[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

THE REACTION OF ALKYLAMINES WITH CHLOROHETEROCYCLIC COMPOUNDS. II.[1] 2-AMINO-4-CHLORO-6-METHYLPYRIMIDINE

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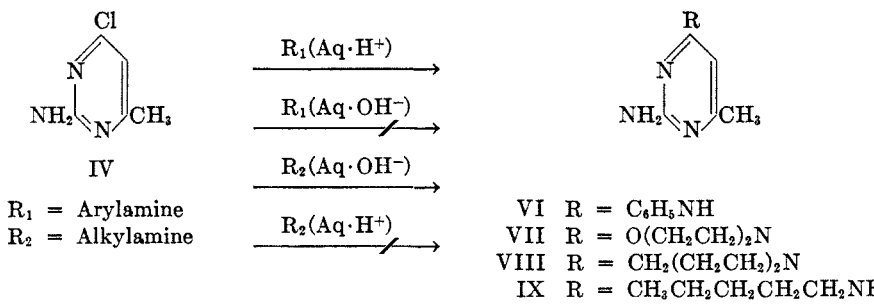
Since the publication of Banks' excellent study and interpretation (1, 2) of the reaction of aromatic amines with "active" chloroheterocyclic compounds in aqueous solutions, other investigators (3, 4, 5) have similarly synthesized numerous arylaminoheterocyclic compounds. It was clearly shown by Banks that the reaction is markedly accelerated by aqueous acid but inhibited under alkaline conditions.

Under analogous aqueous acid conditions (1, 2), Banks obtained yields of 100, 70, and 0% with aniline (I), morpholine (II), and diethylamine (III), respectively, whose individual basic dissociation constants increase in the order 5×10^{-10}, 2×10^{-6}, and 1×10^{-3}. It seemed to us that this marked decrease in yields could be correlated with the relative affinities of the amines for protons.

The reactivity of an electrophilic chloroheterocyclic compound, such as 2-amino-4-chloro-6-methylpyrimidine (IV) toward nucleophilic substituting agents is inherent in the molecular structure (analogous to an acid chloride) and is accentuated by acid catalysts presumably in the fashion outlined by Banks (1). However, the reactivity of the nucleophilic attacking fragments in the reaction depends on the relative electron availability on the nitrogen when considering, as we are here, a series of amines. In the uncatalyzed reaction the initial attack would be relatable to the nucleophilic reactivity of the amine. In the acid-catalyzed process, or after the uncatalyzed reaction had proceded part way, the relative extent of the reaction would be conditioned by the interplay of two factors: (a) the affinity of the amine for the chloroheterocyclic compound, and (b) its affinity for acid in the aqueous medium.



Thus, when equivalent amounts of aniline, 2-amino-4-chloro-6-methylpyrimidine, and hydrochloric acid are heated in aqueous media, excellent yields of 2-amino-4-anilino-6-methylpyrimidine (VI) result rapidly because the low basicity of aniline allows considerable hydrolysis of its conjugate acid, thus simul-

[1] Paper I, *J. Am. Chem. Soc.*, in press.

taneously liberating free aniline for nucleophilic attack and free hydrochloric acid to activate 2-amino-4-chloro-6-methylpyrimidine (1, 2). When, however, equivalent amounts of diethylamine or piperidine (V), with 2-amino-4-chloro-6-methylpyrimidine and hydrochloric acid are heated in aqueous media, practically no reaction occurs, for diethylamine and piperidine are such strong bases that little or no hydrolysis of their conjugate acids occurs. Therefore, diethylamine is not only not available to attack the chloropyrimidine but also no hydrochloric acid is available to activate it. Morpholine (II) occupies an intermediate position with regard to basicity and reactivity under the above conditions.

We have examined the effect of varying acidic strength on the yields for the reaction of aniline, morpholine, and piperidine with 2-amino-4-chloro-6-methylpyrimidine. The results for the interaction of equivalent amounts of amine and the chloropyrimidine in the presence of two equivalents of acid in aqueous media for two hours at 100° are shown in Table I and the figures are the composite of duplicate runs, checking one another within 2–5%.

