Calcd. for $C_{20}H_{22}O_4NI$: C, 53.21; H, 4.88. Found: C, 53.72; H, 4.90.

O,N-Dimethylanolobinemethine (VIII).—O,N-Dimethylanolobine methiodide was decomposed by heating for twenty-four hours on the steam-bath in strongly alkaline solution. The liberated methine base was extracted from the cooled solution with ether. The methine base, which crystallized when its ether solution was evaporated, was recrystallized from dry ether from which it separated as colorless needles melting at 100°. Admixture with the methine obtained from naturally occurring anolobine (m. p. 99°) failed to depress the melting point. Calcd. for $C_{20}H_{21}O_4N$: C, 74.30; H, 6.50; N, 4.33. Found: C, 74.47; H, 6.35; N, 4.29. A small quantity of the methine base was converted to the picrate which was found to be only very sparingly soluble in boiling methanol or acetone. When recrystallized from a large volume of boiling acetone it separated in two forms: long yellow needles and stout orange needles. After standing several hours in contact with the mother liquor the yellow needles had disappeared and the orange needles alone were present; melting point, 258°. Calcd. for $C_{26}H_{24}O_{10}N_4$: C, 56.53; H, 4.35. Found: C, 56.77, 56.67; H, 4.37, 4.38.

Summary

1. The structure of anolobine has been confirmed by synthesis of the methine base of O-methylanolobine.

2. The synthesis has been effected from methylenedioxyphenylethylamine and 2-nitro-5-methoxyphenylacetyl chloride which was condensed to give an amide and this was converted to the corresponding dihydroisoquinoline by an improved Bischler–Napieralsky reaction. The methiodide of the dihydroisoquinoline was reduced and the product transformed by the Pschorr reaction to *dl*-O,N-dimethylanolobine. The methiodide of the synthetic base was decomposed to the corresponding methine base, identical with that obtained from naturally occurring anolobine.

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[CONTRIBUTION FROM THE RESEARCH AND BIOLOGICAL LABORATORIES OF PARKE, DAVIS AND COMPANY]

Arylaminoheterocyclic Compounds. I. Synthetic Method

BY C. KENNETH BANKS

The literature of arylaminoheterocycles is exceedingly scant, considering the innumerable variations possible. Much of the work that has been done is in the patent literature and identification of the compounds, as pure substances, is frequently lacking. The methods used for such preparations indicate that no generally applicable synthetic method exists and frequently the procedure given will work only for the simplest of arylamines. The general approach has been to regard the synthesis as an Ullmann[1] reaction, although a few variations have been tried. In general, a haloheterocycle, in which the halogen occupies a so-called "active" position, reacts with an excess of the aromatic amine under pressure at high temperatures, with or without copper as a catalyst. With the seemingly more "active" halogen compounds, high boiling organic solvents and potassium carbonate have been used[2,3,4,5] and where extreme "activity" was encountered (cyanuric chloride), conditions characteristic of the Schotten–Baumann reaction have been employed.[6,7]

In every case it is apparent that two assumptions have been made. First, the reaction apparently has been regarded as being reversible since the principles of inorganic chemistry have been applied to prevent reversal. Second, the use of copper as a catalyst is indicative of an association with halobenzenoid compounds. Although it has long been recognized that the positions in heterocyclic nuclei, particularly in nitrogen-containing rings, vary greatly in conferring activity upon substituents, it has been common to classify the positions as "aromatic" or "aliphatic" in character. The possible variation of the electronic configuration due to external agents apparently has not been considered.

Recently we had the problem of condensing arsanilic acid with a halotriazine. Because of the physical nature of the reactants, high pressures and temperatures had to be avoided. In this reaction, it was noted that aqueous condensation was effective and that alkali had a definite inhibitory effect, so much so that the haloheterocycle was frequently hydrolyzed before any reaction was noted. Further experimentation indicated that the addition of acid did not inhibit the reaction but actually speeded it to completion. It was possible to follow the course of the reaction by measurement of the diazotizable amine present and it was found that the reaction could be considered irreversible for all practical purposes, K_c for the reaction being greater than 10^{12}. In addition to the increased rate of reaction, the rate of hydrolysis of the haloheterocycle was decreased by acid.

