# PREPARATION AND SOME REACTIONS OF 2,5-SUBSTITUTED PYRIMIDINES*

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2-Substituted 5-(dimethylaminomethyleneamino)pyrimidines have been prepared by condensation of the trimethinium salt *I* with bases *II*. Methylation of the mercapto derivative and the subsequent oxidation has furnished a 2-methylsulfonyl derivative which may be used for nucleophilic substitutions.

The synthetic approach to pyrimidine derivatives consisting in condensation of trimethinium salts with a suitable basic component of the guanidine, thiourea, amidine, and similar type has been developed[1] in this Laboratory and several successful applications of this method have been reported[2-4]. In connection with investigations on synthetic reactions of dimethylformamide, some derivatives of the aminomalonic dialdehyde[5] have been recently obtained, *inter alia* the trimethinium salt *I*. This compound represents an advantageous starting material for the synthesis of pyrimidine compounds by the above mentioned method making possible a direct synthesis of 2,5-substituted derivatives with a blocked amino group at position 5, *i.e.*, compounds that would be otherwise accessible by a multistep synthesis only.

As shown by experiments, the trimethinium salt *I* reacted as expected with bases *II* with the formation of the corresponding pyrimidines *IIIa–IIId*; depending on the other condensation component, the substituent at position 2 of the product is hydrogen, amino group, mercapto group or methylthio group. The condensation reactions were performed in ethanol as follows: the refluxing mixture consisting of the trimethinium salt *I* and a moderate excess of the base *II* was treated dropwise over thirty minutes with the required amount of methanolic sodium methoxide and the reflux was continued.

In the condensation reaction of the salt *I* with formamidine, the expected pyrimidine *IIIa* was accompanied by a by-product, the azatrimethinium perchlorate *IV*. The occurence of this by-product may be explained by reaction of formamidine with dimethylamine which is liberated in the reaction medium by decomposition of the

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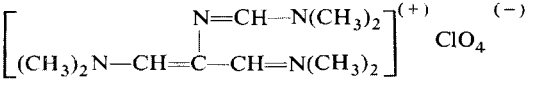
trimethinium salt *I*. The formation of the azatrimethinium salt *IV* has been observed earlier in an analogous reaction[4]. The attempted preparation of the corresponding hydroxy derivative from the trimethinium salt *I* and urea failed under the above mentioned conditions probably because of the low basicity of the urea amino groups. In addition to the trimethinium salt *I*, the condensation reactions were also performed with the use of the bisperchlorate *V* ($V = I + HClO_4$), the intermediate[5] in the preparation of the salt *I*. The yields of pyrimidines are practically the same, but it is necessary to use the corresponding amount of methanolic sodium methoxide, *i.e.*, two equivalents of the methoxide per one equivalent of the salt *V*.

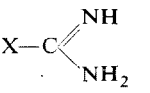
By chemical transformations of functional groups of the pyrimidines *IIIa*–*IIId*, numerous novel derivatives may be obtained. In the present paper, we report the conversion of the mercapto derivative *IIIc* to the corresponding methylsulfonylpyrimidine *IIIf* which readily undergoes nucleophilic substitutions at position 2.

The 2-methylthio derivative *IIId*, obtained by reaction of the salt *I* with S-methyl-

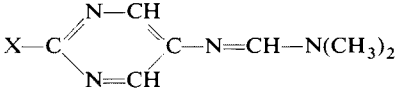


*I*

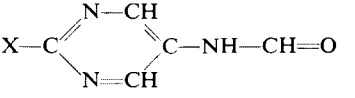
*V* (bisperchlorate)



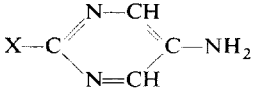
*IIa*, X = H *IIc*, X = SH
*IIb*, X = $NH_2$ *IId*, X = $SCH_3$



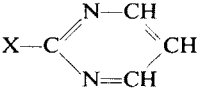
*IIIa*, X = H *IIIe*, X = $SOCH_3$
*IIIb*, X = $NH_2$ *IIIf*, X = $SO_2CH_3$
*IIIc*, X = SH *IIIg*, X = $OCH_3$
*IIId*, X = $SCH_3$ *IIIh*, X = CN