TABLE I

SUBSTITUTED PYRIMIDINE FORMED, %

AMINES	ACIDS → / ↓Diss. Const.	HCl 1.0	HOAc 2×10^{-5}	HOPh 10^{-10}	HOH 10^{-14}
(I) Aniline	5×10^{-10}	100[a]	—	—	100
(II) Morpholine	2×10^{-6}	<20	76	81	72 (100[b])
(V) Piperidine	1×10^{-3}	5	11	51	48 (100[b])

[a] 2-Amino-4-anilino-6-methylpyrimidine, m.p. 171–173°; lit. (2) 170–172°. [b] Three equivalents of amine *per* equivalent of chloropyrimidine.

While aniline gave essentially quantitative yields under all of the conditions tried, the stronger base, piperidine, gave only small yields in the presence of either acetic or hydrochloric acid. In water alone or with phenol present, piperidine gave yields of about 50%. Morpholine, a base of intermediate strength, reacted significantly in the presence of the weak acids, including acetic, but as expected gave much less of the desired product when hydrochloric acid was the catalyst.

As described in the experimental part and stated in footnote 2, extended treatment of the substituted aminopyrimidines with a considerable excess of strong hydrochloric acid left the aminopyrimidines intact while hydrolyzing completely any unreacted chloropyrimidine. Although knowledge of these facts made it unnecessary to consider whether the arbitrarily chosen two hour reaction interval could represent a point beyond optimal yield (due to hypothetical hydrolytic cleavage of the product), it was deemed of interest to compare the yields obtained with morpholine and piperidine at several intervals of time to show whether: (a) the superior yields with morpholine were consistently obtained; (b) the slightly greater yields obtained in the presence of phenol as com-

pared with water alone were real; and (c) whether with extended reaction time the yield would approach the quantitative, or stop significantly short of that.

The figures in Table II represent the percentage yields of product obtained when equivalent amounts of amine and chloropyrimidine were allowed to react either in water alone or in water containing two equivalents of phenol for the time intervals specified, at 100°. From these results it can be seen that in answer to the above listed points: (a) at each reaction time the yield of morpholino product consistently exceeded that from piperidine; (b) the slightly better yields obtained with each of the amines in the presence of phenol, as compared with water alone, which originally might have been accepted as falling within the range of experimental error, now appear to represent a valid result.[3] The margin in favor of the phenol-catalyzed reaction, although usually small, seems quite reproducible and persists for both amines through the early stages of reaction. The differential

TABLE II

SUBSTITUTED PYRIMIDINE FORMED, %

TIME, HOURS	1	2	3	5	20
Morpholine	47	72	88	90	91
Morpholine and Phenol	55	81	90	89	91
Piperidine	38	48	55	65	80
Piperidine and Phenol	42	51	60	67	79

is greatest in the early part of the reaction and after three hours with morpholine and after five hours with piperidine is no longer apparent. This loss of the effectiveness of phenol in facilitating reaction toward the later stages of the reaction may be related to the accumulation of appreciable amounts of the much stronger hydrochloric acid formed in the course of the reaction; (c) the yields in each case were found to approach a maximum significantly below 100%. The maxima are indicated in Table II; for morpholine, it was attained after three hours, 90%, while for piperidine, it was 80% after 20 hours.

Although the work in this paper was not conducted with the refined care re-

[3] The possible ways in which phenol might facilitate this reaction have not been elaborated upon, nor has the principal way been established. The more obvious possibilities are listed below: (a) formation of an intermediate phenoxypyrimidine which subsequently reacts with the amine present to yield aminopyrimidine; (b) a favoring of mutual solubilities of the reactants during the early stages of the reaction; and (c) some "catalytic" effect producing a faster reaction rate at the slightly lower *p*H (8 with piperidine plus phenol as compared with 11 for piperidine alone) prevailing at the start. It is difficult to conceive of anything in the nature of the catalytic activation [discussed by Banks (1, 2) in which a proton combines with the chloropyrimidine] occurring in the basic medium (*p*H 8–10) prevailing throughout most of the reaction. In fact whatever the mode of action of phenol in enhancing the rate of reaction (and this seems to be definitely established) it almost certainly has to be a fundamentally different process than that considered by Banks when hydrochloric acid was the catalyst. A further investigation of the problems suggested by points (a) and (c) is being planned.

quired for an accurate kinetic study, calculations of velocity constants using even the rough figures obtained here show up well the relative effect of acid (formed in the reaction) on the rates of reaction as correlated with the base strength of the amine. Thus using the yields reported in Table II for the reaction of morpholine and piperidine with the chloropyrimidine in water alone, the results shown in Table III are obtained.

