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# INVESTIGATIONS IN THE AREA OF FUNCTIONALLY SUBSTITUTED AZINES. SYNTHESIS AND THERMOLYSIS OF CHLORETHOXYPYRIMIDINES

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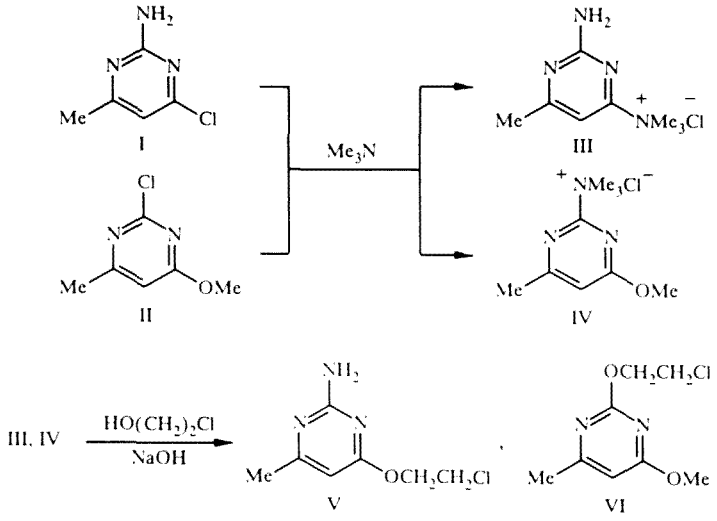
*The 2-amino-4-(2-chlorethoxy)-6-methyl- and 2-(2-chlorethoxy)-4-methoxy-6-methylpyrimidines were synthesized. Depending on the position of the chlorethoxy group in the ring, their thermolysis results in the formation of the oxazolopyrimidinium chloride or the $N_{(1)}$-(2-chlorethyl) derivative.*

We previously showed that, depending on the nature of the alkyl radical, the thermolysis of 2-(2-chlorethoxy)-4-dialkylamino-6-alkoxy-sym-triazines occurs with their rearrangement to N-(2-chlorethyl) derivatives or the formation of oxazolo-sym-triazines by their elimination of alkyl chlorides [1-3].

The aim of the given work was to study these reactions using the example of the pyrimidine analogs and, on this basis, to develop new routes both for the N-chlorethylation of pyrimidine and for the synthesis of its derivatives condensed with the oxazolidine ring. In this connection, the model compounds taken were the comparatively accessible 2-amino-4-chloro-6-methyl- and 2-chloro-4-methoxy-6-methylpyrimidines (I, II), which were converted by trimethylamine to the salts (III) and (IV), readily reacting with ethylene chlorohydrin in the presence of alkali to form the chlorethoxypyrimidines (V) and (VI).




When compound (V) is heated briefly in toluene, it is completely converted to the oxazolopyrimidinium chloride (VII) which, when treated with alkali, gives 2-amino-$N_{(3)}$-(2-hydroxyethyl)-6-methylpyrimidin-4-one (VIII). The formation of the last can be interpreted satisfactorily if attention is given to the quaternary onium character of the salt (VII), since thermolysis could also be expected to result in intramolecular heterocyclization of its imine form (IX) with conversion to the oxazolopyrimidine hydrochloride (XX).

