NUCLEOPHILIC SUBSTITUTIONS IN THE 2-METHANESULFONYLPYRIMIDINE SERIES

Z. BUDĚŠÍNSKÝ and J. VAVŘINA

Research Institute for Pharmacy and Biochemistry, Prague 3

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Oxidation of 2-methylthio-5-R-pyrimidines (*Va—i*) afforded the sulfones *VIa—i*, the nucleophilic substitution of which with sodium methoxide, hydrazine, benzylamine, sodium cyanide, sodium hydrogen sulfide and methyl sodio-cyanoacetate led to the corresponding 2-methoxy-, 2-mercapto-, 2-hydrazino-, 2-benzylamino-, 2-cyano- and 2-(methoxycarbonylcyanomethyl)-5-R-pyrimidines (*VII—XI, XVI*). Treatment of the derivative *VIe* with hydrazine and benzylamine afforded 5-hydrazino(*XVII*) and 5-benzylamino-2-methanesulfonylpyrimidine (*XVIII*), resp. At 10—20°C, the 2-methanesulfonyl-5-halopyrimidines *VIe—g* furnished the corresponding 2-cyano derivatives *XIe—g* which reacted at a higher temperature with the resulting sodium methanesulfinate under the formation of 2-cyano-5-methanesulfonylpyrimidine (*XIV*). 2-Cyano-5-R-pyrimidines *XIb,c,e,f,g* exhibit an intensive sweet taste.

In contrast to the poorly reactive dialkylsulfones and alkylarylsulfones, the nucleophilic substitutions of 2-, 4- and 6-alkanesulfonylpyrimidines are relatively easy. Thus, the 2-methanesulfonylpyrimidines are known to undergo an alkaline and an acidic hydrolysis under the formation of 2-hydroxypyrimidines[1] and substitution reactions with alkoxides[2], aliphatic and aromatic amines[2,3], sodio-sulfanilamide[4], sodium azide[3] and hydrazine[3]. The latter substitutions are also of preparative interest since the 2-alkanesulfonylpyrimidines are readily accessible by reaction of alkylisothioureas with β-dicarbonylic compounds. Some time ago, the substitution of 2-methanesulfonyl-5-alkoxypyrimidines has been used in the preparation of 2-sulfanilamido derivatives[4] (it has been observed that the substituent at position 5 has a strong influence on the mobility of the methanesulfonyl group).

Heating of 4-hydroxy- and 4-amino-2-methanesulfonyl-5-methoxypyrimidine with sodium methoxide at 140°C for 8 hours gave the corresponding 2-methoxy compounds[5]. The relatively low reactivity of the methanesulfonyl group is ascribed by these authors[5] to the influence of the methoxyl group at position 5. According to our observations, however, the reaction of 2-methanesulfonyl-5-methoxypyrimidine (*VIc*) with sodium methoxide proceeds at room temperature. Consequently, the reactivity of 4-hydroxy- and 4-amino-2-methanesulfonyl-5-methoxypyrimidine does not depend only on the methoxyl group at position 5 but also on the presence of the 4-hydroxy or 4-amino group.

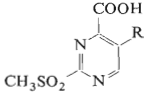
The influence of the substituent at position 5 was investigated in a series of 2-methanesulfonylpyrimidines *VIa—i* on their behaviour towards various nucleophilic agents (the 5-substituents differed by the electroaffinity). Compounds *VIa—i* were

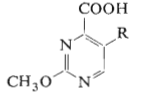
prepared by oxidation of 2-methylthio-5-R-pyrimidines *Va–i* or their intermediates with sodium hypochlorite, gaseous chlorine in aqueous media or with hydrogen peroxide in acetic acid. The oxidation with sodium hypochlorite is especially advantageous since the reaction occurs at room temperature and the product is obtained directly as a solid. The sodium hypochlorite solution must be free of sodium hydroxide (addition of sodium hydrogen carbonate) since the oxidation is considerably slower in the presence of free sodium hydroxide. The oxidation with chlorine is also very fast but it is more difficult to determine the required amount of the agent. The oxidation with 30% hydrogen peroxide in acetic acid is slow and requires about 3–5 days at room temperature.

The reaction of compounds *VIa–i* with methanolic sodium methoxide gave the expected 2-methoxy-5-R-pyrimidines *VIIb–i*. An analogous treatment of 5-chloro-(*If*) and 5-bromo-2-methanesulfonyl-4-pyrimidinecarboxylic acid (*Ig*) afforded readily the corresponding 2-methoxy derivatives *IIf* and *IIg*. At about 0°C, the reaction of 2-methanesulfonyl-5-fluoropyrimidine (*VIe*) and sodium methoxide led to 2-methoxy-5-fluoropyprimidine (*VIIe*) while at a higher temperature and with the use of excess sodium methoxide, 2,5-dimethoxypyrimidine (*VIIc*) resulted because of a simultaneous substitution of the fluoro atom at position 5. 5-Chloro- (*VIf*) and 5-bromo-2-methanesulfonylpyrimidine (*VIg*) afforded exclusively the monosubstituted derivatives, namely, 5-chloro-(*VIIf*) and 5-bromo-2-methoxypyrimidine (*VIIg*) which did not change when refluxed in excess methanolic sodium methoxide. This behaviour might be explained by the –I effect; in the series of halo atoms, this effect is the strongest with the fluoro atom. The anomalous behaviour of the fluoro derivative *VIe* was especially striking in the reaction with hydrazine and benzylamine: a preferential substitution of the fluoro atom occurred under the formation of 5-hydrazino- (*XVII*) and 5-benzylamino-2-methanesulfonylpyrimidine (*XVIII*). The reaction of other 2-methanesulfonyl-5-R-pyrimidines with hydrazine led to the expected 2-hydrazino derivatives *IXb,c,h,i* while the expected 2-benzylamino derivatives *Xa,b,c,f,g* were formed by reaction with benzylamine. On treatment with aqueous sodium hydrogen sulfide, the sulfones *VIc* and *VIf* afforded the expected 2-mercaptopyrimidines *VIIIc* and *VIIIf*, resp.

