[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF STANFORD UNIVERSITY]

The Direct Introduction of the Amino Group into the Aromatic and Heterocyclic Nucleus. I. The Reaction of Quinoline with the Alkali and Alkaline Earth Amides in Liquid Ammonia

BY F. W. BERGSTROM

Naphthalene diamines and aminonaphthols with the substituents in different nuclei result in the fusion of sodium amide with naphthylamine and the naphthols, respectively.[1] Amino groups are introduced into the alpha position when pyridine, quinoline, isoquinoline and many of their derivatives are heated with sodium amide under an inert hydrocarbon, such as toluene or xylene.[2] In the nitration or sulfonation of the naphthols, naphthylamines, pyridine and quinoline, the nitro or sulfonic acid group does not occupy the positions taken by the amino group. According to recent electrochemical theories, the difference between the orienting effects in the two cases is due to the opposite polar character of groups in question, NO_2 and SO_2OH being positively polarized when introduced into the nucleus, while NH_2 is negatively polarized.[3] It is intended in the present series of articles to make fairly detailed studies of reactions similar to those discovered by Sachs and by Chichibabin.

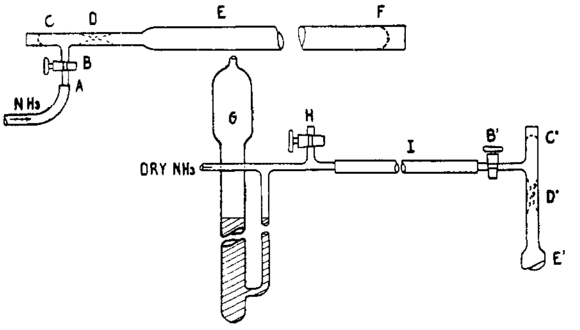

Fig. 1.

In this paper an investigation has been made of the reaction between the alkali and alkaline earth amides and quinoline in liquid ammonia, with the purpose in mind of determining the factors which favor the formation of hydrogen and 2-aminoquinoline. Chichibabin and Zatzepina[4] have previously carried out this reaction in the presence of a boiling hydrocarbon, reporting a 25% yield of 2-aminoquinoline.

The Experimental Method.—In the experiments described below, the technique of Franklin[5] was modified as follows.

A reaction tube of soda glass (Fig. 1) 50–75 cm. long and of 14–17 mm. bore, is connected to a tank of anhydrous liquid ammonia through a flexible lead tube joined at A with sealing wax. With ammonia passing through the system and C stoppered, the desired metal, together with a hooked iron wire, is introduced into the tube, which is sealed and filled with ammonia according to the procedure of Franklin.[5] After the metal has been converted to amide, a small bore rubber tube leading to a water seal is attached at A and the hydrogen swept out with ammonia by partially opening B. (The evolved gas then dissolves in water.) The tube is then cooled in a bath of liquid ammonia and attached at A through pressure tubing, I, to the system in the lower part of Fig. 1. (This has been swept out with ammonia.) With ammonia slowly passing through the mercury bubbler, G, B' is opened, followed by H. The tube is broken open at C', H closed, the iron wire removed and the adhering amide determined by hydrolysis to hydroxide, and conversion to sulfate. Quinoline is introduced, followed by the desired catalyst (see Table III). Tube E' is now constricted at D', the cooling bath partially withdrawn, and 1-2 cc. of solvent boiled off to displace traces of air.[6] The tube is then lowered into the ammonia bath and sealed off at D' (*cf.* B, Fig. 2). The

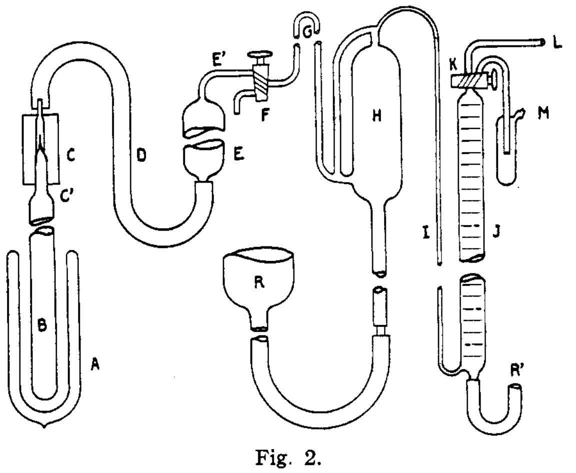

Fig. 2.