Using the equation for a simple bimolecular reaction, k for morpholine nearly *triples* in value between one and three hours, presumably because of increasing catalytic activation of the chloropyrimidine by the hydrochloric acid produced in the process. With piperidine the rate constant is *decreased* by one-third between one and three hours, probably due in large measure to the tying up of the stronger base piperidine to the relatively greater extent by the hydrochloric acid produced in the reaction.

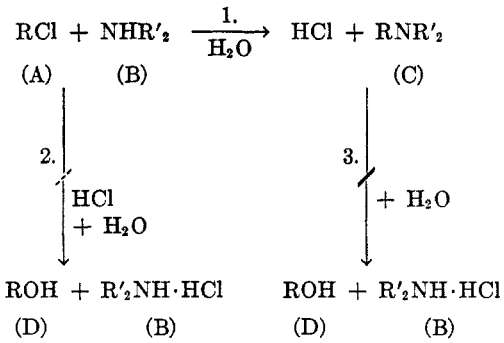
TABLE III

VELOCITY CONSTANTS FOR REACTION OF AMINE WITH CHLOROPYRIMIDINE

$$k = \frac{1}{t} \cdot \frac{x}{a(a - x)}$$

TIME, HOURS ⟶	1	2	3	5
Morpholine k × 10^4	4.0	7.0	11.0	
Piperidine k × 10^4	3.1	2.3	2.0	1.9

Maximum yields well below 100% suggest something of the nature of an equilibrium process, but not of the reversible type. The more probable interactions are shown in the scheme below:



The chloropyrimidine (A) reacts with the amine (B) in aqueous medium to produce the aminopyrimidine product (C) plus hydrochloric acid. (Reaction 1). It has been shown (see experimental part and footnote 2) that the substituted aminopyrimidines are apparently completely stable to prolonged heating with ordinary concentrations of hydrochloric acid (up to 6 *N*) so that yields of less than 100% for C obtained in Reaction 1 cannot be attributed to the hydrolytic Reaction 3. Furthermore the hydrolytic Reaction 2 converting the original

chloropyrimidine to hydroxypyrimidine probably does not occur to any appreciable extent under the basic or very weakly acidic conditions described in this paper. Thus attempts to isolate the hydroxypyrimidine (D) prior to the usual strong acid hydrolysis treatment failed. In other experiments unrelated to the present work, after unsuccessful attempts to combine an unreactive amine with the chloropyrimidine by several hours heating in the presence of an equivalent of hydrochloric acid, nearly quantitative amounts of the unchanged chloropyrimidine (A) were recovered. (Stronger hydrochloric acid solutions, 4–6 *N*, rapidly hydrolyze the chloro- to the hydroxy-pyrimidine, one hour at 100°.)

Since Reaction 1 of formation of C is not reversible under the reaction conditions and the hydrolytic Reactions 2 and 3 have been eliminated from establishing an equilibrium below 100%, there remains the originally hypothesized competition between the chloropyrimidine (A) and hydrogen chloride for the amine reactant (B). The equilibrium is probably attained by the competition between B and C for the hydrochloric acid formed in the reaction which at some point effectively removes amine from reaction and prevents attainment of quantitative yields.

Though it is well known that chloroheterocycles such as 2-amino-4-chloro-6-methylpyrimidine react well when heated at high temperatures with excess alkylamines, a logical extension of our results has not been mentioned. We might expect to increase the yield as well as the rate in the first two hours by running the reaction at a (buffered) nearly neutral *p*H. Thus, piperidine and 2-amino-4-chloro-6-methylpyrimidine under conditions analogous to those of Table I in only two hours gave an 80% yield of 2-amino-4-piperidino-6-methylpyrimidine when run in a medium strongly buffered with sodium acetate—acetic acid. Likewise three equivalents of morpholine and piperidine *per* equivalent of 2-amino-4-chloro-6-methylpyrimidine gave 100% yields of their respective products in aqueous media. A primary amine, *n*-amylamine, one and three equivalents reacting in water alone with the chloropyrimidine for two hours in the usual way, gave 38 and 71% yields of 2-amino-4-*n*-amylamino-6-methylpyrimidine (IX), m.p. 98–99° (6). These latter conditions of excess base are suggestive of the Schotten-Baumann reaction.

Work is being continued along related lines.

EXPERIMENTAL

The procedure given below for the preparation of VII represents the general conditions used for obtaining the results shown in Tables I and II. All yields are based on duplicate runs checking within 2–5%.