The reaction of 2-methanesulfonyl-5-R-pyrimidines with alkali metal cyanides afforded good yields of nitriles *XIb,c,e,f,g,i*. In dimethyl sulfoxide as the solvent of choice, the reaction was exothermic. In ethanol as solvent, the reaction of the bromo derivative *VIg* with sodium cyanide gave a mixture containing a small amount of the expected 2-cyano derivative *XIg* along with the predominant 2-ethoxy-5-bromopyrimidine. At a temperature not exceeding 20°C, the reaction of 5-halopyrimidines *VIe–g* with sodium cyanide led to the expected product. At higher temperatures (*i.e.*, when the reaction mixture was not cooled), mixtures of products were obtained. At temperatures above 100°C, 2-cyano-5-methanesulfonylpyrimidine (*XIV*) was obtained from all the three 2-methanesulfonyl-5-halopyrimidines *VIe–g*. The forma-

tion of compound *XIV* might be explained as follows. The expected replacement of the methanesulfonyl group by the cyano group is accompanied by the formation of sodium methanesulfonate which reacts at a higher temperature with the halo atom at position 5 to give the final 2-cyano-5-methanesulfonylpyrimidine (*XIV*). The corresponding 2,5-dicyanopyrimidine is not formed even with the use of a three- to fivefold molar excess of sodium cyanide. The attempted conversion of compound *XIV* with sodium methoxide to 2-cyano-5-methoxypyrimidine (*XIc*) resultsed in the formation of 2-methoxy-5-methanesulfonylpyrimidine (*XV*). The extraordinary reactivity of the nitrile group at position 2 may be exemplified by additional reactions, for example by the sodium methoxide treatment of 5-chloro- (*XIf*) and 5-bromo-2-cyanopyrimidine (*XIg*) to give the 5-chloro- and 5-bromo-2-methoxypyrimidine and by the sodium mercaptide treatment resulting in the formation of 5-chloro- and 5-bromo-2-methylthiopyrimidine, resp. The stepwise hydrolysis of nitriles *XIf* and *XIg* gave the amides *XIIf* and *XIIg* and then the carboxylic acids *XIIIf* and *XIIIg*.


If,g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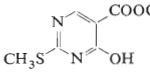
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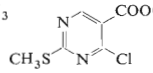
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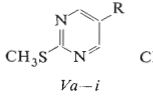
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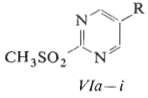
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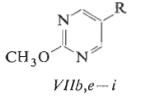
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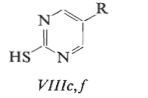
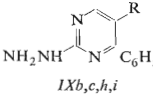
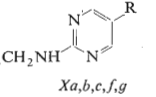
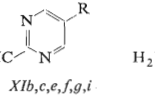
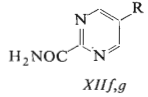
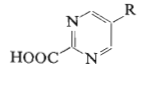

VIIIc,f


IXb,c,h,i


Xa,b,c,f,g


XIb,c,e,f,g,i


XIIf,g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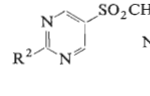
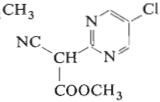
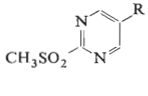

XIV, $R^2 = CN$
XV, $R^2 = CH_3O$


XVI


XVII, R = $NHNH_2$
XVIII, R = $NHCH_2C_6H_5$

a, R = H
b, R = CH_3
c, R = OCH_3
d, R = $OCH_2CH_2OCH_3$
e, R = F
f, R = Cl
g, R = Br
h, R = $COOCH_3$
i, R = CN

The substitution of the 2-methanesulfonyl group by a bulky anion was exemplified by reaction of 2-methanesulfonyl-5-chloropyrimidine with methyl sodio-cyanoacetate in methanol to give a satisfactory yield of methyl (5-chloro-2-pyrimidinyl)cyanoacetate (*XVI*). The attempted reactions of 2-methanesulfonylpyrimidines with weakly nucleophilic agents such as potassium fluoride, bromide and iodide did not meet with success.

Conclusively, the nucleophilic substitution in the 2-methanesulfonyl-5-R-pyrimidine series is primarily controlled by the −M effect of the two heterocyclic nitrogen atoms and then, in the second place, by the substituent at position 5. Consequently, the substitution of all the above mentioned 2-methanesulfonyl-5-R-pyrimidines (except for the 5-fluoro derivative *VIe*) takes place at position 2 which is strongly electron deficient due to the —M and —I effect of vicinal nitrogen atoms of the pyrimidine ring. The nucleophilic substitution of both 2-methanesulfonyl-5-cyanopyrimidine (*VIi*) and 2-cyano-5-methanesulfonylpyrimidine (*XIV*) by a methoxyl group occurs at position 2 in spite of the considerably different —M effect of the corresponding 2-substituents. Similarly, in the case of 2-methanesulfonyl-5-chloropyrimidine (*VIf*), it is the methanesulfonyl group which is replaced by the methoxyl; on the other hand, in the benzene series where the barrier of nitrogen atoms is absent, it is the chloro atom and not the methanesulfonyl group which undergoes the replacement.