*VIIf*, X = $SO_2CH_3$
*VIIg*, X = $OCH_3$
*VIIh*, X = CN

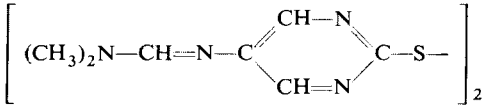


*VIIIf*, X = $SO_2CH_3$
*VIIIg*, X = $OCH_3$
*VIIIh*, X = CN



*IXf*, X = $SO_2CH_3$
*IXg*, X = $OCH_3$
*IXh*, X = CN

*IV*



*VI*

thiourea, may also be prepared by methylation of the corresponding 2-mercapto derivative *IIIc*. The methylation was in this case preferably performed with the use of (dimethoxymethyl)dimethylamine; the ability of this agent to effect methylations on sulfur and nitrogen atoms has been recognised earlier[6]. Because of the almost quantitative yield and simple isolation, this method of the preparation of compound *IIId* was preferred to the direct synthesis from the trimethinium salt *I* and S-methylthiourea. Oxidation of the 2-methylthio group in compound *IIId* with aqueous hypochlorite proceeds smoothly and affords (depending on the reaction conditions) either the 2-methylsulfinyl derivative *IIIe* or the corresponding sulfone *IIIf* as the product of the oxidation to the second degree. According to a recent paper, dimethyl sulfoxide in the presence of a strong acid brings about replacement of two-valent sulfur (or selenium) by the oxygen atom[7]. The attempted application of this reaction to the 2-mercapto derivative *IIIc* with the aim to obtain the corresponding 2-hydroxy--5-(dimethylaminomethyleneamino)pyrimidine resulted in isolation of a substance which was assigned the structure of the disulfide *VI* on the basis of elemental analysis as well as infrared and mass spectra. Such a reaction course is characteristic of thio compounds[8].

When attached to positions 2, 4, and 6 of the pyrimidine nucleus, the methylsulfonyl group readily undergoes the nucleophilic substitution[9]. The methylsulfonyl derivative *IIIf* was thus allowed to react both with methanolic sodium methoxide and potassium cyanide in dimethylformamide. In order to obtain at least preliminary qualitative informations on the influence of various groups at position 5 of the pyrimidine ring on the course of these substitutions, additional 2-methylsulfonylpyrimidines have been included into our investigations, namely those possessing at position 5 a N-formylamino group (*VIIf*), a free amino group (*VIIIf*) and finally, a hydrogen atom (*IXf*). The above mentioned substances afford the corresponding methoxy

TABLE I

Qualitative Data on the Reactivity of 2-Methylsulfonylpyrimidines in Nucleophilic Substitutions

| Compound | Substituent at position 5 | Sodium methoxide | | | Potassium cyanide | | |
|---|---|---|---|---|---|---|---|
| | | °C | min[a] | product | °C | min[a] | product |
| *IIIf* | —N=CHN$(CH_3)_2$ | 20 | 2 | *IIIg*[b] | 100 | 90 | *IIIh*[b] |
| *VIIf* | —NHCHO | 20 | 25 | *VIIg*[c] | 45 | 60 | *VIIh*[c] |
| *VIIIf* | —$NH_2$ | 70 | 30 | *VIIIg*[c] | 120 | 1 200 | *VIIIh*[c] |
| *IXf*[d] | —H | 10 | [e] | *IXg*[f] | 20 | 10 | *IXh*[d] |

[a] After elapse of this time (min), the starting material was absent on thin-layer chromatography; [b] for the preparation see Experimental; [c] ref.[10]; [d] ref.[11]; [e] instantaneous reaction; [f] ref.[12].

derivatives *IIIg*, *VIIg*, *VIIIg*, and *IXg* by reaction with methanolic sodium methoxide and the nitriles *IIIh*, *VIIh*, *VIIIh*, and *IXh* by the action of potassium cyanide. The course of these reactions was checked by thin-layer chromatography. Table I shows temperature data and periods of time necessary for a complete reaction. As indicated by this qualitative evaluation of the reactivity, the reaction rate is lowered by electron-donating substituents at position 5 of the pyrimidine ring but the order of reactivities is not the same in the two reactions. The nucleophilic substitution rate decreases in the order *IXf* > *IIIf* > *VIIf* > *VIIIf* in the reaction with sodium methoxide and in the order *IXf* > *VIIf* > *IIIf* > *VIIIf* in the treatment with potassium cyanide. In addition to electron effects, some other factors are obviously involved from which the effect of the different nucleophile basicity on the detailed reaction mechanism must be to our opinion particularly taken into consideration; the influence of the reaction medium also appears of some importance.

The ultraviolet spectra of the present and some other 2,5-substituted pyrimidines will be reported elsewhere[10].

## EXPERIMENTAL

Melting points were taken on a heated microscope stage (Kofler block). The IR spectra were recorded on a Zeiss Jena UR-10 apparatus. The UV spectra were measured on an Optica Milano CF 4 apparatus. The mass spectra were taken on a double-focal AEI MS-902 apparatus.