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[1] Sachs, *Ber.*, **39**, 3006 (1906).

[2] Chichibabin, *J. Russ. Phys.-Chem. Soc.*, **46**, 1216 ff. (1914), and numerous articles appearing subsequently in the German and Russian journals, *cf. Chem. Reviews*, **12**, 154–161 (1933).

[3] (a) Robinson, *Inst. int. chim. Solvay, Conseil chim.*, **4**, 423–501 (1931); (b) Ingold, *Rec. trav. chim.*, **48**, 797–812 (1929).

[4] Chichibabin and Zatzepina, *J. Russ. Phys.-Chem. Soc.*, **50**, 553 (1920).

[5] Franklin, THIS JOURNAL, **27**, 831 (1905); **29**, 1275 (1907); *J. Phys. Chem.*, **15**, 510 (1911); Bohart, *ibid.*, **19**, 539 (1915).

[6] No hydrogen is evolved in these operations.

tubes are kept in a darkened box (at 18–23°) and are shaken at irregular intervals.

At the completion of the reaction, B is cooled in a bath of solid carbon dioxide and alcohol (Fig. 2), the drawn out tip file scratched and inserted into a heavy rubber pressure tube adapter, C. The entire system is thoroughly evacuated by means of the Töpler pump, H, and tested for leakage. Mercury in the collection buret, J, is drawn by suction (applied at M) just through the two-way stopcock, which is closed. The tip of B is then broken by bending C. Gases are pumped from the tube into J, whence they are transferred through L to reservoirs connected with a gas analysis apparatus. Pumping is continued until ammonia alone is coming off, as is shown by complete absorption of the gases in a dilute sulfuric acid wash pipet. Then the entire constricted top of the tube is cut off, and the contents poured into a beaker with a watch glass suspended above. The reaction product is treated with benzene and alcohol, then with water and the first two solvents distilled off. An excess of sodium carbonate solution is added to precipitate alkaline earth metals, if they are present. The precipitated carbonate, together with tar formed in the reaction, is filtered hot and washed with hot water to remove 2-aminoquinoline, which crystallizes from the cooled filtrate. Unchanged quinoline, if present, must first be removed by steam distillation.

It was found necessary to modify the technique just described in cases where a reactant (such as potassium ammonobarate) must be prepared by precipitation in or crystallization from liquid ammonia. A specially designed two-legged reaction tube was found the most convenient.[7] In order to sweep out all gases before sealing, and in order to remove all gases at the end of a reaction, it was necessary to have liquid ammonia in both legs, which were separately cooled in two small Dewar vessels. The manipulations required are otherwise similar to those described above.

2-Aminoquinoline was identified by its melting point (the best specimens melted from 129–130° corr.; literature, 129°[4]) and by diazotization and conversion to 2-hydroxyquinoline (m. p. 199–200°, corr.) and by a mixed m. p. (199–200° corr.) of this with authentic carbostyryl[8] (m. p. 199–200°).

TABLE I

THE ACTION OF ALKALI AND ALKALINE EARTH AMIDES ON QUINOLINE

No.	Amide[a]	Millimoles Amide	Millimoles Quinoline	Time of action, days	H_2, millimoles	H_2, % calcd.	2-Aminoquinoline, millimoles
1	KNH_2[b]	36.6	9.69	60	0.17	1.8	None
2	KNH_2[c]	16.0	8.5	7			0.96
3	$Sr(NH_2)_2$[d]	14.5	9.46	68	2.57	27.2	.73
4	$Ba(NH_2)_2$[e]	14.6	10.16	0.4 (115°)			
				2 (20°)	8.94	88.0	7.90
5	$Ba(NH_2)_2$[f]	14	11.68	20	11.46	98.2	9.40
6	$Ba(NH_2)_2$	13.4	50.5	37	19.00		18.04
7	$Ba(NH_2)_2$[g]	7.65	10.78	12	Formed		8.06

[a] Calculated from the weight of metal used. Potassium and sodium were cut from calibrated tubes (Bohart, Ref. 5). Lithium was cut under oil. Barium and strontium were sawed from large solid pieces of metal of the highest commercial purity. Oxide was removed as completely as possible with a file.

