SYNTHESES AND REACTIONS OF PYRIMIDINE DERIVATIVES

XVIII. A Study of the Activity of the Methyl Groups in 6-Hydroxy-, 6-Mercapto-, and 6-Amino-2, 4-dimethylpyrimidines*

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By the NMR method, the chemical shifts characterizing the methyl groups in monohydroxymonomethyl derivatives of pyrimidine have been determined. The changes in the chemical shifts and the activities of the methyl groups are symbatic. It has been shown by the NMR method that when 6-hydroxy-2,4-dimethylpyrimidine reacts with benzaldehyde and with p-nitrobenzenediazonium salts reactions take place through the methyl group in position 2. A gradual decrease in the activity of the methyl groups is found in the sequence of 6-hydroxy-, 6-mercapto-, and 6-amino derivatives of 2,4-dimethylpyrimidine.

It has been shown previously that 4-hydroxy-2-methylpyrimidine (I) and 2-hydroxy-4-methylpyrimidine (II) react with p-nitrobenzenediazonium salts while 6-hydroxy-4-methylpyrimidine (III) does not take part in this reaction [1].

In this present work, we have studied the activity of the methyl groups in 6-hydroxy-2,4-dimethylpyrimidine (IV). It was found that when this compound reacts with benzaldehyde only one methyl group takes part in the reaction, as was shown by the elementary analysis of the condensation product. The same compound was obtained when the reaction was carried out with an excess of benzaldehyde, and was confirmed by UV spectroscopy.

To evaluate the different activities of the methyl groups and also to establish the structure of the products of the condensation of compound IV obtained, we used the NMR method. It is known that the chemical shift changes according to the degree of protonation of the hydrogen atoms. It might be expected that the chemical shifts would provide the possibility of evaluating the comparative mobility of the hydrogen atoms of the methyl groups in pyrimidine derivatives. Compounds I–VIII have been studied by the NMR method. The results obtained are given in the table. The NMR spectrum of compound V was taken in trifluoroacetic acid solution and those of the other substances in formic acid solution. Cyclohexane was used as the standard.

It can be seen from the table that the chemical shifts characterizing the active methyl groups (I and II) are, respectively, 2.90 and 2.85 ppm, while for compound III, containing an inactive methyl group, this magnitude is 2.55. The spectra of the azo compounds VII and VIII lack signals corresponding to a methyl group, which confirms the assumption that we have substantiated previously [1] that the azo coupling reaction of compounds I and II takes place through the methyl groups and not in position 5.

Compound IV, which is of interest to us, contains two methyl groups, for which chemical shifts of 2.85 and 2.46 were obtained. By comparing these values with the chemical shifts of the model compounds I–III it must be concluded that the first of the figures given relates to the methyl group in position 2 and the second to the methyl group in position 4. Thus, it may be considered that when compound IV reacts with benzaldehyde and with a p-nitrophenyldiazonium salt only the methyl group in position 2 takes part in the reaction and, therefore, this reaction forms, respectively, 6-hydroxy-4-methyl-2-styrylpyrimidine (V) and 6-hydroxy-4-methyl-2-(p-nitrophenylazomethyl) pyrimidine (VI). In this case the NMR data confirm that the azo coupling reaction of IV takes place through the methyl group: only one signal corresponding to a methyl group remains in the spectrum of the azo compound VI.

The differences in the activities of the methyl groups in 6-hydroxy-2,4-dimethylpyrimidine (IV) established in this way can be explained as follows: in this compound the methyl group in position 4 is conjugated only with the oxygen and not with either of the nitrogen atoms of the pyrimidine ring. The methyl group in position 2 is conjugated both with a nitrogen of the heterocycle and with the carbonyl group. Such an interpretation of the features of the chemical behavior of compound IV is in complete agreement with the NMR data.

The Mannich reaction for 6-hydroxy-2,4-dimethylpyrimidine described in the literature is in agreement with our data: the methyl group in position 2 takes part in the condensation reaction [2].

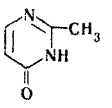
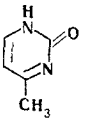
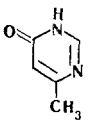
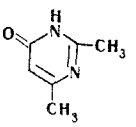
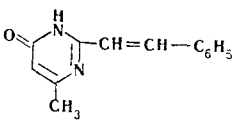
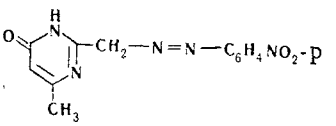
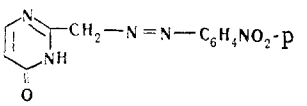
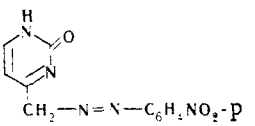
The replacement of the hydroxy group in position 6 of 6-hydroxy-2,4-dimethylpyrimidine (IV) by other electron-donating substituents (SH and NH_2) leads to a lowering of the activity of the methyl group. 6-Mercapto-2,4-dimethylpyrimidine forms a monostyryl derivative on reaction with p-nitrobenzaldehyde but does not react with diazonium compounds. 6-Amino-2,4-dimethylpyrimidine does not react either with aldehydes or with diazonium compounds.