The nitriles *XIb,c,e,f,g* exhibit a strong sweet taste, especially the 5-bromo (*XIg*) and 5-chloro (*XIf*) derivative which are approximately 500 and 250 times, resp., as sweet as saccharose.

EXPERIMENTAL

Melting points were taken on a heated microscope stage (Kofler block). Analytical samples were dried for 2 hours at 0·1 Torr and such a temperature corresponding to the melting point value.

2-Methanesulfonyl-5-chloro-4-pyrimidinecarboxylic Acid (*If*)

A mixture of 2-methylthio-5-chloro-4-pyrimidinecarboxylic (123 g) acid[6] and glacial acid (450 ml) was treated dropwise under stirring over 2 hours with 25% aqueous hydrogen peroxide (175 ml) and the whole kept at room temperature for four days. The solid was collected with suction and washed with water to afford 92 g (65%) of the acid *If*, m.p. 178—180°C (decarboxylation). The analytical sample was recrystallised from water (the melting point value did not change). For $C_6H_5ClN_2O_4S$(236·6) calculated: 30·45% C, 2·13% H, 14·98% Cl, 11·84% N, 13·55% S; found: 30·71% C, 2·13% H, 14·91% Cl, 11·60% N, 13·24% S.

2-Methanesulfonyl-5-bromo-4-pyrimidinecarboxylic Acid (*Ig*)

The title compound was prepared by oxidation of 2-methylthio-5-bromo-4-pyrimidinecarboxylic acid[6] analogously to the preparation of compound *If*. Yield, 75% of the acid *Ig*, m.p. 188—190°C. The analytical sample was recrystallised from water; m.p. 192—193°C. For $C_6H_5BrN_2O_4S$ (281·1) calculated: 25·64% C, 1·79% H, 28·43% Br, 9·96% N, 11·41% S; found: 25·88% C, 2·08% H, 28·23% Br, 9·82% N, 11·67% S.

2-Methoxy-5-chloro-4-pyrimidinecarboxylic Acid (*IIf*)

A solution of compound *If* (4·72 g) in 1M methanolic sodium methoxide (40 ml) was refluxed for one hour and evaporated. The residue was dissolved in water (30 ml) and the solution acidified to Congo Red paper with dilute hydrochloric acid to deposit a solid which was collected with suction and washed with water. Yield, 3·0 g (80%) of the acid *IIf*, m.p. 170—172°C (decomp.). The analytical sample was crystallised from 50% aqueous methanol (the melting point value did not change). For $C_6H_5ClN_2O_3$ (188·6) calculated: 38·22% C, 2·67% H, 18·80% Cl, 14·86% N; found: 38·32% C, 2·84% H, 18·79% Cl, 14·64% N.

2-Methoxy-5-bromo-4-pyrimidinecarboxylic Acid (*IIg*)

The title compound was prepared analogously to the acid *IIf*. Yield, 90% of the acid *IIg*, m.p. 170—173°C. The analytical sample was recrystallised from 50% aqueous methanol; m.p. 171 to 173°C (decomp.). For $C_6H_5BrN_2O_3$ (233·0) calculated: 30·92% C, 2·16% H, 34·29% Br, 12·02% N; found: 31·05% C, 2·30% H, 34·40% Br, 11·89% N.

Methyl 2-Methylthio-6-hydroxy-5-pyrimidinecarboxylate (*III*)

The title compound was prepared analogously to the corresponding ethyl ester[7]. An aqueous solution of methylisothiourea sulfate (104 g) and methyl ethoxymethylenemalonate (155 g) was treated dropwise under stirring at 8—10°C over 50 minutes with a solution of potassium hydroxide (105 g) in water (200 ml). The reaction mixture was kept at room temperature overnight, washed with benzene,and the aqueous layer acidified with concentrated hydrochloric acid (120 ml) to deposit a solid which was collected with suction and washed with water. Yield, 106 g (64·5%) of the methyl ester *III*, m.p. 200—203°C. The analytical sample, m.p. 207—209°C (70% aqueous methanol). For $C_7H_8N_2O_3S$ (200·2) calculated: 41·99% C, 4·03% H, 13·99% N, 16·02% S; found: 41·75% C, 4·35% H, 14·00% N, 15·86% S.

Methyl 2-Methylthio-6-chloro-5-pyrimidinecarboxylate (*IV*)

A mixture of compound *III* (106 g), thionyl chloride (530 ml), and dimethylformamide (16 ml) was refluxed for one hour and the excess thionyl chloride distilled off. The residue was mixed with crushed ice, the solid collected with suction, and dissolved in ether (500 ml). The ethereal solution was washed with aqueous potassium hydrogen carbonate to remove the acidic reaction, dried over calcium chloride, and evaporated to afford 102 g (88·5%) of the ester *IV*, m.p. 69—72°C. The analytical sample, m.p. 76—78°C (60% aqueous methanol). For $C_7H_7ClN_2O_2S$ (218·7) calculated: 38·45% C, 3·23% H, 16·21% Cl, 12·81% N, 14·67% S; found: 38·50% C, 3·51% H, 16·04% Cl, 12·67% N, 14·40% S.