[b] 2-Aminoquinoline was not formed by the action of quinoline on the amides of lithium (20°), sodium (20°) or potassium (20–130°) in liquid ammonia. (The reaction mixtures were hydrolyzed with water.) Tetrahydroquinoline was not isolated in any of these reactions.

[c] Tube cooled at end of reaction period, 1.5 cc. of pure mercury introduced, tube sealed and shaken at intervals during the next five days. 6.89 milliatoms of potassium found in the mercury. Similar results were obtained when the reaction between potassium amide and quinoline was carried out in the presence of mercury. 2-Aminoquinoline was formed in 6% yield when an excess of NH_4I was added to the KNH_2-quinoline reaction mixture after four days.

[d] 4.6 millimoles of quinoline recovered. Strontium amide prepared by the action of liquid ammonia on strontium in the presence of iron wire (contains hydride, Guntz and Benoit, *Ann. chim.*, [9] **20**, 24 (1923). This perhaps accounts for some of the hydrogen gas). Strontium amide, prepared by adding potassium amide to strontium nitrate in liquid ammonia, does not react appreciably with an excess of quinoline in three weeks.

[e] Heated for nine hours at 100–130°. Reaction practically complete at the end of this time.

[f] In the presence of ignited barium oxide. Barium oxide is a good catalyst for the conversion of a liquid ammonia solution of barium to barium amide.

[g] Barium amide from potassium amide and anhydrous barium thiocyanate [Franklin, THIS JOURNAL, **37**, 2298 (1915)], therefore free from oxide and hydroxide.

TABLE II

THE ACTION OF SALTS ON QUINOLINE IN LIQUID AMMONIA

No.	Salt	Millimoles	Quinoline millimoles	Time of reaction, days	H_2	Millimoles 2-aminoquinoline
1	$BaNK \cdot 2NH_3$	6.05	12.7	13	(2.84)[c]	3.13
	$+ KNH_2$	6.0				
2	$BaNK \cdot 2NH_3$	5.15	19.48	71	8.17	6.11

Salts which do not react appreciably with quinoline in liquid ammonia:[d] $Ba(SCN)_2$, $Ba(CN)_2$,[a] barium salt of acetamidine,[a] barium salt of 2-aminoquinoline,[a] (potassium anilide,[a] potassium ammonomagnesiate $+ Mg(NH_2)_2$,[b] potassium ammonoaluminate,[b] slight reaction).

Salts which slowly react with quinoline to form indefinite mixtures, but *no 2-aminoquinoline.*[b] Potassium ammonosodiate, potassium ammonocalciate $+ KNH_2$, potassium ammonostrontiate.

[a] Salts prepared in liquid ammonia solution.

[b] In two-legged reaction tubes. For preparation, see Franklin, *J. Phys. Chem.*, **23**, 41 (1919); THIS JOURNAL, **37**, 2295–2301 (1915); *ibid.*, **35**, 1455–1464 (1913); Bergstrom, *ibid.*, **46**, 1548 (1924).

[c] Hydrogen low because reaction carried out in a tube with stopcock attached.

[d] Time of reaction, 2–8 weeks.

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[7] Bergstrom, THIS JOURNAL, **53**, 4069 (1931). The side tube, A, was longer than shown in the reference, and the stopcock was sealed to it at a greater distance from the bend.

[8] Chichibabin, *Ber.*, **56**, 1879 (1923); *J. Russ. Phys.-Chem. Soc.*, **55**, 7–18 (1924).