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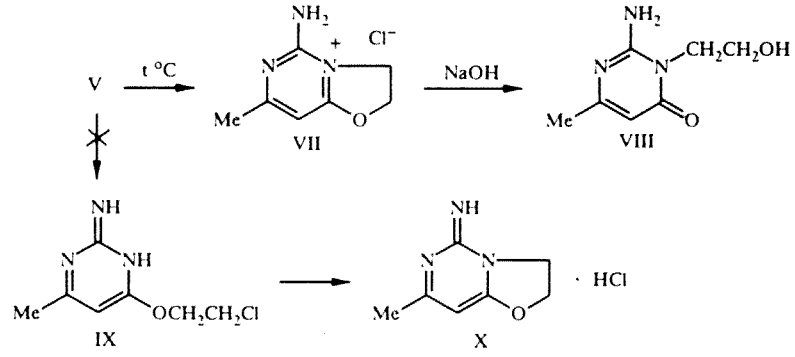
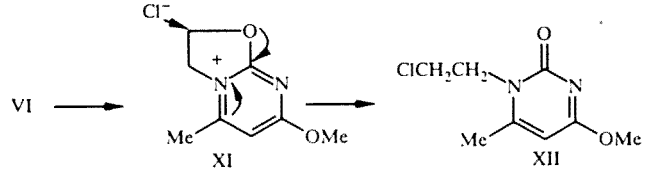
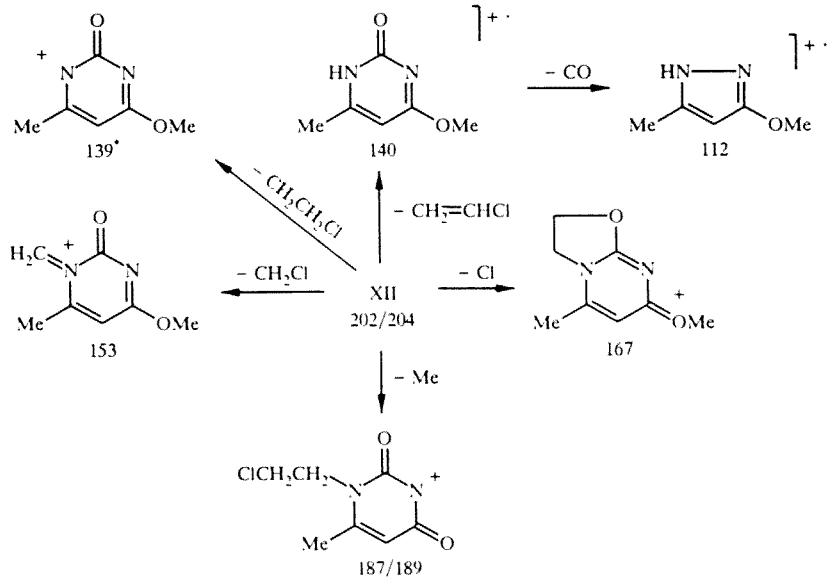


Under analogous conditions, compound (VI) probably also forms the oxazolopyrimidinium chloride (XI) which is, however, unstable and is stabilized as the N-(2-chlorethyl) derivative by undergoing nucleophilic attack by the chlorine anion. This rearrangement, which is, in fact, a new example of the O – N isomerization of pyrimidine derivatives [4], is characterized by high regioselectivity, i.e., the conversion of compound (VI) proceeds not to the $N_{(3)}$- derivative, but to the $N_{(1)}$-(2-chlorethyl) derivative (XII).



In contrast to the analogous $N_3$-(2-chlorethyl)-4-methoxy-6-dimethylamino-sym-triazines [2, 3], the last was found to be thoroughly stable even under conditions of drastic thermolysis. This should be explained by steric factors disadvantageous for the elimination of methyl chloride — the location of the chlorethyl and methoxy groups at the 1,4 positions of the pyrimidine ring, and not the 3,4 positions as occurs in the molecule of the alternative $N_{(3)}$-derivative.



*Here and further, the *m/z* values are given for the mass spectra.

The molecular masses of the compounds (V)-(VIII) and (XII), determined mass spectrometrically, correspond with the calculated values, and the fragmentation scheme of the molecular ion of compound (XII) confirms its structure.

The structure of the compounds together with the data of mass spectrometry and the elemental analysis is also confirmed by the IR spectra and PMR spectra presented in the experimental part.

## EXPERIMENTAL

The IR spectra were recorded on the UR-20 spectrometer in mineral oil or tablets of KBr. The PMR spectra were taken on the Varian T-60 instrument with TMS as the internal standard. The mass spectra were obtained on the MX-1303 spectrometer with the direct introduction of the sample at the ion source. The TLC was carried out on plates of Silufol UV-254 in the 1:2 system of acetone–hexane.

Data of the elemental analyses of the synthesized compounds for C, H, Cl, and N correspond with the calculated data.

