·89% S. ^{1}H-NMR spectrum: 2·54 d, J = 1·0, 3 H (CH_3—C=); 2·62 s, 3 H (CH_3S); 6·50 m, J = 1·0 and 0·8, 1 H (—CH=); 8·57 d, J = 0·8, 1 H (arom. H). The last eluate gave

an oily residue, *IIIa*; 1·0 g (31%) which crystallized after trituration with ethanol and cooling. An analytical sample had m.p. 99·1—101·1°C (ethanol), R_F 0·55 (DC-Fertigplatte, Merck, tetrachloromethane–ethyl acetate 2 : 1). For $C_{13}H_{14}N_4O_2S_2$ (322·4 calculated: 48·43% C, 4·38% H, 17·38% N, 19·89% S; found: 48·41% C, 4·35% H, 17·43% N, 19·83% S. ^{1}H-NMR spectrum: 2·55 s, 3 H (CH_3S); 2·57 s, 3 H (CH_3S); 4·84 dd, J = 6·8 and 1·3, 2 H (OCH_2); 5·20 dt, J = 6·8 and 6·1, 1 H (CH=C—O); 6·54 dt, J = 6·1 and 1·3, 1 H (C=CH—O); 8·30 s, 2 H (arom. H); 8·37 s, 2 H (arom. H).

2-(2-Methylthio-5-pyrimidinyloxy)-2-propenol (*VI*) and
cis-3-(2-Methylthio-5-pyrimidinyloxy)-2-propenol (*V*)

A mixture of 2-propinol (28·0 g; 0·50 mol), powdered potassium hydroxide (7·0 g; 0·125 mol) and *I* (35·5 g; 0·25 mol) was heated at 150°C in a 100 ml autoclave for 2 h. The reaction mixture was rinsed with methanol (60 ml) and evaporated under reduced pressure. The residue was mixed with 5M-NaOH (30 ml) and extracted with diethyl ether (10 × 100 ml). The combined ethereal extracts were washed with 5M-NaOH (10 ml) and water, dried over anhydrous magnesium sulfate and evaporated. The residue (23·5 g) was dried at 100°C *in vacuo* (water pump) and the residue (16·4 g) was dissolved in benzene and chromatographed on a silica gel column (240 g, Lachema L 100/160). Benzene was used for elution first, followed by benzene–chloroform mixtures with increasing concentration of chloroform (10, 20 and 30 vol.%). The eluates were analysed by thin-layer chromatography on Silufol, using tetrachloromethane–ethyl acetate 1 : 1 for development. The first fraction: 9·75 g of crude *VI* or 4·27 g (9·62%) after crystallization from benzene. An analytical sample had m.p. 55·7—56·2°C (benzene). For $C_8H_{10}N_2O_2S$ (198·2) calculated: 48·47% C, 5·08% H, 14·13% N, 16·17% S; found: 48·76% C, 5·25% H, 14·46% N, 16·14% S.: R_F 0·42 (DC-Fertigplatte, Merck, tetrachloromethane–ethyl acetate 1 : 1). ^{1}H-NMR spectrum 2·57 s, 3 H (SCH_3); 2·64 bs, 1 H (OH); 4·11 d, J = 3·0, 1 H and 4·57 m, J = 3·0 and 0·7, 1 H (C=CH_2); 4·27 d, J = 0·7, 2 H (CH_2O); 8·37 s, 2 H (arom. H). ^{1}H-NMR ($CDCl_3$ + TAI): 2·57 s, 3 H (SCH_3); 4·30 d, J = 3·4, 1 H and 4·72 d, J = 3·4, 1 H (C=CH_2); 4·91 s, 2 H (OCH_2); 8·38 s, 2 H (arom. H); 8·78 bs, 1 H (NH). Evaporation of subsequent fraction gave 5·26 g (10·6%) of crude compound *V*. Crystallization from aqueous ethanol (1 : 1) gave 4·45 g (9·2%) of a compound with m.p. 91·1—91·8°C. R_F 0·28 (DC-Fertigplatte Kieselgel, Merck, tetrachloromethane –ethyl acetate 1 : 1). For $C_8H_{10}N_2O_2S$ (198·2) calculated: 48·47% C, 5·08% H, 14·13% N, 16·17% S; found: 48·35% C, 5·17% H, 14·08% N, 15·90% S. ^{1}H-NMR spectrum: 2·21 bs, 1 H (OH); 2·55 s, 3 H (SCH_3); 4·39 bd, 2 H (CH_2O); 5·22 m, J = 7·4, 6·3 and 6·1, 1 H (O—C=CH); 6·37 d, J = 6·1, 1 H (O—CH=C); 8·33 s, 2 H (arom. H). ^{1}H-NMR ($CDCl_3$ + TAI): 2·56 s, 3 H (SCH_3); 5·04 d, 2 H (CH_2O); 5·16 m, J = 7·0 and 6·0 (CH=C—O); 6·55 d, J = 6·0, 1 H (C=CH—O); 8·36 s, 2 H (arom. H); 8·57 bs, 1 H (NH).