With this information it was evident that the nature of the reaction could not be easily explained on the basis of existing information. After some preliminary syntheses, the reaction rates of several amines and haloheterocycles were studied, using varying concentrations of acid and alkali. The haloheterocycles chosen for the study were

(1) Ullmann, *Ann.*, **355**, 312 (1907).
(2) Bremer, *ibid.*, **514**, 279 (1934).
(3) Mangini and Frenguelli, *Gass. chim. ital.*, **69**, 86, 97 (1939).
(4) Phillips, *J. Chem. Soc.*, 9 (1941).
(5) Hatlelid, Ph.D. Thesis, University of Nebraska, 1942.
(6) British Patent 309,102 (1929).
(7) U. S. Patent 2,295,574 (1942).

2-chloro-4,6-diamino-*s*-triazine and 2-amino-4-chloropyrimidine. Availability was a deciding factor in their choice. Also both of these compounds, particularly the triazine, have physical and chemical properties that make them very useful. They are obtainable in a high degree of purity, they are relatively stable toward hydrolysis, their reaction products are formed in quantitative or nearly quantitative amounts and are easily isolated and identified, and they are relatively stable toward other types of decomposition (oxidation, etc.).

The first reaction studied was that between 2-chloro-4,6-diamino-*s*-triazine and aniline (I) to give 2-anilino-4,6-diamino-*s*-triazine.[8] Aqueous mixtures of the reactants were refluxed with varying amounts of alkali and acid. In each case the amount of reaction was determined by withdrawing a sample, diluting sufficiently to determine the concentration of unreacted primary benzenoid amine in an aliquot by diazotizing and coupling with N-dimethyl-α-naphthylamine (the amino groups of the heterocycles used are not diazotizable under these conditions). The color produced was then compared with standard color solutions obtained from known amounts of aniline. This method is only semi-quantitative but is sufficiently indicative to show the rate of reaction. Such a method will determine 99.99% reaction with as great or greater accuracy than it will 10% reaction. Examination of the results shown in Table I shows that reaction is absent or at least insignificant when the theoretical amount of alkali required to take up the hydrochloric acid formed in the reaction is added. This reaction has been run for twenty-four hours with the same result. When only half as much alkali is added, there is a perceptible reaction after an initial period of no reaction. The next two experiments, using, respectively, 0.1 and 0.01 eq. of alkali, explain this initial lag. Not only is the reaction inhibited by the alkali, but also it is necessary that at least a portion of the alkali be neutralized by hydrolysis of the haloheterocycle before reaction is apparent. This explains why some reaction can be noted when such compounds as sodium acetate are used as alkaline buffers. In water alone, the reaction was completed in an hour (less than 0.01% free amine remaining). The addition of 0.01 eq. of hydrochloric acid doubled the reaction rate and 0.1 eq. of acid quadrupled the rate. Higher concentrations of acid further increased the rate of reaction, although not in a strict progression. The presence of 10 eq. of acid caused extremely rapid reaction but also led to a high rate of hydrolysis to 2-hydroxy-4,6-diamino-*s*-triazine.

To confirm these data, aniline was replaced by a different type of arylamine, *p*-arsanilic acid (II). Taking into consideration the effect of the acid nature of *p*-arsanilic acid, the data in Table II are quite comparable with those in Table I. Aniline was also substituted by *p*-chloroaniline, sulfanilic acid, *p*-nitroaniline and *p*-anisidine. The results were similar to those given in Tables I and II.

After considering the data, several questions became evident. The question of kind of alkali used was dismissed as being adequately answered by the evidence. To determine whether it was the hydrogen ion or specifically hydrochloric acid that acted as the catalyst, the reaction (II) was repeated with sulfuric and tartaric acids. The results in Table III indicate that it is the hydrogen ion that is effective and this has been confirmed in a qualitative manner with phosphoric, acetic, arsenic, citric, malonic, oxalic and boric acids.

Another obvious question was whether the effect of the acid was solely to solubilize the rather insoluble 2-chloro-4,6-diamino-*s*-triazine. Experiments to determine the relative solubility of the compound did not indicate that it was a sole factor, but to eliminate the question, the heterocycle 2-amino-4-chloropyrimidine was substituted for the triazine in reaction II, and the reaction was run in 10% acetone in water (IVa) and in water (IVb). With acetone, the reactants are completely soluble in all of the runs; whereas, in the alkaline and neutral runs in water alone, the haloheterocycle is not completely soluble. Comparison of Table IVa and IVb shows that solubility of reactants is not the dominant factor. Comparison of IVa or IVb with II shows a general quantitative relationship based on *p*H. Tables V and VI, based on the reaction of the pyrimidine with aniline (V) and *p*-aminophenol (VI), give additional confirmatory evidence.