### Condensation (preparation of compounds *IIIa*—*IIId*)

A refluxing mixture of the trimethinium salt[5] *I* (3 g; 0·01 mol), the condensation component *II* (thiourea, urea) or its salt such as guanidine hydrochloride, formamidine acetate, S-methylthiuronium sulfate (0·012 mol each), and ethanol (30 ml) was treated dropwise with stirring over 30 min with 1M methanolic sodium methoxide (24 ml). The mixture was refluxed for additional 2 h, cooled down, and the dimethylamine removed under diminished pressure.

5-(*Dimethylaminomethyleneamino*)*pyrimidine* (IIIa). The mixture was neutralised with conc. perchloric acid and then treated with additional 0·01 mol of perchloric acid to deposit a salt which was collected with suction, washed with ethanol, and dried. Yield, 1·9 g (76%), m.p. 208—220°C (decompositon). Analytical sample of the perchlorate of compound *IIIa*, m.p. 215—220°C (ethanol) (decomp.). For $C_7H_{11}ClN_4O_4$ (250·6) calculated: 33·5% C, 4·4% H, 14·2% Cl, 22·3% N; found: 33·6% C, 4·6% H, 14·4% Cl, 22·2% N. The base was liberated with aqueous potassium carbonate and extracted with benzene. The analytical sample of compound *IIIa* was distilled at 125—130°C/0·3 Torr. For $C_7H_{10}N_4$ (150·2) calculated: 56·0% C, 6·7% H, 37·3% N; found: 56·5% C, 7·1% H, 37·2% N.

*Isolation of the salt* IV. The mixture obtained by the condensation reaction was evaporated, the residue extracted with two 20 ml portions of dichloromethane, the extract taken down, and the residue crystallised from a little ethanol to afford 0·3 g of the salt *IV*, m.p. 109—111°C,; after recrystallisation from ethanol, m.p. increased to 110—111°C. For $C_6H_{14}ClN_3O_4$ (227·6) calculated: 31·7% C, 6·1% H, 15·6% Cl, 18·5% N; found: 32·1% C, 6·1% H, 15·6% Cl, 18·4% N. UV spectrum (ethanol): $\lambda_{max}$ 246 nm (log $\varepsilon$ 3·16). The IR and UV spectra are identical with those of an authentic specimen prepared according to Gold[13].

2-Amino-5-(dimethylaminomethyleneamino)pyrimidine (*IIIb*)

The mixture was concentrated to deposit a solid which was collected with suction, washed with a little ice-cold ethanol, and recrystallised from ethanol. Yield, 1·4 g (85%) of compound *IIIb*, m.p. 184—186°C; after recrystallisation from ethanol, m.p. 187—188°C. For $C_7H_{11}N_5$ (165·2) calculated: 50·9% C, 6·7% H, 42·4% N; found: 51·1% C, 6·7% H, 42·2% N.

2-Mercapto-5-(dimethylaminomethyleneamino)pyrimidine (*IIIc*)

The mixture was neutralised with acetic acid to deposit a solid which was collected with suction and washed with ethanol. Yield, 1·5 g (83%), m.p. 183—190°C. The solid was dissolved in 1M-NaOH (10 ml) and the solution precipitated with 1M-HCl. M.p. of the purified compound *IIIc*, 192—196°C (decomp.). The purification by crystallisation should be avoided since the heating in a solvent is accompanied by a partial decomposition of the substance. For $C_7H_{10}N_4S$ (182·3) calculated: 46·1% C, 5·5% H, 30·7% N, 17·6% S; found: 46·4% C, 5·6% H, 30·8% N; 17·6% S.

2-Methylthio-5-(dimethylaminomethyleneamino)pyrimidine (*IIId*)

*A.* Methanol and ethanol were evaporated, the residue extracted with three 20 ml portions of benzene, the extracts combined, and taken down to afford 1·5 g (75%) of compound *IIId*, m.p. 92—96°C; after crystallisation from cyclohexane, m.p. 102—103°C. For $C_8H_{12}N_4S$ (196·3) calculated: 48·9% C, 6·2% H, 28·5% N, 16·3% S; found: 48·8% C, 6·1% H, 28·1% N, 16·4% S.

*B.* A suspension containing compound *IIIc* (9 g; 0·05 mol), benzene (40 ml), and dimethylformamide dimethylacetal (7 ml; 0·0055 mol) was refluxed until homogeneous (30 min), the benzene evaporated, the residue thoroughly triturated with little ether, and the solid collected with suction to yield 9·4 g (96%) of compound *IIId*, m.p. 98—101°C; after crystallisation from cyclohexane, m.p. 102·5—103·0°C. For $C_8H_{12}N_4S$ (196·3) calculated: 48·9% C, 6·2% H, 28·5% N, 16·3% S; found: 48·9% C, 6·1% H, 27·9% N, 16·2% S.