2,3-Bis(2-methylthio-5-pyrimidinyloxy)-1-propene (*VIII*)

Thionyl chloride (1·19 g; 10 mmol) was added dropwise over one hour to a solution of *VI* (1·98; 10 mmol) and pyridine (0·98 g) in diethyl ether (10 ml) and the mixture was allowed to stand overnight. Ether was decanted and the substance precipitated on the walls was rinsed with ether and then dissolved in oxy water (15 ml). The solution was extracted with ether (3 × 10 ml) and the combined extracts were washed with 10% sodium carbonate (10 ml) and water (5 ml) and dried calcium chloride. After evaporation of the solvent 2·02 g (93·2%) of *VII* were obtained which was used without further purification for the further reaction step. A mixture of chloro derivative *VII* (1·93 g; 8 mmol), compound *I* (1·14 g; 8 mmol), anhydrous potassium carbonate (1·1 g; 8 mmol) and potassium iodide (0·66 g; 4 mmol) in acetone (10 ml) was refluxed for 2 h,

then evaporated and the residue dissolved in water (10 ml) and extracted with benzene (3 × 10 ml). The benzene extracts were washed with water (5 ml), dried over anhydrous magnesium sulfate and evaporated. The residue was dissolved in benzene and chromatographed on silica gel (12·5 g of Kieselgel 60 reinst, 0·063—0·200 mm Merck). The column was eluted with benzene and then a mixture of benzene with increasing amounts of chloroform (10, 20 and 40 vol.%). The process was followed by thin-layer chromatography (Silufol, tetrachloromethane–ethyl acetate 1 : 1). The residue *VIII* (1·25 g; 48·5%) was crystallized from 60% ethanol, m.p. 85·0—85·8°C, R_F 0·62 (DC-Fertigplatte Kieselgel, Merck, tetrachloromethane–ethyl acetate 1 : 1). For $C_{13}H_{14}N_4O_2S$ (322·4) calculated: 48·43% C, 4·38% H, 17·38% N, 19·89% S; found: 48·49% C, 4·41% H, 17·76% N, 19·67% S. ^{1}H-NMR spectrum: 2·55 s, 3 H (SCH_3); 2·57 s, 3 H (SCH_3); 4·30 d, J = = 3·3, 1 H (C=CH); 4·68 d, J = 3·3, 1 H (C=CH); 4·71 s, 2 H (OCH_2); 8·34 s, 2 H (arom. H); 8·37 s, 2 H (arom. H).

1,3-Bis(2-methylthio-5-pyrimidinyloxy)-2-propanol (*XI*)

1,3-Dibromo-2-propanol (22·0 g; 0·1 mol) in dimethyl sulfoxide (20 ml) was added dropwise over half-an-hour into a mixture of *I* (28·4 g; 0·2 mol), anhydrous potassium carbonate (55·0 g) and dimethyl sulfoxide (100 ml), heated to 70°C. The temperature was increased to 90°C and after 30 min the mixture was cooled to 30°C and poured into water (1 200 ml). The product separated was filtered off under suction and washed with water. Crude *XI* (26·65; 78·3%) was mixed with hot ethanol (300 ml), the undissolved part was filtered off and washed with ethanol. The combined filtrates were diluted with hot water and cooled. The separated material (18·2 g; 53·5%) had unsharp m.p. A sample for analysis was crystallized from ethanol and dried in a vacuum at boiling point of ethanol, m.p. 100·2—100·8°C, R_F 0·12 (Silufol, tetrachloromethane–ethyl acetate 7 : 3). For $C_{13}H_{16}N_4O_2S_2$ (340·4) calculated: 45·87% C, 4·74% H, 16·46% N, 18·84% S; found: 45·77% C, 4·87% H, 16·59% N, 18·68% S. ^{1}H-NMR spectrum: 2·53 s, 6 H (2 × SCH_3); 3·59 d, J = 5·5, 1 H (OH); 4·20 d, J = 4·5, 4 H (2 × OCH_2); 4·36 m, J = 5·5 and 4·5, 1 H (CH—O); 8·31 s, 4 H (2 × arom. H). ^{1}H-NMR ($CDCl_3$ + TAI): 2·53 s, 6 H (2 × SCH_3); 4·37 d, J = 4·5, 4 H (2 × OCH_2); 5·57 m, J = 4·5, 1 H (CH—O); 8·31 s, 4 H (2 × arom. H); 9·27 bs, 1 H (NH).