Experimental

TABLE I

2-ANILINO-4,6-DIAMINO-*s*-TRIAZINE

Aniline and 2-chloro-4,6-diamino-*s*-triazine: One-hundredth mole of each reactant was placed in a 250-ml. flask and heated in a reaction volume of 100 ml. under total reflux with varying amounts of sodium hydroxide and hydrochloric acid in water. Samples were withdrawn at stated intervals and the amount of unreacted amine determined by diazotization, coupling with dimethyl-α-naphthylamine and comparison with known standards, by use of a visual colorimeter. The temperature of mixing was 95° and refluxing occurred within thirty seconds. Each reaction was repeated at least once.

	Acid or alkali	% Primary amine remaining after min. 2	5	10	15	30	60	120
1	1 eq. NaOH	100	100	100	100	100	100	100
		100	100	100	100	100	100	100
2	0.5 eq. NaOH	100	100	100	95	95	90	80
		100	100	95	85	85	80	75
3	0.1 eq. NaOH	100	100	95	95	90	90	55
		100	100	95	90	90	85	60
4	0.01 eq. NaOH	100	95	85	75	10	1.0	1.0
		100	100	90	80	8	0.7	1.0
5	None	90	80	50	30	1.0	<0.01	<0.01
		90	80	60	35	5	<0.01	<0.01
6	0.01 eq. HCl	85	60	5	2	<0.01	<0.01	..
		85	65	10	3	<0.01	<0.01	..

(8) Klason, *Svensha Vet.-Akad. Handlingar*, **19**, 11 (Beilstein XXVI, 247).

TABLE I (*Concluded*)

	Acid or alkali	% Primary amine remaining after min. 2	5	10	15	30	60	150
7	0.1 eq. HCl	20	5	0.5	<0.01	<0.01	..	..
		20	7	1.0	<0.01	<0.01	..	..
8	1 eq. HCl	10	2	<0.01	<0.01	<0.01	..	..
		15	5	0.2	<0.01	<0.01	..	..
9	2 eq. HCl	10	1	0.01	0.01	0.3	..	..
		10	2	0.01	0.01	0.1	..	..
10	10 eq. HCl	10	0.3	13	40	65	95	100
		8	1.2	14	45	85	95	100

TABLE II

2-(4'-ARSONOANILINO)-4,6-DIAMINO-*s*-TRIAZINE[7]

p-Arsanilic acid and 2-chloro-4,6-diamino-*s*-triazine. The reactants (0.01 mole each) reacted as in I.

	Acid or alkali	% Primary amine remaining after min. 2	5	10	15	30	60
1	10 eq. NaOH	100	100	100	100	100	100
		100	100	100	100	100	100
2	2 eq. NaOH	100	100	100	100	100	100
		100	100	100	100	95	100
3	1.5 eq. NaOH	100	100	100	95	95	95
		100	100	100	100	95	95
4	1 eq. NaOH	100	100	90	90	80	70
		100	100	95	90	85	70
5	None	100	60	30	4	<0.01	<0.01
		100	65	35	5	<0.01	<0.01
6	0.1 eq. HCl	90	40	5	1.0	<0.01	<0.01
		85	40	8	2.0	<0.01	<0.01
7	1 eq. HCl	10	0.2	<0.01	<0.01	0.1	0.2
		15	0.5	<0.01	<0.01	0.1	0.2
8	2 eq. HCl	8	0.1	<0.01	<0.01	0.2	0.3
		9	0.1	<0.01	<0.01	0.2	0.4
9	10 eq. HCl	20	15	8	40	50	..
		25	20	10	35	50	..

TABLE III

EFFECT OF DIFFERENT ACIDS. II WAS REPEATED USING THE OTHER ACIDS

	Acid	% Primary amine remaining after min. 2	5	10	15	30	60
1	1 eq. HCl	10	0.2	<0.01	<0.01	0.1	0.2
2	1 eq. H_2SO_4	30	3	<0.01	<0.01	<0.01	0.1
3	1 eq. tartaric acid	40	5	1.0	<0.01	<0.01	<0.01
4	No acid	100	60	30	4	<0.01	<0.01

TABLE IVa

2-AMINO-4-(4'-ARSONOANILINO)-PYRIMIDINE

p-Arsanilic acid and 2-amino-4-chloropyrimidine. The reactants (0.01 mole each) were mixed and the reaction run as in I except that the reaction volume was 200 ml. of 10% acetone in water to enable complete solution of reactants. Only single runs were made.