2-Methylthio-5-(2-methoxyethoxy)pyrimidine (*Vd*)

A solution of sodium 2-methoxyethoxide (prepared from 13·8 g of sodium and 120 ml of 2-methoxyethanol) was treated at 100—120°C with 2-methylthio-5-hydroxypyrimidine[8] (72 g) in 2-methoxyethanol (100 ml) and then with 2-methoxyethyl chloride (57 g). The dark mixture was heated under stirring for 3 hours at 110—130°C. The 2-methoxyethanol was then evaporated under diminished pressure and the residue triturated (while hot) with ethanol (150 ml) to deposit sodium chloride which was filtered off and washed with ethanol. The filtrate was concentrated to a small volume and the concentrate cooled in a refrigerator to deposit crystals which were collected with suction and washed with a small amount of ethanol and benzene. Yield, 51 g (51%) of com-

pound *Vd*, m.p. 56–58·5°C. The analytical sample was recrystallised from aqueous ethanol (the melting point value did not change). For $C_8H_{12}N_2O_2S$ (200·3) calculated: 47·97% C, 6·04% H, 13·99% N, 16·01% S; found: 47·76% C, 6·04% H, 14·16% N, 16·03% S.

Methyl 2-Methylthio-5-pyrimidinecarboxylate (*Vh*)

A solution of compound *IV* (32·5 g) in a mixture of ethanol (125 ml) and water (30 ml) was treated portionswise at 80°C under stirring with Zn powder (98 g) and the mixture refluxed for one hour. The zinc was filtered off, washed with hot ethanol, and the combined filtrates evaporated. The residue was dissolved in ether (250 ml) and the ethereal solution evaporated to afford 12·5 g (45%) of the ester *Vh*, m.p. 86–88°C. The analytical sample was recrystallised from methanol; m.p. 95–96°C. For $C_7H_8N_2O_2S$ (184·2) calculated: 45·64% C, 4·38% H, 15·21% N, 17·41% S; found: 45·81% C, 4·61% H, 15·35% N, 17·32% S.

2-Methylthio-5-chloropyrimidine (*Vf*)

2-Methylthio-5-chloro-6-pyrimidinecarboxylic acid[9] (51·1 g) was decarboxylated by heating in anisol (100 ml) at 160–170°C. When the evolution of carbon dioxide ceased (after about two hours), the anisol was evaporated under diminished pressure and the residue crystallised

TABLE I

2-Methoxy-5-R-pyrimidines *VII*, Yields, Properties and Analyses

Compound (yield, %)	Temperature, °C (time, min)	M.p., °C (solvent)	Formula (mol.w.)	Calculated/Found			
				% C	% H	% N	% Hal
VIIb (79)	reflux (60)	[a]	$C_6H_8N_2O$ (124·1)	58·05 / 58·09	6·50 / 6·78	22·57 / 22·43	
VIIe (42)	−5–0 (120)	[b]	$C_5H_5FN_2O$ (128·1)	46·88 / 46·55	3·93 / 3·86	21·87 / 21·64	14·83 / 14·90
VIIf (71)	20–30 (10)	51–52 (50% methanol)	$C_5H_5ClN_2O$ (144·6)	41·54 / 41·61	3·49 / 3·73	19·38 / 19·10	24·53 / 24·31
VIIg (66)	20–30 (10)	57–57·5 (50% methanol)	$C_5H_5BrN_2O$ (189)	31·77 / 31·96	2·66 / 2·96	14·82 / 14·99	42·28 / 42·45
VIIh (78)	30–35 (60)[c]	128–129 (benzene–light petroleum)	$C_7H_8N_2O_3$ (168·2)	50·00 / 50·09	4·80 / 5·07	16·66 / 16·65	
VIIi (66)	20–30 (60)	81–81·5 (light petroleum)	$C_6H_5N_3O$ (135·1)	53·33 / 53·11	3·73 / 4·00	31·10 / 30·80	

[a] B.p. 78–79°C/8·5 Torr, n_D^{18} 1·5040; [b] b.p. 52°C/12 Torr, n_D^{20} 1·4785; [c] sodium methoxide was diluted to the concentration of 0·5M-$NaOCH_3$.

from 50% aqueous methanol. Yield, 26 g (65%) of compound *Vf*, m.p. 55–56°C. The analytical sample, m.p. 55–57°C (50% aqueous methanol). For $C_5H_5ClN_2S$ (160·6) calculated: 37·40% C, 3·14% H, 22·08% Cl, 20·00% S; found: 37·62% C, 3·20% H, 22·22% Cl, 19·50% S.

2-Methylthio-5-cyanopyrimidine (*Vi*)

A mixture containing 2-methylthio-4-chloro-5-cyanopyrimidine[9] (44·0 g), ethanol (400 ml), water (80 ml), and zinc powder (78·0 g) was refluxed under stirring for 30 minutes, the zinc filtered off, washed with hot ethanol, and the combined filtrates evaporated under diminished pressure. The residue solidified after the addition of water (10 ml). Crystallisation from 50% aqueous ethanol afforded 11·5 g (32%) of compound *Vi*, m.p. 78–80°C. The analytical sample, m.p. 81–81·5°C (ethanol). For $C_6H_5N_3S$ (151·2) calculated: 47·66% C, 3·33% H, 27·80% N, 21·21% S; found: 47·92% C, 3·58% H, 27·60% N, 21·21% S.

