SYNTHESIS OF SOME ETHYLENEIMINE DERIVATIVES OF PYRIMIDINE

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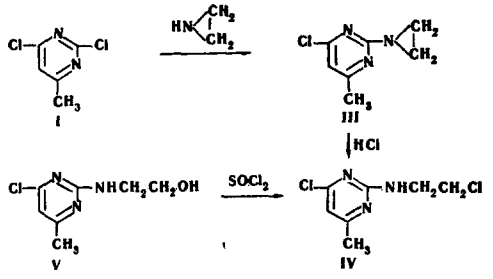
It has been shown that 2,6-dichloro-4-methylpyrimidine reacts with ethyleneimine in benzene solution in the presence of triethylamine or in an aqueous alkaline medium with the formation of 6-chloro-2-ethyleneimino-4-methylpyrimidine. The condensation of 2,6-dichloro-4-methyl-5-nitropyrimidine with an excess of ethyleneimine and in benzene solution in the presence of triethylamine has given 2,6-diethyleneimino-4-methyl-5-nitropyrimidine.

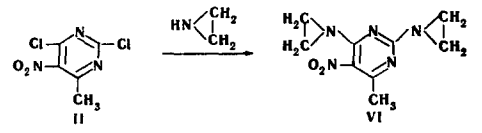
Ethyleneimine derivatives of pyrimidine are of interest as substances possessing potential antitumoral action. The synthesis of these compounds has been described fairly widely in the literature [1–4].

To obtain ethyleneimine derivatives of pyrimidine, we have used 2,6-dichloro-4-methylpyrimidine (I) and 2,6-dichloro-4-methyl-5-nitropyrimidine (II).

The reaction of ethyleneimine with I both in aqueous solution in the presence of sodium carbonate and in dry benzene in the presence of diethylamine yielded 2-ethyleneimino-4-methyl-6-chloropyrimidine (III). It was not possible to obtain even a monoethyleneimine derivative of pyrimidine with N-lithioethyleneimine in dry ether in a current of nitrogen at various temperatures. It was impossible to obtain a diethyleneimine derivative of 4-methylpyrimidine, obviously because of its instability.



To prove the structure of compound III, the ethyleneimine ring was cleaved with dry hydrogen chloride in dry benzene [5]. The substance so formed proved to be identical with 6-chloro-2-(β-chloroethylamino)-4-methylpyrimidine (IV), synthesized by the reaction of 6-chloro-2-(β-hydroxyethylamino)-4-methylpyrimidine with thionyl chloride.



The reaction of 2,6-dichloro-4-methyl-5-nitropyrimidine (II) with an excess of ethyleneimine in dry benzene in the presence of triethylamine gave 2,6-diethyleneimino-4-methyl-5-nitropyrimidine (VI), which is in harmony with the activating influence of a nitro group on a halogen atom in the pyrimidine ring [4].

EXPERIMENTAL

6-Chloro-2-ethyleneimino-4-methylpyrimidine (III). a) With constant stirring and cooling, a suspension of 8.15 g (0.05 mole) of I in dry benzene was added in small portions to a solution of 11.2 g (0.11 mole) of triethylamine and 4.5 g (0.11 mole) of ethyleneimine in 40 ml dry benzene, and then, with continued stirring, the reaction mixture was kept at 35–40° C for 1 hr. After cooling, the triethylamine hydrochloride was filtered off, the benzene was distilled off in vacuum, and the residue was purified by two crystallizations from petroleum ether (1:12). Yield 3.7 g (46.2%). Mp 51–52° C. Colorless crystals, readily soluble in benzene, chloroform, and ethanol, and sparingly soluble in water, with a peculiar sharp smell. On standing in the air the substance polymerized. Found, %: C 49.65; 49.50; H 4.87; 4.83; N 25.03; 25.25. Calculated for $C_7H_8ClN_3$, %: C 49.71; H 4.74; N 24.87.

b) 8.15 g (0.05 mole) of I was suspended in 65 ml of water, and 6.5 g of anhydrous sodium carbonate was added, after which the mixture was heated to 35° C and then a solution of 5 ml of ethyleneimine in 50 ml of water was slowly added. The reaction was carried out at 35°–40° C for 2 hr with constant stirring. After cooling, the water was distilled off in vacuum and the residue was crystallized from petroleum ether. Mp 50°–51° C. A mixture with the material described above melted without depression.