	Acid or alkali	% Primary amine remaining after min. 2	5	10	15	30	60	120
1	1 eq. NaOH	100	100	80	70	65	60	60
2	0.1 eq. NaOH	80	45	20	14	11	10	10
3	None	40	20	3	1.5	<0.01	<0.01	..
4	0.1 eq. HCl	30	5	0.5	<0.01	<0.01	<0.01	..
5	1 eq. HCl	20	4	<0.01	<0.01	<0.01	<0.01	..
6	2 eq. HCl	15	2	<0.01	<0.01	<0.01	<0.01	..

TABLE IVb

REACTION IVa WAS REPEATED, OMITTING THE ACETONE

	Acid or alkali	% Primary amine remaining after min. 2	5	10	15	30	60
1	1 eq. NaOH	100	100	90	75	65	60
2	0.1 eq. NaOH	80	50	25	15	10	10
3	None	50	30	5	2	<0.01	<0.01
4	0.1 eq. HCl	40	6	0.8	<0.01	<0.01	<0.01
5	1 eq. HCl	20	4	<0.01	<0.01	<0.01	<0.01
6	2 eq. HCl	16	3	<0.01	<0.01	<0.01	<0.01

TABLE V

2-AMINO-4-ANILINOPYRIMIDINE

Aniline and 2-amino-4-chloropyrimidine. The conditions of IVb were repeated with these results.

	Acid or alkali	% Reaction after min. 2	5	10	15	30	60
1	1 eq. NaOH	100	100	100	100	100	100
2	0.1 eq. NaOH	100	100	95	95	90	85
3	None	30	25	5	2	<0.01	<0.01
4	0.1 eq. HCl	20	5	0.2	<0.01	<0.01	<0.01
5	1 eq. HCl	10	1.0	<0.01	<0.01	<0.01	<0.01
6	2 eq. HCl	10	0.7	<0.01	<0.01	<0.01	<0.01

TABLE VI

2-AMINO-4-(4'-HYDROXYANILINO)-PYRIMIDINE

p-Aminophenol and 2-amino-4-chloropyrimidine. The conditions of IVb were repeated with these results.

	Acid or alkali	% Primary amine remaining after min. 2	5	10	15	30	60
1	1 eq. NaOH	100	100	90	80	70	70
2	0.1 eq. NaOH	100	70	40	20	15	10
3	None	50	30	10	2	<0.01	<0.01
4	0.1 eq. HCl	40	10	1.0	<0.01	<0.01	<0.01
5	1 eq. HCl	30	5	<0.01	<0.01	<0.01	<0.01
6	2 eq. HCl	25	2	<0.01	<0.01	<0.01	<0.01

Discussion

Not only do these two heterocycles react more readily in acid solution, but also many others, such as 2-bromothiazole, 4-amino-2-chloropyrimidine, 2-chlorobenzothiazole, 3,9-dichloro-7-methoxyacridine, 2- and 4-chloroquinoline, 2-chloro-4,6-di-(β-hydroxyethylamino)-*s*-triazine and other similarly substituted triazines. Messrs. Andres and Cragoe of the University of Nebraska have condensed 2-bromo-4-methylthiazole, 5-nitro-2-chloropyrimidine, 2-amino-4-chloro-6-methylpyrimidine, 2- and 4-halobenzo(*h*)quinoline, 5-nitro-2-chloropyridine and 4-halobenzo(*f*)-quinolines with various arsanilic acids under acid conditions.[9] Their observations have been extended in this Laboratory by condensing the same haloheterocycles with aniline. In every reaction it was found that condensation occurred under acidic conditions, while little or no reaction was noted under alkaline conditions. The extent of reaction varied considerably, from 60 to 100% of the primary aromatic amine being used in the reaction. The rate of reaction also varied greatly between heterocycles and between halogen in different positions on the same heterocycle. Under identical conditions of *p*H and amine concentration, the time for maximum reaction of the heterocycle varied from fifteen minutes to fifty hours.