2-Methanesulfonylpyrimidine (*VIa*)

Aqueous sodium hypochlorite (1130 ml containing 1·28 mol of NaOCl) was added dropwise over 90 minutes under vigorous stirring at 40–45°C into a suspension of compound[10] *Va* (73·0 g) in water (130 ml). The reaction mixture was then extracted with four 400 ml portions of chloroform, the extracts evaporated, and the residue crystallised from ethanol to afford 79 g (86%) of compound *VIa*, m.p. 72–73°C (ethanol); reported[3], m.p. 73–74°C for a specimen obtained by oxidation of compound *Va* with gaseous chlorine.

2-Methanesulfonyl-5-methylpyrimidine (*VIb*)

A. *Oxidation with chlorine.* Chlorine gas was introduced into a suspension of compound[11] *Vb* (40·5 g) in water (350 ml) until the coloration disappeared. The reaction mixture was extracted with four 100 ml portions of chloroform, the extracts combined, washed with water, and evaporat-

TABLE II

2-Hydrazino-5-R-pyrimidines *IX* Yields, Properties and Analyses

Compound (yield, %)	Temperature, °C (time, min)	M.p., °C solvent	Formula (mol.w.)	Calculated/Found		
				% C	% H	% N
IXb (71)	100 (30)	137–140 (ethanol)	$C_5H_8N_4$ (124·2)	48·37 48·39	6·49 6·63	45·13 45·37
IXc (71)	100 (180)	141·5–142·5 (ethanol)	$C_5H_8N_4O$ (140·2)	42·85 43·04	5·75 6·00	39·98 39·76
IXh (82)	40 (30)	224–226 (50% methanol)	$C_6H_8N_4O_2$ (168·2)	42·86 43·06	4·80 5·06	33·32 32·99
IXi (74)	50 (15)	163–164,5 (ethanol)	$C_5H_5N_5$ (135·1)	44·44 44·62	3·73 4·00	51·83 51·65

ed to afford 45·1 g (90%) of compound *VIb*, m.p. 70—75°C. The analytical sample, m.p. 79—81°C (ethanol–light petroleum). For $C_6H_8N_2O_2S$ (172·2) calculated: 41·85% C, 4·68% H, 16·27% N, 18·62% S; found: 42·09% C, 4·97% H, 16·33% N, 18·90% S.

B. *Oxidation with hydrogen peroxide.* A solution of compound *Vb* (14·0 g) in acetic acid (40 ml) was treated with 25% aqueous hydrogen peroxide (40 ml) and set aside. In the course of 75 minutes, the temperature rose spontaneously from 20°C to 30°C. After 5 days, the reaction mixture was diluted with water (200 ml) and extracted with three 100 ml portions of chloroform. The combined extracts were washed with saturated aqueous sodium carbonate, dried over sodium sulfate, and evaporated. Yield, 10·2 g (59%) of compound *VIb*, m.p. 72—74°C. After recrystallisation from light petroleum, the melting point rose to 79—81°C.

2-Methanesulfonyl-5-(2-methoxyethoxy)pyrimidine (*VId*)

Aqueous sodium hypochlorite previously neutralised with sodium hydrogen carbonate (435 ml of a 1·285M solution) was added dropwise under stirring at 20—40°C into a suspension of compound *Vd* (50·0 g) in water (60 ml). The excess hypochlorite was destroyed by the addition of sodium sulffite, the product collected with suction, and washed with water. Yield, 53·0 g (91·5%) of compound *VId*. The analytical sample, m.p. 87—88°C (water). For $C_8H_{12}N_2O_4S$ (232·3) calculated: 41·37% C, 5·21% H, 12·06% N, 13·80% S; found: 41·20% C, 5·37% H, 11·99% N, 13·50% S.

2-Methanesulfonyl-5-chloropyrimidine (*VIf*)

A. Compound *If* (114·0 g) was refluxed in anisol (115 ml) until the evolution of carbon dioxide ceased (2 hours). The reaction mixture was then cooled down to deposit a solid which was collected with suction and washed with light petroleum. Yield, 82·0 g (88%) of compound *VIf*, m.p. 120—123°C. The analytical sample, m.p. 123—125°C (ethanol). For $C_5H_5ClN_2O_2S$ (192·6) calculated: 31·18% C, 2·62% H, 18·41% Cl, 14·55% N, 16·65% S; found: 31·38% C, 2·83% H, 18·52% Cl, 14·69% N, 16·86% S.

B. The oxidation of compound *Vf* with hydrogen peroxide was effected analogously to the preparation of compound *VIb* from *Vb*. The product crystallised in the course of 5 days. Yield, 60% of compound *VIf*, m.p. 120—123°C.

2-Methanesulfonyl-5-bromopyrimidine (*VIg*)

The decarboxylation of compound *Ig* was performed under analogous conditions as that of compound *If*. Yield, 78% of compound *VIg*, m.p. 126—130°C. The analytical sample, m.p. 132 to 133°C (ethanol). For $C_5H_5BrN_2O_2S$ (237·1) calculated: 25·33% C, 2·12% H, 33·71% Br, 11·82% N, 13·52% S; found: 25·58% C, 2·35% H, 33·67% Br, 11·98% N, 13·74% S. Compound *VIg* was also obtained by oxidation of compound *Vg* in a 62% yield.

