SYNTHESES AND REACTIONS OF PYRIMIDINE DERIVATIVES

XVIII. A Study of the Activity of the Methyl Groups in 2-Methylpyrimidine Derivatives*

V. A. Serzhanina, N. V. Khromov-Borisov, and R. S. Karlinskaya

Khimiya Geterotsiklicheskikh Soedinenii, Vol. 4, No. 3, pp. 524–526, 1968

UDC 547.853.4

An increase in the electron-donating capacity of a substitution in position 4 of the pyrimidine ring (OH < SH < NH_2) leads to a decrease in the reactivity of a methyl group in position 2. The methyl group in 2-methylpyrimidine is less active than that in 4-methylpyrimidine. The hypothesis has been put forward that the lowering of the reactivity of 2-methylpyrimidine is due to the symmetry of its structure.

In a series of 4-substituted derivatives of 2-methylquinazone, a relationship between the activity of the methyl groups and the electron-donating capacity of the substituent was clearly shown (H < OH < SH < NH_2) [1].

Table 1

Activity of the Methyl Groups in Compounds I–IV

Compound	R	Electrophilic reagent				
		A	B	C	D	E
I	H	+[5]	not performed	+[6]	–	–
II	OH	+	+	+	+	–
III	SH	+	+	+	–	–
IV	NH_2	–	–	–	–	–

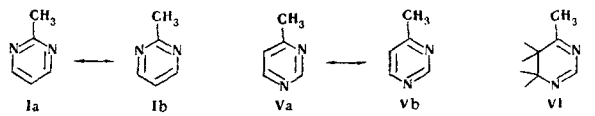
In the present work, we have studied the activity of the methyl groups in a series of corresponding derivatives of 2-methylpyrimidine.

I R = H
II R = OH
III R = SH
IV R = NH_2

The question of the activity of the methyl groups in derivatives of 4-methylpyrimidine has been elucidated fairly satisfactorily in the literature. Thus, 4-methylpyrimidine is capable of condensing with aldehydes giving 4-styrylpyrimidines [2] and of undergoing the azo coupling reaction with p-nitrobenzenediazonium salts through the methyl group [3]. When passivators (OH, NH_2) which become conjugated with the nitrogen atom of the heterocycle are introduced into the meta position with respect to the methyl group, the activity of the methyl group falls: neither 2,6-dihydroxy-4-methylpyrimidine nor 6-hydroxy-4-methylpyrimidine can condense with benzaldehyde even under very severe conditions [4]. So far as concerns derivatives of 2-methylpyrimidine, no systematic study of the activity of the methyl groups in these compounds has yet been carried out.

We evaluated the activity of the methyl groups in compounds I–IV from their capacity for condensing with aldehydes and undergoing the azo coupling reaction with diazonium salts. In our investigations, the condensations of compounds I–IV with benzaldehyde (A), p-nitrobenzaldehyde (B), and p-dimethylaminobenzaldehyde (C) were carried out by fusing the components or heating them in acetic anhydride solution. The azo coupling reactions with p-nitrobenzenediazonium (D) and benzenediazonium (E) salts were carried out in acetic acid solutions. The results obtained are given in Table 1.

It was found that I, II, and III react with aldehydes while IV does not. Of all the compounds investigated, only II [7] takes part in the azo coupling reaction (with a p-nitrobenzenediazonium salt). The results obtained interest us particularly because in both 2-methylpyrimidine and 4-methylpyrimidine the methyl group is conjugated with both nitrogen atoms of the pyrimidine ring. In spite of this, the methyl group in 2-methylpyrimidine proved to be less active than in the isomeric 4-methylpyrimidine. The following explanation can apparently be given for this: the molecule of 2-methylpyrimidine (I) is symmetrical about the methyl group. Consequently, the two mesomeric structures (Ia) and



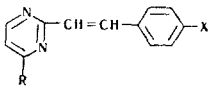
Ia Ib Va Vb VI

(Ib) are equivalent and the double-bondedness of C_2N_1 and C_2N_3 is the same. In the molecule of 4-methylpyrimidine, there is no symmetry with respect to the methyl group and structures Va and Vb are not equivalent. It must be assumed that this is responsible for some fixation of the double bonds, which leads to a greater degree of conjugation of the methyl group with the heteroatom. The literature data [8] on the considerably higher activity of the methyl group in position 4 in derivatives of 5,6-dihydropyrimidine (VI), where the fixation of the double bonds is maximum, agree with this hypothesis.

The higher activity, as compared with 2-methylpyrimidine, of the methyl group in 2-methylquinazoline which, according to our data [1], forms an azo compound through the methyl group with both D and E is due, it must be assumed, to the absence of symmetry of the molecule of 2-methylquinazoline with respect to the methyl group.

*For part XVI, see [1].