When an attempt was made to obtain 2,6-diethyleneimino-4-methylpyrimidine by condensing III with an excess of ethyleneimine in benzene in the presence of triethylamine, the III was recovered unchanged even when the mixture was heated for 10 hr.

Reaction of 2,6-dichloro-4-methylpyrimidine (I) with N-lithioethyleneimine. 1.4 g (0.2 g-atom) of lithium in the form of small pieces was mixed with 30 ml of dry ether in a current of nitrogen. Then, with constant stirring and ice-cooling, a solution of 14.2 g (0.1 mole) of methyl iodide in 30 ml of dry ether was added over 30 min. The mixture was stirred in a current of nitrogen for a further 30 min and then a solution of 3.65 ml of ethyleneimine in dry ether was added in drops over half an hour at room temperature. After the addition of the ethyleneimine, a solution of 3.26 g (0.02 mole) of I in 50 ml of dry benzene was run in carefully in drops with constant stirring. The reaction was carried out at room temperature for 30 min and then at 45° C for 10 min. After the addition of the very first drops of the solution of I, the mixture became brown, and on heating cherry-red. The colored precipitate that deposited was a polymerization product insoluble in petroleum ether. Similar experiments were carried out without heating and with cooling. It was impossible to isolate a mono- or a diethyleneimino derivative.

6-Chloro-2-(β-chloroethylamino)-4-methylpyrimidine (IV). a) With vigorous cooling, a current of dry hydrogen chloride was passed into a solution of 0.003 mole of III in 30 ml of dry benzene for 35 min. The hydrochloride of the base IV that deposited was washed with 20 ml of dry benzene and dried in vacuum. Mp 145°–146° C. To a solution of 0.001 mole of the hydrochloride in 30 ml of anhydrous acetone was added 0.002 mole of anhydrous triethylamine. The triethylamine hydrochloride was filtered off and washed with a small amount of anhydrous acetone. The acetone was distilled off in vacuum. The residue was treated with propanol; colorless crystals deposited with mp 165°–167° C (decomp). Found, %: N 20.30; 20.42; Cl 34.72; 34.80. Calculated for $C_7H_9Cl_2N_3$, %: N 20.04; Cl 34.47.

b) With stirring, a cooled suspension of 9.5 g (0.05 mole) of 6-chloro-2-β-hydroxyethylamino-4-methylpyrimidine in 15 ml of dry chloroform was added slowly to a solution of 7.2 ml (0.11 mole) of

thionyl chloride in 14 ml of dry chloroform cooled to 0° C. The mixture was left at room temperature for 16 hr, and then the chloroform was distilled off in vacuum. The residual mass was treated with 8 ml of propyl alcohol, whereupon colorless crystals deposited. They were purified by recrystallization from propanol (1:10). The substance was readily soluble in water and, on heating, in alcohols, and sparingly soluble in benzene, toluene, xylene, and chloroform. Yield 4.7 g (46.8%), mp 165°–167° C (decomp.). Found, %: C 41.32; 41.60; H 4.26; 4.13; N 20.38; 20.36; Cl 34.72; 34.80. Calculated for $C_7H_9Cl_2N_3$, %: C 41.23; H 4.36; N 20.04; Cl 34.47%. A mixture of the two samples melted without depression.

2,6-Diethyleneimino-4-methyl-5-nitropyrimidine (VI). With stirring and cooling, a suspension of 4.14 g (0.022 mole) of 2,6-dichloro-4-methyl-5-nitropyrimidine in 7 ml of dry benzene was added to a mixture of 4.5 g (0.11 mole) of ethyleneimine and 30.3 g (0.4 mole) of triethylamine over 30 min. The mixture was stirred for another 20 min (at not above 25° C). The precipitate was filtered off, washed with cold water to eliminate triethylamine hydrochloride, and dried in vacuum. It was purified by three crystallizations from petroleum ether (1:10). Yellow crystals, sparingly soluble in water, soluble in alcohols on heating. Yield 1.1 g (20%), mp 118°–119° C (decomp.). Found, %: C 48.64; 48.52; H 5.18; 5.22; N 31.45; 31.56. Calculated for $C_9H_{11}N_5O_2$, %: C 48.87; H 4.98; N 31.67.

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