1,3-Bis(2-methylthio-5-pyrimidinyloxy)-2-bromopropane (*XII*)

Compound *I* (3·6 g; 10·6 mmol) dried by azeotropic distillation with benzene was dissolved in dimethylformamide (15 ml) and treated by dropwise addition at temperatures below 10°C of phosphorus tribromide (1 ml). The mixture was allowed to stand overnight in a melting ice bath and then poured onto ice and alkalized with sodium carbonate. The separated product was extracted with benzene (5 × 50 ml). The benzene extracts were dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue (7·35 g) was dissolved in benzene (7 ml) and chromatographed on a silica gel column (150 g, Lachema L 100/160). The components were eluted with benzene and benzene–chloroform mixtures (gradient from 1—50 vol.% of chloroform). The eluates were analysed by thin-layer chromatography. Yield, 0·79 g (19·6%) of crude *XII* which was crystallized from benzene–ethanol (1 : 5) to afford a product with m.p. 119·6—120·6°C, R_F 0·28 (Silufol, tetrachloromethane–ethyl acetate 7 : 3). For $C_{13}H_{15}Br.N_4O_2S_2$ (403·3) calculated: 38·71% C, 3·75% H, 19·81% Br, 13·89% N, 15·90% S; found: 39·02% C, 3·81% H, 20·08% Br, 13·96% N, 15·89% S.

cis- and *trans*-1,3-Bis(2-methylthio-5-pyrimidinyloxy)-1-propene (*IIIa*, *IIIb*)

A solution of *XII* (1·61 g; 4 mmol) in benzene (20 ml) was freed of traces of moisture by distilling off of about one half of the solvent. 1,8-Diazabicyclo[5.4.0]undec-7-ene (0·77 g; 5·06 mmol) was then added to the solution and the mixture was refluxed for 6 h. After cooling, the liquid material was separated from the solid hydrobromide sticking to the wall. The latter was dissolved in water and the solution was extracted with benzene (2 × 10 ml). The main solution and the combined benzene extracts were washed with water (5 ml) under addition of hydrochloric acid, till distinctly acid reaction. The benzene layer was then dried over sodium sulfate and evaporated under reduced pressure. The residue (1·66 g) was crystallized from ethanol; yield, 0·83 g (64·4%) of a mixture of *IIIa* (49%) and *IIIb* (51%), m.p. 85·8—86·6°C. *IIIa* R_F 0·54, *IIIb* R_F 0·50 (DC-Fertigplatte, Kieselgel, Merck, tetrachloromethane–ethyl acetate 2 : 1). For $C_{13}H_{14}N_4O_2S_2$ (322·4) calculated: 48·43% C, 4·38% H, 17·38% N, 19·89% S; found: 48·15% C, 4·33% H, 17·64% N, 19·69% S. ^{1}H-NMR spectrum of compound *IIIa*, see above; for compound *IIIb*: 2·55 s, 3 H (SCH_3); 2·56 s, 3 H (SCH_3); 4·59 dd, J = 7·1 and 1·1, 2 H (CH_2O); 5·59 dd, J = 12·2 and 7·1, 1 H (CH=C—O); 6·81 dd, J = 12·2 and 1·1, 1 H (C=CH—O); 8·27 s, 2 H (arom. H); 8·35 s, 2 H (arom. H).

