[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

THE ROLE OF PHENOL IN THE REACTION OF 2-AMINO-4-CHLORO-6-METHYLPYRIMIDINE WITH PIPERIDINE

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Earlier (1) a study was made of the effect of variation of the base strength of the amine and of the strength of the acid catalyst upon the reaction between amines and 2-amino-4-chloro-6-methylpyrimidine (I). It was observed, in parallel experiments, in the reaction of morpholine or piperidine with I in aqueous solution that slightly greater yields were obtained in the early phases of the reaction when phenol was present than in its absence. At that time the mode of action of the phenol was not known and only some tentative possibilities concerning this were suggested in a footnote. In the meanwhile Surrey[1] and Cutler (2) reported the results of their careful investigation of the role of phenol in facilitating the reaction between chloroquinolines and aliphatic amines. The usefulness of phenol in these replacement reactions of chloroquinolines and chloracridines had been well known by earlier workers[2] only as an empirical result.

Since one of the possible modes of action of phenol, which we had considered, was the formation of an intermediate phenoxypyrimidine, 2-amino-4-phenoxy-6-methylpyrimidine (II) was prepared and numerous attempts were made to induce reaction between it and piperidine under a variety of reaction conditions. The results of these experiments and the conditions used are shown in Table I. In every case all of the phenoxypyrimidine (II) was recovered unchanged. Some of the conditions selected were similar to those used in the earlier work (1).

Because no reaction was observed between piperidine and II a further series of experiments was performed in order to determine the effect of reaction conditions on the formation of II from I and phenol. Again several sets of conditions somewhat similar to those of the earlier study (1) were employed. The results of these investigations are summarized in Table II. Only one set of conditions (expt. 6) gave any appreciable amount of II. A control run (expt. 10) with piperidine present gave 52% of 2-amino-4-piperidino-6-methylpyrimidine (III) (1).

The data of Tables I and II show that the 4-phenoxypyrimidine (II) does not react with piperidine nor is it formed from I and phenol under the conditions used for the reaction of I and piperidine to give III (1). It is inconceivable that II can be an active intermediate responsible for the more favorable yields of III obtained in the presence of phenol.

It is also unreasonable to consider that the weakly acidic phenol could activate the chloropyrimidine in the fashion demonstrated by Banks (3, 4). It is believed now that phenol must exert its beneficial influence on the displacement reaction under discussion by a solvolytic pull on the chlorine atom according to the method elaborated by Swain (5).

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[1] Dr. Surrey was kind enough to call our attention to the possible relationship between their results and our findings.

[2] Surrey and Cutler, reference 2, have summarized the pertinent earlier work.

Thus while chloropyrimidines (such as I) are much more reactive toward amines than chloroquinolines (such as 4,7-dichloroquinoline), they are less reactive than the latter toward phenols, and phenoxypyrimidines do not mediate the reaction of I with piperidine in aqueous phenol.

TABLE I

RESULTS OF ATTEMPTS TO REACT PIPERIDINE WITH 2-AMINO-4-PHENOXY-6-METHYLPYRIMIDINE (II)

(Reaction mixture was heated for two hours at 100°)

EXPT.	II; MOLES	PIPERIDINE; MOLES	REACTION MEDIUM	OTHER REACTANT	PRODUCTS YIELD, %	
					II	III
1	0.01	0.04	None[a]	None	100	0
2	.01	.02	H_2O, 50 cc.	None	100	0
3	.01	.02	H_2O, 50 cc.	HCl, 0.01 mole	100	0
4	.01	.02	EtOH, 75 cc.	HCl, 0.01 mole	100	0

[a] Reaction temperature was 180°.

TABLE II

RESULTS OF ATTEMPTS TO REACT PHENOL WITH 2-AMINO-4-CHLORO-6-METHYLPYRIMIDINE (I)

(Reaction mixture was heated for two hours at 100°)

EXPT.	I; MOLES	PHENOL; MOLES	REACTION MEDIUM	OTHER REACTANT	PRODUCTS YIELD, %		
					I	II	III
5	0.02	0.10	None	None	>90	<10	—
6	.02	.10	None	KOH, 0.02 mole	0	100	—
7	.02	.04	H_2O, 50 cc.	None	>97	<3	—
8	.02	.04	H_2O, 50 cc.	KOH, 0.02 mole	>95	<5	—
9	.02	.04	H_2O, 50 cc.	HCl, 0.02 mole	65[a]	0	—
10	.02	.04	H_2O, 50 cc.	Piperidine, 0.02 mole	40	<2	52

[a] The HCl initially present in this run seems to have induced a partial hydrolysis of the starting compound (I).

EXPERIMENTAL

Preparation of 2-amino-4-phenoxy-6-methylpyrimidine (II). Equimolar amounts of I and potassium hydroxide (pellets) were mixed in 5 molar-equivalents of phenol and heated for two hours at 100°. Excess 10% aqueous potassium hydroxide was added to the reaction mixture, and after cooling, the product (II) was collected and washed with much water. When recrystallized from methanol the white product melted at 194–195°; yield, 98%.

Anal. Calc'd for $C_{11}H_{11}N_3O$: C, 65.6; H, 5.5; N, 20.9.

Found: C, 65.5; H, 5.6; N, 20.8.

Typical attempt to react piperidine with II (expt. 4). A solution of 2 g. (0.01 mole) of II and 1.7 g. (0.02 mole) of piperidine in 75 cc. of ethanol, containing 1 cc. (0.01 mole) of concentrated hydrochloric acid, was heated for two hours at 100°. The reaction mixture was diluted with water and and basified with 50% aqueous alkali. In this way 2 g. (100%) of II was recovered unchanged. When recrystallized from methanol the white crystals melted at 193–195°.

Typical attempt to react I with phenol (expt. 8). A mixture of 2.9 g. (0.02 mole) of I, 3.8 g. (0.04 mole) of phenol, and 1.2 g. (0.02 mole) of potassium hydroxide in 50 cc. of water was heated for two hours at 100°. Excess alkali was added to *p*H 11, and after cooling, the white precipitate was collected and washed repeatedly with water. Total yield was 3.1 g. slightly moist; melting point 153–165°; strong positive Beilstein test for halogen.

This product was almost entirely recovered chloropyrimidine (I). In order to determine how much II was present the crude product was heated for two hours at 100° with 20 cc. of 12–15% aqueous hydrochloric acid. This treatment hydrolyzed both I and II to the 4-hydroxypyrimidine and liberated phenol from any II present. The cooled aqueous mixture was brought to *p*H 11 with alkali but gave no precipitate. The solution was reacidified to *p*H 1 with concentrated hydrochloric acid and the phenol was extracted with ether. The dried ether extract upon evaporation left <0.1 g. of phenol corresponding to <0.2 g. (<5%) of II.

A control sample of 1 g. of pure II when treated according to the above procedure yielded 0.4 g. of phenol or >90% recovery.

SUMMARY

The facilitating effect of phenol on the reaction of amines with 2-amino-4-chloro-6-methylpyrimidine (I) is attributed to its strong solvolytic action on the chlorine of the pyrimidine.

It has been shown that the phenoxypyrimidine (II) is not an active intermediate in the reaction with amines.

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REFERENCES

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(4) BANKS, *J. Am. Chem. Soc.*, **66**, 1131 (1944).
(5) SWAIN, *J. Am. Chem. Soc.*, **70**, 1119 (1948) and subsequent papers.