**2-Amino-4-methylpyrimidinyl-6-trimethylammonium Chloride (III) ($C_8H_{15}ClN_4$).** This compound is obtained by the heating of 7.2 g (0.05 mole) of compound (I) and 3.3 g (0.055 mole) of trimethylamine in 30 ml of abs. benzene in a closed vessel for 12 h. The yield was 9.1 g (90%). The temperature of decomposition was 202-203°C.

**4-Methoxy-6-methylpyrimidinyl-2-trimethylammonium Chloride (IV) ($C_9H_{16}ClN_3O$).** This compound was obtained according to the method described earlier [5] with the yield of 80%. The temperature of decomposition was 111-112°C.

The chlorethoxypyrimidines were obtained by a known method [5] from compound (III), (IV), and ethylene chlorohydrin in the presence of alkali at low temperatures.

**2-Amino-4-methyl-6-(2-chlorethoxy)pyrimidine (V) ($C_7H_{10}ClN_3O$).** The yield was 74%. The mp was 68-70°C. The $R_f$ was 0.41. The PMR spectrum (acetone-$D_6$) was as follows: 2.15 ppm (3H, s, $CH_3$), 3.8 ppm (2H, t, $ClCH_2$), 4.4 ppm (2H, t, $OCH_2$), 5.83 ppm (1H, s, CH), and 6.05 ppm (2H, broad s, $NH_2$).

**2-(2-Chlorethoxy)-4-methoxy-6-methylpyrimidine (VI) ($C_8H_{11}ClN_2O_2$).** The yield was 96%. The mp was 60-62°C. The $R_f$ was 0.34. The PMR spectrum (acetone-$D_6$) was as follows: 2.2 ppm (3H, s, $CH_3$), 3.8 ppm (3H, s, $OCH_3$), 3.82 ppm (2H, t, $ClCH_2$), 4.45 ppm (2H, t, $OCH_2$), and 6.2 ppm (1H, s, CH).

**Thermolysis of Compound (V).** The solution of 1.88 g (0.01 mole) of compound (V) in 10 ml of abs. toluene is boiled for 3 h and filtered. The residue is washed with 10 ml of abs. ether prior to the isolation of 2-amino-8-methyl-4,5,dihydrooxazolo[1,2-*a*]pyrimidinium chloride (VII). The yield was 1.8 g (96%). The temperature of decomposition was >300°C. In contrast to compound (V), it dissolves very well in water. The $M^+$ was 187. The PMR spectrum ($D_2O$) was as follows: 2.5 ppm (3H, s, $CH_3$), 4.6 ppm (2H, t, $NCH_2$), 5.2 ppm (2H, t, $OCH_2$), and 6.6 ppm (1H, s, CH).

**2-Amino-$N_{(3)}$-(2-hydroxyethyl)-6-methylpyrimidin-4-one (VIII) ($C_7H_{11}N_3O_2$).** To the solution of 0.4 g (0.01 mole) of sodium hydroxide in 3 ml of water are added 1.88 g (0.01 mole) of compound (VII). After 24 h, the solution is evaporated, and compound (VIII) is extracted with acetone. After the evaporation of the acetone, 1.13 g (67%) of the substance are obtained; it had the mp 170-172°C and the $R_f$ 0.41. The IR spectrum was as follows: 3200-3500 $cm^{-1}$ (OH, $NH_2$), 1560 $cm^{-1}$ (C=N), and 1670 $cm^{-1}$ (C=O). The $M^+$ was 169.

**Thermolysis of Compound (VI).** The solution of 2.0 g (0.01 mole) of compound (VI) in 10 ml of abs. toluene is boiled for 4 h. The toluene is distilled off. The residue is treated with 10 ml of petroleum ether, and compound (XII) is filtered off. The yield is 1.95 g (97%). The mp is 133-135°C. The PMR spectrum (acetone-$D_6$) was as follows: 2.35 ppm (3H, s, $CH_3$), 3.72 ppm (3H, s, $OCH_3$), 3.8 ppm (2H, t, $ClCH_2$), 4.13 ppm (2H, t, $NCH_2$), and 5.7 ppm (1H, s, CH). The IR spectrum was as follows: 1650 $cm^{-1}$ (C=O), 1020 $cm^{-1}$, and 1130 $cm^{-1}$ (C–O).

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