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INVESTIGATIONS IN THE AREA OF FUNCTIONALLY SUBSTITUTED AZINES.

5.* REACTIONS OF AZINES WITH NUCLEOPHILES AND HYDROGEN CHLORIDE

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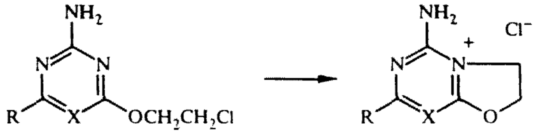
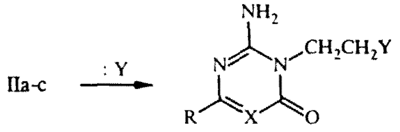
It was shown that oxazolopyrimidinium and sym-triazinium chlorides give $N_{(3)}$-(2-Y-ethyl)-substituted azines with nucleophiles. Oxazolo-sym-triazine also reacts analogously, being converted by hydrogen chloride to the $N_{(3)}$-(2-chloroethyl) derivative.

On thermolysis, 2-amino-4-chloroethoxy-6-methylpyrimidine (Ia) and 2-amino-4-dialkylamino-6-chloroethoxy-sym-triazines (Ib,c) undergo intramolecular quaternization with the formation, in contrast to other analogs [2-4], of the completely stable onium salts (IIa-c) [1, 5]. We found that the salts (IIa-c) react with alkali to form the $N_{(3)}$-(2-hydroxyethyl)pyrimidin-4-one and sym-triazin-4-ones (IIIa-c), instead of the usual substitution of the chlorine anion by the hydroxyl anion [1, 5]. It was shown in the present paper that other nucleophiles also react with the salts (IIa-c) analogously.



Ia-c IIa-c

I, II a R = Me, X = CH; b R = NMe$_2$, X = N; c R = NEt$_2$, X = N



IIIa-e

IIIa R = Me, X = CH, Y = NHCN; b R = Me, X = CH, Y = 2-ClC$_6$H$_4$SO$_2$NH; c R = NMe$_2$, X = N, Y = OEt; d R = NEt$_2$, X = N, Y = OEt; e R = NMe$_2$, X = N, Y = MeNHC


$\mathrm{MeNHC}(=\mathrm{S})\mathrm{S}$

The formation of the $N_{(3)}$-(2-Y-ethyl) functionally substituted ethylazines (IIIa-e) proceeds readily using the 1:1 molar ratio of the reacting substances in water at room temperature for 3 h or by the brief heating of their mixtures in acetone or alcohol.

The ease of the nucleophilic cleavage of the O-CH$_2$ bond of the oxazolidine ring was also established using the example of the reaction of the previously described oxazolo-sym-triazine (IV) [3] with alkali. This resulted in the synthesis of the O-

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*For Communication 4, see [1].

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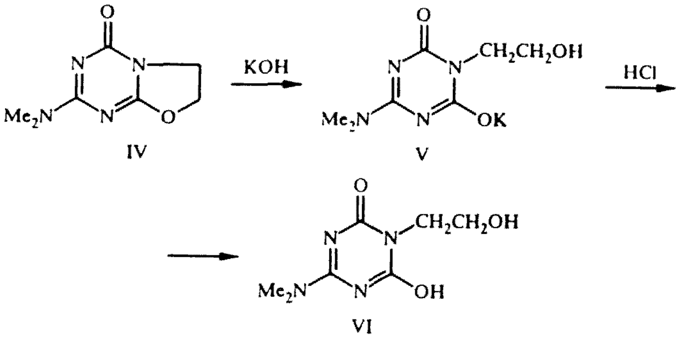
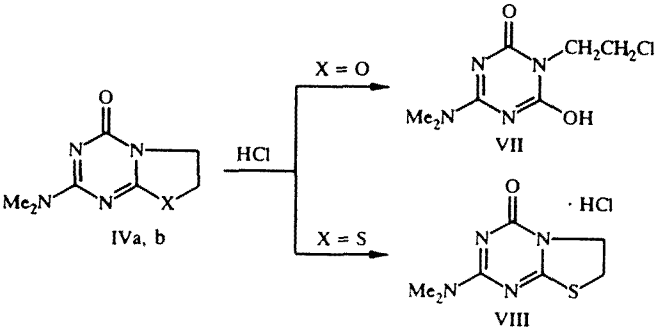
potassium salt of 3-hydroxyethyl-4-hydroxy-6-dimethylamino-sym-triazin-2-one (V), which is converted by hydrochloric acid to the compound (VI).