2-Methylsulfinyl-5-(dimethylaminomethyleneamino)pyrimidine (*IIIe*)

A suspension of compound *IIId* (0·2 g; 0·001 mol) in water (5 ml) was treated with sodium hydrogen carbonate (0·1 g) and then (dropwise) with 1M-NaClO (1·2 ml). The mixture was stirred at 10—15°C for 20 min, extracted with three 20 ml portions of dichloromethane, the extracts combined, dried over calcinated potassium carbonate, and evaporated to yield 0·16 g (76%) of compound *IIIe*, m.p. 100—103°C; after recrystallisation from tetrachloromethane, m.p. 103—104°C. For $C_8H_{12}N_4OS$ (212·3) calculated: 45·3% C, 5·7% H, 26·4% N, 15·1% S; found: 45·0% C, 5·7% H, 26·0% N, 15·0% S.

2-Methylsulfonyl-5-(dimethylaminomethyleneamino)pyrimidine (*IIIf*)

Sodium hydrogen carbonate (3 g) was added into a suspension of compound *IIId* (19·6 g; 0·1 mol) and water (30 ml), the whole was treated dropwise at 20—25°C with 1M-NaClO (300 ml) under ice-cooling and stirring. The stirring was then continued at room temperature for 30 min and the mixutre cooled down to 0°C to deposit a solid which was collected with suction, washed with a little ice-cold water, and dried. Yield, 16 g; m.p. 131—132°C. The mother liquor was extracted with three 100 ml portions of dichloromethane, the extracts combined, dried over calcinated potassium carbonate, and evaporated to afford an additional crop of the product (4·8 g), m.p. 127—130°C. Overall yield of compound *IIIf*, 20·8 g (91%). Analytical sample, m.p. 132—133°C

(ethanol). For $C_8H_{12}N_4O_2S$ (228·3) calculated: 42·1% C, 5·3% H, 24·5% H, 13·9% S; found: 42·2% C, 5·4% H, 24·2% N, 14·0% S.

Bis[5-(dimethylaminomethyleneamino)pyrimidin-2-yl] Disulfide (*VI*)

A mixture of compound *IIIc* (0·36 g; 0·002 mol), dimethyl sulfoxide (20 ml), and conc. sulfuric acid (0·1 ml) was kept at room temperature for 4 days, evaporated under diminished pressure, the residue diluted with water, the solution filtered with active charcoal, and the filtrate neutralised with aqueous potassium carbonate. The solid was collected with suction, washed with water, and dried to yield 0·25 g (69%) of compound *VI*, m.p. 172—175°C; after reprecipitation from acidic media, m.p. 175—177°C. For $C_{14}H_{18}N_8S_2$ (362·5) calculated: 46·4% C, 5·0% H, 30·9% N, 17·7% S; found: 45·9% C, 4·9% H, 30·2% N, 17·6% S. Mass spectrum: $M^+$ 362.

2-Methoxy-5-(dimethylaminomethyleneamino)pyrimidine (*IIIg*)

Compound *IIIf* (1·1 g; 0·005 mol) was dissolved in 1M methanolic sodium methoxide (25 ml), the solution stirred at room temperature for 10 min, neutralised with acetic acid, and evaporated. The residue was extracted with two 50 ml portions of benzene, the extracts combined, and evaporated to yield 0·85 g (95%) of compound *IIIg*, m.p. 78—83°C; after crystallisation from tetrachloromethane, m.p. 87—88°C. For $C_8H_{12}N_4O$ (180·2) calculated: 53·3% C, 6·7% H, 31·1% N; found: 53·5% C, 6·8% H, 31·2% N.

2-Cyano-5-(dimethylaminomethyleneamino)pyrimidine (*IIIh*)

A mixture of compound *IIIf* (0·23 g; 0·001 mol), potassium cyanide (0·1 g), and dimethylformamide (6 ml) was heated at 100°C for 2 h and evaporated. The residue was extracted with dichloromethane (20 ml) and the extract evaporated to yield 0·15 g (85%) of compound *IIIh*, m.p. 135 to 137°C; after crystallisation from tetrachloromethane, m.p. 136—137°C. For $C_8H_9N_5$ (175·2) calculated: 54·9% C, 5·2% H, 40·0% N; found: 54·8% C, 5·1% H, 40·7% N.

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