Methyl 2-Methanesulfonyl-5-pyrimidinecarboxylate (*VIh*)

Chlorine gas was introduced under stirring at 30—35°C into a solution of compound *Vh* (12·2 g) in 70% aqueous methanol (20 minutes), the reaction mixture cooled down, and the solid collected with suction. Yield, 9·2 g (64%) of compound *VIh*, m.p. 120—122°C. The analytical sample, m.p. 129—131·5°C. For $C_7H_8N_2O_4S$ (216·2) calculated: 38·85% C, 3·73% H, 12·96% N, 14·83% S; found: 38·95% C, 3·68% H, 13·04% N, 14·82% S.

2-Methanesulfonyl-5-cyanopyrimidine (*VIi*)

Chlorine gas was introduced under stirring at 20—25°C into a solution containing compound *Vi* (15·1 g), ethanol (450 ml), and water (150 ml) for 15 minutes and the reaction mixture cooled in a refrigerator to deposit a solid which was collected with suction and washed with ethanol (10 ml). Yield, 16·5 g (90%) of compound *VIi*, m.p. 160—162°C. The analytical sample, m.p. 172—173°C (ethanol). For $C_6H_5N_3O_2S$ (183·2) calculated: 39·34% C, 2·75% H, 22·94% N, 17·50% S; found: 39·59% C, 2·95% H, 22·68% N, 17·58% S.

2-Methoxy-5-R-pyrimidines (*VIIb,e—i*)

The corresponding 2-methanesulfonyl-5-R-pyrimidine *VIb,e—i* (0·01 mol) was dissolved in 12 ml (10 ml, *i.e.* 1 equivalent in the case of the 5-fluoro derivative *VIe*) of methanolic 1M sodium methoxide. When the reaction was accomplished, the mixture was neutralised with dilute hydrochloric acid, evaporated under diminished pressure, and the residue mixed with a small amount of water (5—10 ml). The product was either collected with suction (when solid) or isolated by extraction with ether or chloroform and evaporation of the solvent under diminished pressure (Table I).

2-Mercapto-5-methoxypyrimidine (*VIIIc*)

A suspension of compound *VIc* (18·8 g) in 8·38M-NaSH (24 ml) was heated under stirring on a steam bath for one hour and the resulting solution adjusted to pH 2 with dilute hydrochloric acid to deposit an orange-coloured product which was collected with suction and washed with water. Yield, 10·5 g (74%) of compound *VIIIc*, m.p. 176—178°3C. The analytical sample, m.p. 179—181°C (60% aqueous ethanol). For $C_5H_6N_2OS$ (142·2) calculated: 42·24% C, 4·25% H, 19·70% N, 22·55% S; found: 42·24% C, 4·54% H, 19·83% N, 22·68% S.

2-Mercapto-5-chloropyrimidine (*VIIIf*)

A solution of compound *VIg* (3·86 g) in dimethyl sulfoxide was treated dropwise under stirring with 7M-NaSH (3·6 ml). When the exothermic reaction ceased (47°C), the mixture was stirred for additional 30 minutes, diluted with water (50 ml), and acidified with hydrochloric acid. The orange precipitate was collected with suction and washed with water. Yield, 2·7 g (92%) of compound *VIIIf*, m.p. 218—221°C (reported[12], m.p. 221—222°C.)

2-Hydrazino-5-R-pyrimidines (*IXb,c,h,i*)

A solution of the corresponding 2-methanesulfonyl-5-R-pyrimidine (0·1 mol) and hydrazine hydrate (0·2 mol) in dimethyl sulfoxide (30—120 ml) was heated at a temperature given in Table II, the reaction mixture diluted with an equal volume of water, and the precipitate of the crude product collected with suction (Table II).

2-Methanesulfonyl-5-hydrazinopyrimidine (*XVII*)

A solution of compound[13] *VIe* (1·76 g) and hydrazine hydrate (1·1 g) in ethanol (20 ml) was refluxed for 15 minutes and the ethanol evaporated under diminished pressure. Yield, 1·6 g (85%) of compound *XVII*, m.p. 182—184°C. The analytical sample, m.p. 186—189°C (50% aqueous ethanol). For $C_5H_8N_4O_2S$ (188·2) calculated: 31·91% C, 4·28% H, 29·77% N, 17·04% S; found: 32·18% C, 4·47% H, 29·63% N, 17·00% S.

2-Benzylamino-5-R-pyrimidines (*Xa,b,c,f,g*)

A mixture of the corresponding 2-methanesulfonyl-5-R-pyrimidine (0·01 mol), 0·02 or 0·03 mol (Table III) of benzylamine, and dimethyl sulfoxide (5 ml) was heated at the given temperature for the given period of time, the whole diluted with water (5—10 ml), the precipitate collected with suction, and recrystallised. For melting points and elemental analyses see Table III.

2-Cyano-5-methylpyrimidine (*XIb*)

A mixture of compound *VIb* (5·16 g), sodium cyanide (1·5 g), and dimethyl sulfoxide (10 ml) was heated under stirring for one hour at 100°C, diluted with water (25 ml), and the precipitate collected with suction to afford 2·4 g (67%) of compound *XIb*, m.p. 55—62°C. After recrystallisation from 20% aqueous ethanol, the m.p. was 66—67°C. For $C_6H_5N_3$ (119·1) calculated: 60·49% C, 4·23% H, 35·27% N; found: 60·38% C, 4·52% H, 35·04% N.