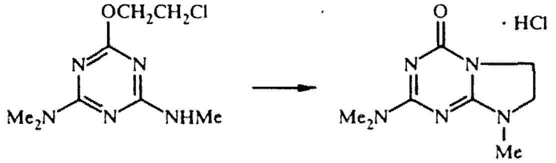


Compound (IV) is converted by hydrogen chloride not to the hydrochloride, but to the product of acidolysis — $N_{(3)}$-(2-chloroethyl)-4-hydroxy-6-dimethylamino-sym-triazin-2-one (VII). The more stable imidazo- and triazolo-sym-triazines [6, 7] do not react with nucleophiles under the conditions indicated, and give the hydrochlorides (VIII) with hydrogen chloride.



IVa X = O, b X = S

Moreover, the hydrochlorides of imidazo-sym-triazines are so stable that they are the final products of the rearrangement of 2-chloroethoxy-4-alkylamino-6-dialkylamino-sym-triazines [6].



EXPERIMENTAL

The IR spectra were taken on the UR-20 instrument using mineral oil. The PMR spectra were taken on the Varian T-60 instrument using HMDS as the internal standard. The TLC was performed on plates of Silufol UV-254.

The data of the elemental analysis of the compounds obtained for C, H, Cl, and N agree with the calculated data.

2-Amino-$N_{(3)}$-(2-cyanamidoethyl)-6-methylpyrimidin-4-one (IIIa). To the solution of the sodium salt of cyanamide, obtained from 0.5 g (0.012 mole) of NH_2CN and 0.5 g (0.012 mole) of NaOH in 3 ml of water, are added, in portions with stirring at 0°C, 1.88 g (0.01 mole) of compound (IIa). The reaction mixture is maintained at 20°C for 3 h, and the precipitated residue of compound (IIIa) is filtered off. The yield is 1.35 g (70%). The mp is 226-227°C, and the R_f is 0.44 (the 10:10:3 mixture of hexane—acetone—H_2O). The IR spectrum is as follows: 1550 cm^{-1}, 1600 cm^{-1} (C=N, C=C), 1690 cm^{-1} (C=O), 2160 cm^{-1} (CN), and 3400 cm^{-1} (NH). The PMR spectrum ($CDCl_3$) is as follows: 2.21 ppm (3H, s, CH_3), 3.77 ppm (2H, m, CH_2-N), 4.18 ppm (2H, m, CH_2NH), and 6.21 ppm (1H, s, CH).

2-Amino-N$_{(3)}$-[2-(o-chlorobenzenesulfonamido)ethyl]-6-methylpyrimidin-4-one (IIIb). To the suspension of 0.01 mole of N-potassio-o-chlorobenzenesulfonamide, obtained from 1.9 g (0.01 mole) of o-chlorobenzenesulfonamide and 0.66 g (0.01 mole) of KOH in 15 ml of acetone, are added 1.88 g (0.01 mole) of compound (IIa). The reaction mixture is heated for 3 h at 40-45°C, and the KCl is filtered off. The filtrate is evaporated prior to the treatment of the residue with 10 ml of water. Compound (IIIb) is filtered off with the yield of 2.0 g (60%). It has the mp 176-178°C and the R_f 0.38 (the 1:1 mixture of acetone—hexane). The IR spectrum is as follows: 1670 cm^{-1}, 1690 cm^{-1} (C=O), 1530 cm^{-1}, 1570 cm^{-1}, 1600 cm^{-1} (C=N, C=C), 3330 cm^{-1} (NH), and 1310-1335 cm^{-1} (O=S=O). The PMR spectrum ($CDCl_3$ + DMSO) is as follows: 2.03 ppm (3H, s, CH_3), 3.69 ppm (2H, m, CH_2-N), 4.00 ppm (2H, m, CH_2-NH), 5.53 ppm (1H, s, CH), 7.4-8.2 ppm (4H, m, Ph), and 9.2 ppm (1H, broad s, $NHSO_2$).

2-Amino-N$_{(3)}$-(2-ethoxyethyl)-6-dialkylamino-sym-triazin-4-ones (IIIc,d). To 0.01 mole of sodium ethoxide, obtained from 0.23 g (0.01 mole) of sodium and 5 ml of abs. ethanol, is added 0.01 mole of the compound (IIb,c). The mixture is boiled for 3 h. The ethanol is then distilled off, and the residue is treated with 5 ml of water. The compounds (IIIc,d) are filtered off.

Compound (IIIc) [R = $N(CH_3)_2$]. The yield is 95%. The mp is 210-211°C. The R_f is 0.46 (the 1:1 mixture of acetone—hexane). The IR spectrum is as follows: 1695 cm^{-1} (C=O), 1100-1180 cm^{-1} (C−O−C), 1520 cm^{-1}, 1570 cm^{-1}, 1590 cm^{-1} (C=N), 3345 cm^{-1}, and 3370 cm^{-1} (NH_2). The PMR spectrum (DMSO + HMDS) is as follows: 1.1 ppm (3H, t, $CH_2\underline{CH_3}$), 3.0 ppm [6H, s, $N(CH_3)_2$], 3.58 ppm (4H, q, $\underline{CH_2}CH_3$), and 7.2 ppm (2H, broad s, NH_2).