EXPERIMENTAL

6-Hydroxy-4-methyl-2-styrylpyrimidine (V). A mixture of 1.24 g (0.01 mole) of 6-hydroxy-2,4-dimethylpyrimidine [2, 3] (IV) and 2.3 g (0.02 mole) of benzaldehyde was heated at 175–190°C for 2 hr 30 min. The excess of benzaldehyde was washed out sucessively with ether and ethanol. The yield of V was 1.7 g (80%). Faintly yellowish powder, mp 218–220° C from 50% acetic acid). Found, %: N 12.87, 12.93. Calculated for $C_{13}H_{12}N_2O$, %: N 13.20.

*For part XVII, see [5].

Chemical Shifts of the Protons of the CH_3 Groups in Pyrimidine Derivatives

No.	Compound	Chemical shift, ppm
I		2.90
II		2.85
III		2.55
IV		2.85 2.46
V		2.56
VI		2.71
VII		none
VIII		none

UV spectrum: λ_{max} 325 nm, ε 27 200 (in 50% acetic acid). The same substance was obtained with an excess of benzaldehyde.

6-Hydroxy-4-methyl-2-(p-nitrophenylazomethyl)pyrimidine (VI). A diazonium solution prepared from 2.2 g (0.016 mole) of p-nitroaniline in 6.5 ml of hydrochloric acid (2 : 1) and 1.1 g (0.016 mole) of sodium nitrite in 4 ml of water was gradually added to a solution of 2 g (0.016 mole) of **IV** and 5 g of sodium acetate in 10 ml of glacial acetic acid. The reaction mixture immediately become red. After 12 hr, the red-brown precipitate was filtered off, and it was washed five or six times with hot water. Weight 2.2 g (50%); Mp 248–249°C (after four treatments with boiling ethylene glycol). A 3 N solution of ethanolic alkali colors it green-blue. Found, %: N 25.10, 25.15. Calculated for $C_{12}H_{11}N_5O_3$, %: N 25.64.

6-Mercapto-2,4-dimethylpyrimidine (IX). A mixture of 1.86 g (0.015 mole) of 6-hydroxy-2,4-dimethylpyrimidine (**IV**) and 5 g (0.023 mole) of phosphorus pentasulfide in 50 ml of pyridine was heated at 125–127°C for 2 hr. The excess of pyridine was distilled off in vacuum and the residue was boiled with 30 ml of water for 20 min and the solution was filtered hot. The cooled filtrate was brought to pH 9 with ammonia. The ammonium sulfate that precipitated was filtered off and the filtrate was acidified with hydrochloric acid to pH 5 and evaporated to half bulk. The precipitate that deposited after cooling was treated with absolute ethanol. The ethanolic solution was evaporated. This gave 1.5 g (70%) of an orange residue. Mp 226–228°C (from nitromethane) [4]. Found, %: N 19.99, 19.89. Calculated for $C_6H_8N_2S$, %: N 20.00.

6-Amino-2,4-dimethylpyrimidine [4]. A mixture of 1 g (0.007 mole) of **IX** and 10 ml of 28% ammonia was boiled in a sealed tube for 5 hr. The tube was opened and the ammonia was evaporated off. The residue was washed with water. Weight 0.4 g (30%). Qualitative reaction for sulfur negative. Mp 190° C (from ethanol).

6-Mercapto-4-methyl-2-styrylpyrimidine. A mixture of 1.2 g (0.008 mole) of **IX** and 1.2 g (0.008 mole) of p-nitrobenzaldehyde was heated at 150–175°C for 2 hr 30 min. The melt was treated with ethanol. Weight 1.65 g (92%). Brown precipitate. Mp 205–207°C (from butanol). Found, %: N 14.88, 14.92. Calculated for $C_{13}H_{11}N_3O_2S$, %: N 15.35.

When an attempt was made to carry out the azo coupling reactions of 6-mercapto-2,4-dimethylpyrimidine and 6-amino-2,4-methylpyridine with a p-nitrobenzenediazonium salt, the starting materials were recovered. 6-Amino-2,4-dimethylpyrimidine does not take part in condensation reactions with aldehydes, either.

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