2-Cyano-5-fluoropyrimidine (*XIe*)

A solution of compound *VIe* (1·76 g) in acetonitrile (20 ml) was treated portionwise with 0·5 g of sodium cyanide, the whole refluxed for 30 minutes, and evaporated under diminished pressure almost to dryness. The residue was extracted with three 20 ml portions of benzene, the extract evaporated to dryness, and the residue dissolved in a small amount of a mixture of ethyl acetate

TABLE III

2-Benzylamino-5-R-pyrimidines *X*, Yields, Properties and Analyses

Compound (yield, %)	Temperature, °C (time, h)	M.p., °C (% ethanol)	Formula (mol.w.)	Calculated/Found		
				% C	% H	% N
Xa (97·2)	100 (1)[a]	81—82 (50)	$C_{11}H_{11}N_5$ (185·2)	71·33 71·22	6·00 6·59	22·69 22·83
Xb (40·2)	100 (2)[b]	107—108 (50)	$C_{12}H_{13}N_3$ (199·3)	72·33 72·57	6·58 7·33	21·09 20·88
Xc (26)	150 (2)[a]	101·5—102·5 (80)	$C_{12}H_{13}N_3O$ (215·3)	66·95 66·92	6·08 6·44	19·52 19·27
Xf[c] (79·5)	100 (1)	130—132	—	—	—	—
Xg (98·5)	100 (1)[a]	136·5—138 (50)	$C_{11}H_{10}BrN_3$[d] (264·1)	50·02 50·04	3·82 4·36	15·91 16·02

[a] 0·01 mol of the sulfone and 0·03 mol of benzylamine; [b] 0·01 mol of the sulfone, 0·02 mol of benzylamine, and 5 ml of dimethyl sulfoxide; [c] reported[14], m.p. 130—132°C, for a specimen obtained by reaction of benzyl chloride with 2-amino-5-chloropyrimidine; [d] % Br, calculated: 30·25; found: 30·13.

and tetrachloromethane (1 : 1). The solution was applied to a column of silica gel (5 g). The elution was performed with the same solvent mixture, 10 ml fractions being taken and evaluated by thin-layer chromatography on silica gel. Fraction 2 which contained the product, was evaporated under diminished pressure to afford 0·53 g of a solid which was crystallised from pentane and purified by sublimation. M.p. of compound *XIe*, 44·0—44·7°C. For $C_5H_2FN_3$ (123·1) calculated: 48·79% C, 1·64% H, 15·43% F; found: 48·91% C, 1·93% H, 15·34% F.

2-Cyano-5-chloropyrimidine (*XIf*)

A solution of compound *VIf* (11·5 g) in dimethyl sulfoxide (30 ml) was treated portionwise at 10°C with sodium cyanide (3·0 g). The reaction mixture was then diluted with ice-cold water (100 ml), the precipitate collected with suction, and washed with water. Yield, 6·5 g (78%) of compound *XIf*, m.p. 76—79°C. The analytical sample, m.p. 85—86°C (light petroleum). For $C_5H_2ClN_3$ (139·5) calculated: 43·04% C, 1·44% H, 25·41% Cl, 30·11% N; found: 43·30% C, 2·00% H, 25·43% Cl, 30·23% N.

2-Cyano-5-bromopyrimidine (*XIg*)

The title compound was prepared from the derivative *VIg* analogously to the preparation of compound *XIf* from *VIf*. Yield, 75% of compound *XIg*, m.p. 115—118°C. The analytical sample, m.p. 120—121°C (benzene–light petroleum). For $C_5H_2BrN_2$ (184·0) calculated: 32·64% C, 1·10% H, 43·43% Br, 22·84% N; found: 32·75% C, 1·30% H, 43·08% Br, 22·63% N.

2,5-Dicyanopyrimidine (*XIi*)

A solution of sodium cyanide (1·72 g) in water (10 ml) was added dropwise into a boiling solution of compound *VIi* (5·45 g) in chloroform (120 ml) and the whole mixture refluxed under stirring for 15 minutes. The chloroform layer was then separated, washed with water, dried over anhydrous calcium chloride, and evaporated to afford 3·0 g (76·5%) of compound *XIi*, m.p. 124—126°C. The analytical sample, m.p. 127—128°C (water). Compound *XIi* may be sublimed at 100°C/0·3 Torr. For $C_6H_2N_4$ (130·1) calculated: 55·39% C, 1·55% H, 43·07% N; found: 55·11% C, 2·02% H, 42·84% N.

2,5-Dimethoxypyrimidine (*VIIc*)

A solution of compound *VIe* (1·76 g) in methanolic sodium methoxide (from 0·69 g of sodium and 10 ml of methanol) was refluxed for one hour, evaporated, and the residue dissolved in water (5 ml). The aqueous solution was extracted with two 20 ml portions of chloroform and the extract evaporated. Yield, 0·55 g (39%) of compound *VIIc*. After crystallisation from water the m.p. was 70·0—70·6°C. Compound *VIIc* has been prepared earlier on treatment of 2-methanesulfonyl-5-methoxypyrimidine with sodium methoxide[8] and has shown the same melting point value.

