SYNTHESIS AND TRANSFORMATIONS OF PYRIMIDINE DERIVATIVES

XIX.* INVESTIGATION OF THE ACTIVITY OF METHYL GROUPS IN MONOMETHOXYMETHYLPYRIMIDINE DERIVATIVES

R. S. Karlinskaya, N. V. Khromov-Borisov, and O. V. Maksimova

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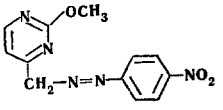
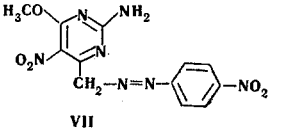
A methoxyl group in the 4 and 6 positions has a passivating effect on the ability of the methyl group in monomethoxymethylpyrimidine derivatives to enter into azo coupling; at the same time, a methoxyl group in the 2 position does not have an appreciable effect on the activity of the methyl group because the conjugation effect of the methoxyl group in this position is less than in the 4 and 6 positions.

We have previously investigated the reactivity of methyl groups in a number of monohydroxymethylpyrimidine derivatives [2]. This paper is devoted to a study of the reactivity of methyl groups in monomethoxymethylpyrimidine derivatives: 2-methoxy-4-methyl- (I), 4-methyl-6-methoxy- (II), 2-methyl-4-methoxy- (III), 2,4-dimethyl-6-methoxy- (IV), and 2-amino-4-methyl-5-nitro-6-methoxypyrimidines (V).

It was shown that only I and V react with p-nitrobenzenediazonium chloride to form 2-methoxy-4-(p-nitrobenzeneazomethyl)pyrimidine (VI) and 2-amino-4-(p-nitrobenzeneazomethyl)-5-nitro-6-methoxypyrimidine (VII), respectively.



VI



VII

The inability of II, III, and IV to enter into azo coupling is evidence that the +C effect of the OCH_3 group is less in the 2 position than in the 4 and 6 positions.

The activity of the methyl group in I and the absence of activity of the methyl group in 2-amino-4-methylpyrimidine [3] should be explained by the fact that the amino group has greater electron-donor properties than the methoxyl group.

A comparison of the structures of 2-amino-4-methyl-5-nitro-6-hydroxypyrimidine (VIII) [4] (in the form of the quasi-quinoid oxo tautomer with an inactive methyl group) and V (which contains an active methyl group) reveals that the nitro group does not have an appreciable effect on the methyl group in the absence of conjugation of the methyl group with the heteroatoms of the ring (VIII) while, when such conjugation is present (V), the nitro group substantially increases the activity of the methyl group. It should be noted that 2,6-diamino-4-methyl-5-nitropyrimidine is also capable of azo coupling with p-nitrobenzenediazonium chloride at the methyl group [5].

Thus the mechanisms for activation and deactivation of the methyl groups in monohydroxymethylpyrimidines [2] and monomethoxymethylpyrimidines (I-V) are different and are due to the peculiarities of

*See [1] for Communication XVIII.

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TABLE 1

Compound	pK_a [6]
4-Methoxypyrimidine	2,5
4-Methoxy-6-methylpyrimidine	3,65
2-Methoxypyrimidine	1,0
2-Methoxy-4-methylpyrimidine	2,1

their structures. On transition of the hydroxypyrimidine derivatives to the corresponding oxo form (as in VIII), conjugation of the ring heteroatoms with the methyl group is destroyed, and the methyl group loses its activity, even when there is a nitro group in the 5 position. In methoxypyrimidines (as in aminopyrimidines) the CH_3 and CH_3O groups (just like NH_2 groups) are in conjugation with the ring heteroatoms. The degree of conjugation of these substituents increases in the order $CH_3 < OCH_3 < NH_2$, and conjugation is greater in the 4 position than in the 2 position. Evidence in favor of this assumption is found in a comparison of the pK_a values for pyrimidine derivatives containing an OCH_3 group in the 2 or 4 positions (see Table 1).

EXPERIMENTAL

2-Methyl-4-methoxypyrimidine (III). 2-Methyl-4-chloropyrimidine [7] [6.3 g (0.048 mole)] was gradually added to a solution of 2 g (0.087 g-atom) of sodium metal in 35 ml of absolute methanol. The reaction was exothermic. The solution was heated for 15 min on a water bath, poured into 50 ml of water, and the product (III) was extracted with 500 ml of ether. The ether solution was dried over calcined magnesium sulfate, the ether was removed, and the residue was distilled in vacuo to give 2.4 g (39.3%) of a transparent, colorless liquid with bp 60° (17 mm). The picrate had mp 164° (from ethanol). Found %: N 19.9. $C_6H_8N_2O \cdot C_6H_3N_3O_7$. Calculated %: N 19.8.

2,4-Dimethyl-6-methoxypyrimidine (IV). This was similarly obtained from 3.1 g (0.02 mole) of 2,4-dimethyl-6-chloropyrimidine [8]. The yield was 1.5 g (50%), and the transparent liquid with a sharp odor had bp 78° (11 mm). The picrate had mp 123-124° (from ethanol). Found %: N 19.4. $C_7H_{10}N_2O \cdot C_6H_3N_3O_7$. Calculated %: N 19.1.

2-Amino-4-methyl-5-nitro-6-methoxypyrimidine (V). This was similarly obtained from 1.88 g (0.01 mole) of 2-amino-4-methyl-5-nitro-6-chloropyrimidine [9]. The yield of V was 0.7 g (38%), and it had mp 185°. Found %: N 30.6. $C_6H_8N_4O_3$. Calculated %: N 30.4.

2-Methoxy-4-(p-nitrobenzeneazomethyl)pyrimidine (VI). Compound I [10] [0.32 g (0.0028 mole)] was dissolved in 4.8 ml of glacial acetic acid, and a solution of p-nitrobenzenediazonium chloride, prepared from 0.32 g (0.002 mole) of p-nitroaniline in 2.5 ml of dilute (2 : 1) hydrochloric acid and 0.17 g (0.0024 mole) of sodium nitrite in 3-4 ml of water, was added to it with stirring at room temperature. Sodium acetate (2.4 g) was then added to the reaction mixture, and the solution was kept for 2 h at room temperature and placed in a refrigerator for 1 day. The solution gradually turned red; the red-brown precipitate was filtered as it formed. The product was purified by successive treatment in the cold with benzene, acetone (repeatedly), and ether to give 0.4 g (60%) of VI with mp 224°. The compound gives a blue color with alcoholic alkali. Found %: N 25.3. $C_{12}H_{11}N_5O_3$. Calculated %: N 25.6. λ_{max} 620 nm (in 0.1-N alcoholic sodium hydroxide).

2-Amino-4-(p-nitrobenzeneazomethyl)-5-nitro-6-methoxypyrimidine (VII). This was obtained in the same way as VI from 0.7 g (0.003 mole) of V. The yield was 0.56 g (44%) of a product with mp 165° (from butanol). The compound dissolves in alcoholic alkali to give a blue solution. Found %: N 29.0. $C_{12}H_{11}N_7O_5$. Calculated %: N 29.4.

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