2-Amino-4-morpholino-6-methylpyrimidine (VII). To 60 ml. of distilled water[4] was added 2.9 g. (0.033 mole) of morpholine and 4.8 g. (0.033 mole) of 2-amino-4-chloro-6-methylpyrimidine. The contents were heated on the steam-bath for two hours, and to this was added 25 ml. of concentrated hydrochloric acid with continued heating for one hour at 100°.[2] The cooled solution diluted to 225 ml. with water was made basic with 50% sodium

[4] All procedures of Table I used 0.033 mole of reactants, 0.066 mole of acids, and 60 ml. of water.

[2] This method completely hydrolyzed any unreacted chloropyrimidine and had no effect on the resulting alkyl- and aryl-aminopyrimidines.

hydroxide, total volume 250 ml., to give 3.2 g. (50%) of white crystals, m.p. 176–177°. Recrystallization from hot water gave crystals, m.p. 176–177°.

Anal. Calc'd for $C_9H_{14}N_4O$: N, 28.8. Found: N, 29.0.

2-Amino-4-piperidino-6-methylpyrimidine (VIII). To 4.2 g. of piperidine, and 7.0 g. of 2-amino-4-chloro-6-methylpyrimidine was added a 75 ml. aqueous solution[5] containing 41 g. of sodium acetate and 0.6 ml. of glacial acetic acid. The contents (initial *p*H 8) were heated on the steam-bath for two hours (final *p*H 6), and then adjusted to *p*H 10 with 50% sodium hydroxide. After standing overnight, the gray crystalline solid was filtered off and treated with a 70 ml. water solution containing 25 ml. of concentrated hydrochloric acid for one hour at 100°. The 225 ml. solution upon being made alkaline with 50% sodium hydroxide yielded 76% of gray-white crystals, m.p. 150–151°. Recrystallization from benzene-hexane gave white needles, m.p. 152–153°.

Anal. Calc'd for $C_{10}H_{16}N_4$: N, 29.2. Found: N, 29.2.

Solubility determinations of the above products carried out under the identical experimental conditions above (salt concentration, alkalinity, temperature, and volume) showed that 1.4 g. of 2-amino-4-morpholino-6-methylpyrimidine and 0.25 g. of 2-amino-4-piperidino-6-methylpyrimidine were dissolved in 250 ml. of solution. These amounts of dissolved products corresponded to 22% and 4% respectively of the calculated yields for the standard reaction quantities employed in all experiments. The yields reported in Tables I and II have been corrected by the addition of 22% to the actual isolated % yields for the morpholino product and by the addition of 4% to the isolated % yields for the piperidino product.

Attempted isolation of 2-amino-4-hydroxy-6-methylpyrimidine from one preparation. A mixture of 0.033 mole of 2-amino-4-chloro-6-methylpyrimidine and 0.033 mole of piperidine was suspended in 60 ml. of water and heated for 20 hours at 100° in a stoppered flask. The initial *p*H was 11, after three hours it had fallen to 8 and finally was 7. After chilling the reaction mixture 15 ml. of 50% aqueous potassium hydroxide was added (to *p*H 11) liberating the piperidinopyrimidine and dissolving any 4-hydroxypyrimidine which might have been produced as a side product. Piperidinopyrimidine was filtered off quickly and heated with aqueous hydrochloric acid (as in the general procedure) to destroy any contaminating, unreacted chloropyrimidine. After reliberation of this product 4.9 g. (77%; corrected for solubility 80–81%) of pure VIII was obtained.

The aqueous alkaline filtrates from the original reaction mixture acidified (to *p*H 6) with concentrated hydrochloric acid gave a clear solution. No 4-hydroxypyrimidine precipitated indicating that *less than* 0.6 g. must have been present, since a solubility determination showed it to be 0.6 g. in 100 ml. of water (which was the final volume of this reaction mixture).

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SUMMARY

In contrast to the acid-catalyzed reaction between arylamines and "active" chloropyrimidines, we have found that excellent yields of the products can be obtained from strong aliphatic type amines by maintaining basic conditions in the reaction.

Any acid present either as a catalyst at the start or formed during the course of the reaction serves to bind these stronger amines in direct relation to their base strengths as relatively stable salts which are then available for reaction with the chloroheterocyclic compound only insofar as they may be partially

[5] General procedure modified because of sodium acetate content.

liberated, in some equilibrium fashion, by interaction with the weaker base, the substituted aminopyrimidine formed in the reaction.

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