It has not been possible to demonstrate any change in the rate of reaction of compounds in which the halogen atom is substituted on a carbon atom removed by a carbon or equivalent atom from the ring nitrogen (*i. e.*, β), as in 3-bromopyridine, or in which the halogen atom is on a carbon atom which is both α and β to ring nitrogen, as in 2-chloro-5-amino-1,3,4-thiodiazole. Active halogen compounds of the alicyclic and homocyclic series have been studied. No in-

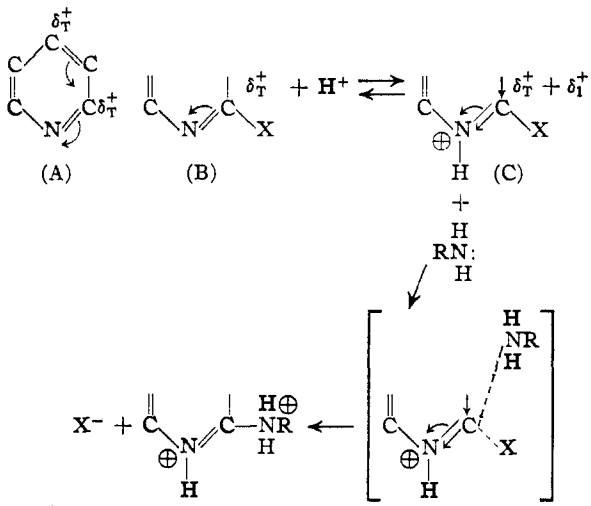
(9) Private communication.

crease in reactivity in acid reaction media was shown by allyl chloride, ethyl bromide or 2,4-dinitrochlorobenzene.

The reaction was found to be general for primary aromatic amines, about forty being tried in the reaction. Morpholine will also react in the same manner but no reaction could be demonstrated with diethylamine or diethylaminopropylamine.

The factors which have been determined for the reaction may be summarized as follows. (1) Certain halogen-substituted, ring-nitrogen containing heterocycles, in which the halogen is considered "active," react with primary aromatic amines more rapidly in acid suspension or solution than they do under alkaline conditions. (2) The increased solubility of the reactants in acid solution is not a factor in this increased reactivity. (3) The possible decrease in rate of hydrolysis of the haloheterocycle in acid solution compared to the hydrolysis in basic solution is not the determining factor in the increase in reactivity. (4) The activation does not extend to active-halogen compounds of the benzenoid and alicyclic series. It is associated with pre-existing activity in ring nitrogen heterocycles. (5) It appears to be a reaction of the amine group and not of the ammonium ion.

Mechanism of Reaction.—Electronic theories have not been applied to heterocyclic ring systems to any degree. A comparison of pyridine to nitrobenzene has been made[10] and Remick[11] has applied the electronic theories of the English school to the pyridine ring. It is held that pyridine undergoes tautomeric electron displacement from the double bond to the ring nitrogen resulting in a small positive charge, δ_T^+, on the α and γ positions (A). If this is generalized to include all similar nitrogen-containing heterocycles, the configuration of the molecule, disregarding all atoms other than the nitrogen and α carbon atoms, can be represented by B. However, the "ammonium" ion is formed in acid solution and a formal positive charge is placed on the nitrogen. The positive pole has an inductive effect (—I) on the ring, which can be represented by C, resulting in an additional positive charge on the α carbon, δ_I^+. Since the effects are additive, the α position becomes more vulnerable to attack by nucleophilic reagents.



By the usual mechanisms this effect can be transmitted to the β and γ carbon atoms, with a resulting additional activation of the γ position. Similarly, the theory can be extended to account for the influence of two or three nitrogen atoms in a ring. A similar mechanism can be postulated by consideration of the resonance forms under neutral and acid conditions, from which the same conclusions can be drawn.

Although these experiments have not covered all types of nitrogen-containing heterocycles, some generalization can be made. If activity is already inherent in the heterocyclic system so that halogen can be replaced readily, this reactivity can be reënforced or intensified by reaction under acid conditions.

Summary

1. The reaction rate of heterocyclic compounds containing "active" halogen with aromatic amines in aqueous solution or suspension is increased by an increase in the hydrogen ion concentration.

2. The reaction of haloheterocycles with aromatic amines in aqueous media is not reversible, but high concentrations of hydrogen ions may cause hydrolytic decomposition.

3. A mechanism for the intensification of activity of halogen substituted heterocycles has been postulated on the basis of experimental evidence and the commonly postulated electronic forces.

DETROIT, MICHIGAN RECEIVED APRIL 13, 1944

(10) Sidgwick, "Organic Chemistry of Nitrogen," Taylor and Baker, p. 523 (1942).

(11) Remick, "Electronic Interpretations of Organic Chemistry," J. Wiley and Sons, Inc., New York, N. Y., 1943, p. 105.