Amide of 5-Chloro-2-pyrimidinecarboxylic Acid (*XIIf*)

A suspension containing compound *XIf* (6·95 g), ethanol (40 ml), and 30% hydrogen peroxide (20·4 ml) was treated dropwise under stirring with 5M-KOH (2·8 ml). When the exothermic reaction subsided, the mixture was stirred at 50°C for additional 3 hours. The resulting solution was neutralised with dilute hydrochloric acid and evaporated to a half of the original volume to deposit 6·4 g (82%) of the amide *XIIf*, m.p. 202—204°C. The analytical sample, m.p. 207—208°C

water). For $C_5H_4ClN_3O$ (157·6) calculated: 38·11% C, 2·56% H, 22·50% Cl, 26·67% N; found: 38·40% C, 2·72% H, 22·50% Cl, 26·45% N.

Amide of 5-Bromo-2-pyrimidinecarboxylic Acid (*XIIg*)

The title compound was prepared from the nitrile *XIg* analogously to the preparation of compound *XIIf* from the nitrile *XIf*. Yield, 75% of the amide *XIIg*, m.p. 203–205°C. The analytical sample, m.p. 208–210°C (water). For $C_5H_4BrN_3O$ (202·0) calculated: 29·73% C, 2·00% H, 39·55% Br, 20·80% N; found: 29·71% C, 2·30% H, 39·32% Br, 21·03% N.

5-Chloro-2-pyrimidinecarboxylic Acid (*XIIIf*)

A mixture of compound *XIf* (1·40 g) and 2M-NaOH (10 ml) was refluxed for 5 hours, cooled down, acidified with dilute hydrochloric acid, and the precipitate collected with suction. Yield, 0;97 g (61%) of the acid *XIIIf* which was recrystallised twice from water; m.p. 206·3–206·8°C. For $C_5H_3ClN_2O_2$ (158·6) calculated: 37·89% C, 1·91% H, 22·37% Cl, 17·67% N; found: 37·74% C, 1·98% H, 22·57% Cl, 17·91% N.

5-Bromo-2-pyrimidinecarboxylic Acid (*XIIIg*)

The title acid was prepared from the nitrile *XIg* analogously to the preceding preparation of the acid *XIIIf* from the nitrile *XIf*. M.p. of *XIIIg*, 197–198°C; reported, m.p. 192–193°C, for a specimen obtained by oxidation of 2-styryl-5-bromopyrimidine[15].

2-Cyano-5-methanesulfonylpyrimidine (*XIV*)

A solution of compound *VIg* (9·5 g) in dimethyl sulfoxide (20 ml) was treated under stirring with sodium cyanide (2·0 g). When the exothermic reaction subsided, the mixture was heated at 100°C for one hour, cooled down, diluted with water (120 ml), the precipitate collected with suction, and washed with water and ethanol to afford 5·1 g (71%) of the nitrile *XIV*, m.p. 185–187°C. The analytical sample, m.p. 191·0–192·5°C (water). For $C_6H_5N_3O_2S$ (183·2) calculated: 39·34% C, 2·75% H, 22·94% N, 17·50% S; found: 39·56% C, 2·95% H, 22·78% N, 17·52% S.

2-Methoxy-5-methanesulfonylpyrimidine (*XV*)

A mixture of compound *XIV* (1·83 g) and methanolic sodium methoxide (prepared from 0·23 g of sodium and 35 ml of methanol) was refluxed for one hour and then cooled down to deposit a solid which was collected with suction and recrystallised from water. Yield, 1·3 g (69%), m.p. 157–160°C. The analytical sample, m.p. 160–160·5°C (water). For $C_6H_6N_2O_3S$ (188·2) calculated: 38·29% C, 4·30% H, 14·89% N, 17·04% S; found: 38·37% C, 4·60% H, 14·78% N, 17·17% S.

Methyl (5-Chloro-2-pyrimidinyl)cyanoacetate (*XVI*)

A mixture of methyl cyanoacetate (2·4 g), methanolic sodium methoxide (prepared from 0·46 g of sodium and 50 ml of methanol), and compound *VIf* (3·85 g) was refluxed for 5 hours. The methanol was then evaporated, the residue dissolved in water, the solution neutralised with dilute hydrochloric acid, the precipitate collected with suction, and recrystallised from 80% aqueous methanol to afford 2·2 g (57%) of the ester *XVI*, m.p. 215–218°C. For $C_8H_6ClN_3O_2$ (211·6) calculated: 45·41% C, 2·85% H, 16·75% Cl, 19·86% N; found: 45·52% C, 3·00% H, 16·99% Cl, 19·85% N.

2-Methanesulfonyl-5-benzylaminopyrimidine (*XVIII*)

A mixture of compound *VIe* (1·77 g), benzylamine (2·14 g), and dimethyl sulfoxide (5 ml) was heated on a steam bath for one hour, cooled down, and diluted with water. The precipitate was collected with suction and purified by trituration with water. Yield, 2·5 g of compound *XVIII*, m.p. 100—107°C; the analytical sample, m.p. 114·5—115·5°C (ethanol). For $C_{12}H_{13}N_3O_2S$ (263·3) calculated: 54·73% C, 5·00% H, 15·96% N, 12·18% S; found: 54·80% C, 5·24% H, 16·82% N, 12·58% S.

Elemental analyses were performed in the Analytical department (Dr J. Körbl, Head) of our Institute.

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