1-Chloro-3-(2-methylthio-5-pyrimidinyloxy)-2-propanol (*XIII*)

A mixture of *I* (14·2; 0·1 mol), 1-chloromethyloxirane (50 ml), acetonitrile (100 ml) and potassium carbonate (21·0 g) was heated under stirring at 60°C for 6 h. The separated salt were filtered off, washed with toluene (2 × 20 ml), and the combined filtrates were evaporatedsunder reduced pressure. The residue (22·71 g) was dissolved in benzene and chromatographed on silica gel (600 g, Lachema L 100/160). Elution was carried out gradually with benzene and benzene–chloroform mixtures (20 and 50 vol.%) and finally with pure chloroform. The course of the chromatography was monitored by thin-layer chromatography on Silufol, using tetrachloromethane–ethyl acetate 2 : 1 for development. The fraction which contained a small amount of compound *X* was not worked up. The fraction containing *XIII* was evaporated: 5·24 g (22·3%). An analytical sample had m.p. 79·4—80·1°C and R_F 0·5 (Silufol, tetrachloromethane–ethyl acetate 2 : 1). For $C_8H_{11}ClN_2O_2S$ (234·7) calculated: 40·94% C, 4·72% H, 15·10% Cl, 11·93% N, 13·66% S; found: 41·22% C, 4·79% H, 15·26% Cl, 12·12% N, 13·66% S. ^{1}H-NMR spectrum: 2·55 s, 3 H (SCH_3); 2·73 bs, 1 H (OH); 3·77 d, J = 4·5, 2 H (CH_2Cl); 4·14 d, J = 4·0, 2 H (CH_2O); 4·24 m, J = 4·5 and 4·0, 1 H (CH—O); 8·29 s, 2 H (arom. H). ^{1}H-NMR ($CDCl_3$ + + TAI) spectrum: 2·54 s, 3 H (SCH_3); 3·88 d, J = 5·5, 2 H (CH_2Cl); 4·32 d, J = 5·0, 2 H (CH_2O); 8·29 s, 2 H (arom. H); 8·69 bs, 1 H (NH).

1,2-Epoxy-3-(2-methylthio-5-pyrimidinyloxy)propane (*X*)

A methanolic solution of *I* (14·2 g; 0·1 mol) was mixed with a methanolic sodium methoxide solution (2·3 g of sodium in 40 ml of methanol) and evaporated to dryness. The residue was distilled with toluene (2 × 25 ml), dissolved in dimethyl sulfoxide (50 ml) and treated with 1-chloromethyloxirane (8·65 ml; 0·11 mol). After standing overnight the starting component *I* disappeared from the reaction mixture. This was poured into water (400 ml) and extracted with chloroform (4 × 100 ml). The combined chloroform extracts were washed with water (100 ml), dried over anhydrous magnesium sulfate and evaporated. The residue (15·2 g; 76·7%) was dissolved in benzene and chromatographed on silica gel (450 g, Lachema L 100/160) with benzene and benzene–chloroform mixtures (10, 20 and 50 vol.% of chloroform). The chromatography course was followed by thin-layer chromatography (Silufol, tetrachloromethane–ethyl acetate 2 : 1). The fraction containing only a small amount of chlorohydrin *XIII* was not worked up. The fraction

containing epoxide *X* was evaporated under reduced pressure; yield, 1·24 g (6·26%). An analytical sample was crystallized from benzene, under addition of light petroleum, and then from diethyl ether, under addition of cyclohexane; m.p. 51·6—52·7°C, R_F 0·5 (the same system as above). For $C_8H_{10}N_2O_2S$ (198·2) calculated: 48·47% C, 5·08% H, 14·13% N, 16·17% S; found: 48·27% C, 5·15% H, 14·60% N, 16·05% S.

Diethyl Chloromalonate (see ref.[6])

Sulfuryl chloride (170 g; 1·25 mol) was added dropwise over one hour to stirred diethyl malonate (200 g; 1·25 mol) kept at 60—70°C. After another hour the mixture was heated to 160°C and then submitted to fractional distillation *in vacuo* (water pump). After four times repeated fractionation the yield was 216·2 g (88·9%) of a product with b.p. 98—103°C/1·2 kPa, lit.[6] gives 113°C/ /1·3 kPa.