Compound (IIId) [R = $N(C_2H_5)_2$]. The yield is 93%. The mp is 78-80°C. The R_f is 0.54. The PMR spectrum (DMSO + HMDS + CF_3COOH) is as follows: 1.1 ppm (9H, t, $3CH_3$) and 3.4-4.0 ppm [10H, m, $(CH_2)_5$].

2-Amino-N$_{(3)}$-(2-dimethyldithiocarbamoylethyl)-6-dimethylamino-sym-triazin-4-one (IIIe). To the solution of 2.2 g (0.01 mole) of compound (IIb) in 10 ml of water are added 1.55 g (0.012 mole) of sodium methyldithiocarbamate in 5 ml of water. The reaction mixture is left for 6 h at 20°C, and the compound (IIIe) is filtered off. The yield is 1.76 g (61%). The mp is 165-167°C. The R_f is 0.41 (the 1:1 mixture of acetone—hexane). The PMR spectrum (DMSO + HMDS + CF_3COOH) is as follows: 2.98 ppm (3H, d, $NHCH_3$), 3.1 ppm [6H, s, $N(CH_3)_2$], 3.46 ppm (2H, t, NCH_2), 4.1 ppm (2H, t, SCH_2), and 10.06 ppm (1H, q, NH).

2-Oxo-N$_{(3)}$-(2-hydroxyethyl)-4-o-potassio-6-dimethylamino-sym-triazine (V). The solution of 1.82 g (0.01 mole) of compound (IV) and 0.66 g (0.01 mole) of KOH in 4 ml of water is boiled for 5.5 h. The water is distilled off *in vacuo*, and 5 ml of abs. ethanol are added to the residue. Compound (V) is filtered off. The yield is 2.0 g (84%). The mp is > 280°C. The PMR spectrum (D_2O + CF_3COOH) is as follows: 2.93 ppm [6H, s, $N(CH_3)_2$], 3.47 ppm (2H, m, NCH_2), and 3.62 ppm (2H, m, OCH_2).

2-Oxo-N$_{(3)}$-(2-hydroxyethyl)-4-hydroxy-6-dimethylamino-sym-triazine (VI). The solution of 2.38 g (0.01 mole) of compound (V) in 10 ml of water is acidified with hydrochloric acid, and the mixture is then evaporated. Compound (VI) is extracted with ethanol. The evaporation of the ethanolic solution leads to the isolation of 1.6 g (80%) of the substance with the mp 190-191°C. The PMR spectrum (CCl_4 + HMDS + $CDCl_3$) is as follows: 3.15 ppm [6H, s, $N(CH_3)_2$], 3.58 ppm (2H, m, NCH_2), and 3.85 ppm (2H, m, OCH_2).

2-Oxo-N$_{(3)}$-(2-chloroethyl)-4-hydroxy-6-dimethylamino-sym-triazine (VII). To the solution of 3.64 g (0.02 mole) of compound (IV) in 6 ml of water are added 2.4 ml (0.022 mole) of 33.4% hydrochloric acid. The resulting solution is evaporated to dryness at room temperature. Compound (VII) is obtained with the yield of 4.1 g (94%). It has the mp 233-234°C (from ethanol, with decomposition). The IR spectrum is as follows: 1500 cm^{-1}, 1520 cm^{-1}, 1600 cm^{-1} (C=N), 1740 cm^{-1} (C=O), and 3300-3100 cm^{-1} (OH). The PMR spectrum ($CDCl_3$) is as follows: 3.15 ppm [6H, s, $N(CH_3)_2$], 3.71 ppm (2H, t, CH_2Cl), 4.18 ppm (2H, t, NCH_2), and 8.73 ppm (1H, s, OH).

2-Dimethylamino-4-oxo-4,5,6,7-tetrahydrothiazolo[1,2-*a*]-sym-triazine Hydrochloride (VIII). To the solution of 1.98 g (0.01 mole) of compound (IVb) in 6 ml of water is added 1 ml (0.01 mole) of 33.4% hydrochloric acid. The solution is evaporated to dryness at room temperature prior to the isolation of 2.25 g (96%) of compound (VIII) with the mp 224-225°C ($CHCl_3$, with decomposition). In contrast to compound (VII), it contains ionic chlorine. The IR spectrum is as follows: 1605 cm^{-1}, 1640 cm^{-1}, 1660 cm^{-1} (C=N), 1745 cm^{-1} (C=O), and 2400-2750 cm^{-1} (salt effect). The PMR spectrum (D_2O) is as follows: 3.08 ppm [6H, s, $N(CH_3)_2$], 3.67 ppm (2H, t, SCH_2), and 4.47 ppm (2H, t, NCH_2).

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