Table 2



Compound	R	X	Mp, °C (solvent for crystallization)	Empirical formula	Found, %		Calculated, %		Yield, %
					N	S	N	S	
VII	OH	$(CH_3)_2N$	251—252 (butanol)	$C_{14}H_{15}N_3O$	17.33; 17.43	—	17.42	—	30
VIII	SH	H	198—199 (treatment with ethanol)	$C_{12}H_{10}N_2S$	—	14.94; 14.92	—	15.00	60
IX	SH	NO_2	>310*	$C_{12}H_9N_3O_2S$	—	12.18; 12.01	—	12.35	50
X	SH	$(CH_3)_2N$	264—265 (treatment with hot nitromethane	$C_{14}H_{15}N_3S$	—	12.23; 12.05	—	12.45	75

*Dissolution in dimethylformamide and subsequent precipitation with ethanol.

A comparison of 4-substituted 2-methylpyrimidines with the corresponding 2-methylquinazoline derivatives shows that the condensed benzene ring has no appreciable influence on the activity of the methyl group in these compounds: 4-substituted 2-methylquinazolines do not differ in the reactivity of the methyl groups from the corresponding 2-methylpyrimidines.

EXPERIMENTAL

4-Mercapto-2-methylpyrimidine (III). A mixture of 2 g (0.02 mole) of 4-hydroxy-2-methylpyrimidine [9] (II) and 8 g (0.04 mole) of phosphorus pentasulfide in 70 ml of pyridine was heated at 125–130°C for 3 hr. The excess of pyridine was distilled off in vacuum and the residue was treated with 70 ml of water, the mixture was boiled for 30 min, and the hot solution was filtered. After cooling, it was brought to pH 9 with ammonia, the ammonium sulfate was filtered off, and the filtrate was acidified with hydrochloric acid to pH 5 and evaporated to half bulk. The yellow precipitate that deposited on cooling was filtered off. Weight 1.4 g (60%). Mp 145–146°C (from glacial acetic acid). Found, %: N 22.24, 22.34. Calculated for $C_5H_6N_2S$, %: N 22.22.

4-Hydroxy-2-styrylpyrimidine (V). A mixture of 1.1 g (0.01 mole) of II and 5 ml (0.05 mole) of benzaldehyde was heated at 180–190°C for 2 hr 30 min. The excess of benzaldehyde was washed out with ether. Yield of V 1.85 g (95%). Yellow powder. Mp 196–198°C (from ethanol). Found, %: N 14.15, 14.13. Calculated for $C_{12}H_{10}N_2O$, %: N 14.14.

The styryl derivatives VII, IX and X were obtained similarly, while the synthesis of the styryl pyrimidine VIII was carried out in the presence of CH_3COONa (see Table 2).

4-Hydroxy-2-(p-nitrostyryl)pyrimidine (VI). A solution of 1.1 g (0.01 mole) of II and 1.6 g (0.013 mole) of p-nitrobenzaldehyde in 25 ml of acetic anhydride was heated at 130–150°C for 1 hr. After cooling, a cream-colored precipitate was obtained. Weight 1 g (45%). Mp 295–296°C (from acetic anhydride). Found, %: N 17.28, 17.22. Calculated for $C_{12}H_9N_3O_3$, %: N 17.28.

In an attempt to condense 4-amino-2-methylpyrimidine [10] (IV) with A, B, and C (see Table 1), only that initial IV was isolated.

2-Methylpyrimidine [11] (I) does not undergo azo coupling with benzenediazonium and p-nitrobenzenediazonium salts in either hydrochloric or acetic acid solutions.

REFERENCES

1. V. A. Serzhanina, N. V. Khromov-Borisov, and R. S. Karlinskaya, ZhOrKh, 1, 1303, 1965.

2. S. Gabriel and J. Colman, Ber., 36, 3383, 1903.

3. N. V. Khromov-Borisov, R. S. Karlinskaya, and L. N. Ageeva, ZhOKh, 25, 2295, 1955.

4. H. Poss, J. Chem. Soc., 1128, 1948.

5. H. Holland, Chem. Ind., 27, 786, 1954.

6. E. D. Parker and A. Furst, J. Org. Chem., 23, 201, 1958.

7. R. S. Karlinskaya, N. V. Khromov-Borisov, and V. A. Ivanova, ZhOKh, 34, 3734, 1964.

8. N. V. Khromov-Borisov and A. M. Savchenko, ZhOKh, 22, 1680, 1952.

9. S. Gabriel, Ber., 37, 3638, 1904.

10. Z. Földi and G. V. Fodor, Ber., 75, 755, 1942.

11. H. Vanderhaeghe and M. Claesen, Bull. Soc. Chim. Belg., 66, 2766, 1957.

26 May 1966

Institute of Experimental Medicine AMS USSR, Leningrad