Diethyl (2-Methylthio-5-pyrimidinyloxy)malonate (*IX*)

Dry sodium ethoxide (5·0 g; 0·22 mol) was dissolved in dimethyl sulfoxide (100 ml) and then added *I* (28·4 g; 0·2 mol). After dissolving and cooling to 20°C the mixture was treated with diethyl chloromalonate (38·7 g; 0·2 mol). After 40 min the temperature rose from 22 to 36°C. The next day the mixture was poured into ice-cold water (400 ml) and acidified weakly with hydrochloric acid. The precipitate was filtered off with suction, washed with water and dried in air: 58·2 g (96·9%). Crystallization from ethanol and water mixture (2 : 1) gave 45·5 g of a product with m.p. 48·8—49·3°C. For $C_{12}H_{16}N_2O_5S$ (300·3) calculated: 47·99% C, 5·37% H, 9·33% N, 10·67% S; found: 48·22% C, 5·32% H, 9·18% N, 10·68% S.

cis-3-(5-Methoxy-2-pyrimidinylthio)-2-propenol (*XV*) and
2-(5-Methoxy-2-pyrimidinylthio)-2-propenol (*XVI*)

A mixture of *XIV* (ref.[8]) (4·26 g; 30 mmol), 2-propinol (6·9 ml, 120 mmol) and powdered KOH (84 mg; 1·5 mmol) was heated at 130°C for 1 h, then neutralized with alcoholic HCl, evaporated under reduced pressure and then twice more with 10 ml benzene. The residue (6·0 g) was dissolved in benzene and applied onto a silica gel column (120 g, Kiseelgel 60 reinst, Merck) and chromatographed with benzene and benzene with increasing amounts of chloroform (5, 10, 20 and 40 vol.%). The elution was monitored by thin-layer chromatography on Silufol, using tetrachloromethane–ethyl acetate 1 : 2 for development. Evaporation of the first fraction gave 1·51 g (25·4%) of compound *XVI*, m.p. 42—44°C. An analytical sample had m.p. 43·0—43·7°C (benzene–cyclohexane 1 : 1). R_F 0·39 in the above system. For $C_8H_{10}N_2O_2S$ (198·2) calculated: 48·47% C, 5·08% H, 14·13% N, 16·17% S; found: 48·91% C, 5·13% H, 14·48% N, 15·80% S. ^{1}H-NMR spectrum: 3·86 s, 3 H (OCH_3); 3·90 bs, 1 H (OH) and 4·37 bs, $J \approx$ 1·2 and 0·8, 2 H (CH_2O); 5·81 bs, $J \approx$ 0·8 and 0·4, 1 H; 5·94 bs, $J \approx$ 1·2 and 0·4, 1 H ($C{=}CH_2$); 8·25 s, 2 H (arom. H). ^{1}H-NMR ($CDCl_3$ + TAI): 3·88 s, 3 H (OCH_3); 5·09 bs, $J \approx$ 1·2 and 0·8, 2 H (CH_2O); 5·92 bs, $J \approx$ 0·8 and 0·4, 1 H and 6·02 bs, $J \approx$ 1·2 and 0·4, 1 H ($C{=}CH_2$); 8·25 s, 2 H (arom.H);8·65bs, 1 H (NH). After the next, intermediary fraction which contained both substances (0·36 g) the fraction containing pure compound *XV* followed. Yield, 2·76 g (46·4%). It was crystallized from a water–ethanol mixture 5 : 1, affording 2·1 g (35·3%) of a product melting at about 47°C. Distillation at 80°C (bath temperature) and 30 Pa a substance was obtained with m.p. 54·2—55·1°C; R_F 0·48 (Silufol, tetrachloromethane–ethyl acetate 1 : 2). For $C_8H_{10}N_2O_2S$ (198·2) calculated: 48·47% C, 5·08% H, 14·13% N, 16·17% S; found: 48·64% C, 5·12% H, 14·27% N, 16·36% S. ^{1}H-NMR spectrum: 2·00 t, J = 5·5, 1 H (OH); 3·87 s, 3 H (OCH_3); 4·34 m, J = 5·5, 6·5 and 1·2,

2 H (CH_2O); 4·95 dd, J = 6·5 and 1·2, 2 H (CH_2O); 6·05 dd, J = 10·0 and 6·5, 1 H (CH=C—S); 7·08 dd, J = 10·0 and 1·2, 1 H (C=CH—S); 8·33 s, 2 H (arom. H). ^{1}H-NMR ($CDCl_3$ + TAI): 3·91 s, 3 H (OCH_3); 4·95 dd, J = 6·5 and 1·2, 2 H (CH_2O); 6·01 dd, J = 9·0 and 6·5, 1 H (CH=C—S); 7·33 dd, J = 9·0 and 1·2, 1H (C=CH—S); 8·30 s, 2 H (arom. H); 8·50 bs, 1 H (NH).

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