TABLE III

CATALYSIS IN THE FORMATION OF 2-AMINOQUINOLINE[a]

No.	Amide	Milli-moles	Salt added	Milli-moles	Quinoline millimoles	Time of action, days	H_2 milli-moles	H_2, % of calcd.	2-Amino-quinoline millimoles
1[b]	$Sr(NH_2)_2$	3.0	$Ba(SCN)_2$	5.33	7.78	22	2.77	46	2.58
2	$Ba(NH_2)_2$	14.6	$Ba(SCN)_2$	4.06	12.0–12.16	1.00	7.46–11.50	62–95	6.5–10.28
3[c]	$Ba(NH_2)_2$	2.97	$Ba(SCN)_2$ KSCN	4.28 5.95	18.07	28	4.98	84	4.09
4[d]	$Ba(NH_2)_2$	14.6	$LiNO_3$	9.0	11.95	1.00	7.80	65.2	7.64
5	$Ba(NH_2)_2$	14.6	$Sr(NO_3)_2$	4.07	12.20	1.00	10.09	82.7	8.69
6	$Ba(NH_2)_2$	14.6	$Ba(NO_3)_2$	4.12	12.05	1.00	10.02	83.2	8.85
7[e]	$Ba(NH_2)_2$	14.6	Controls (average)		12.3	1.00	2.16	17.6	

[a] $BaBr_2$, LiSCN, KSCN, NaSCN do not increase the amount of hydrogen formed in the $Ba(NH_2)_2$-quinoline reaction. Conditions as in Expts. 4–8 inclusive. The nitrates of potassium, sodium and calcium exert some catalytic effect, although inferior to that observed in Expts. 4, 5 and 6. All salts mentioned were anhydrous. 2-Aminoquinoline was the only isolable product in all experiments, except the one with LiSCN.

[b] No hydrogen or aminoquinoline in a control experiment. Strontium amide prepared from $Sr(NO_3)_2$. *Cf.* note *g*, Table I. Strontium determined at end of reaction. Under similar conditions barium thiocyanate does not catalyze a reaction between quinoline and calcium amide.

[c] The KNH_2 from 5.946 milliatoms of potassium added to 7.26 millimoles of $Ba(SCN)_2$ in a two-legged tube. It is suggested that 2-aminoqunioline can be prepared on a larger scale by modifying this procedure (autoclave).

[d] Experiments (4–7) were carried out under conditions as identical as possible: temp., 20 ± 2°; vol. 27–31 cc. Same amount of iron catalyst, left in during the reaction. Specimens of barium amide forming in less than two to three days were discarded.

[e] Average of controls run at beginning and at end of expts. (Footnote *a*, Nos. 4–7.)

Discussion and Conclusions

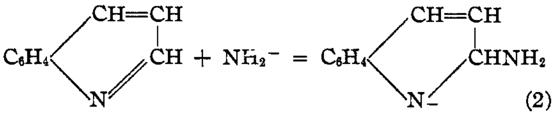
A. The Action of the Alkali Amides on Quinoline.—The formation of resins and other substances of indefinite composition is not due exclusively to the relatively high concentration of amino ions in the ammonia solutions of the amides, for the same resins are obtained when quinoline and potassium amide react in *n*-butylamine or triethylamine, in which the amide is insoluble. 2-Aminoquinoline is formed in 5–11% yield if the reaction is carried out in the presence of mercury, or if the previously prepared reaction mixture is shaken with mercury. A dilute potassium amalgam also is obtained. Destruction of the potassium amide in the mixture with an excess of ammonium iodide results in a 6% yield of aminoquinoline. Apparently there is formed in the reaction an intermediate of relatively high potassium content, which is destroyed by water or alcohol without the production of aminoquinoline.

B. The Action of the Alkaline Earth Amides on Quinoline.—The solubility of the metallic amide does not alone determine the nature and extent of the reaction, as may be inferred from the different modes of action of lithium and barium amides, which appear to have roughly the same solubilities in liquid ammonia.[9] Of the two, barium amide alone reacts with quinoline to form hydrogen and 2-aminoquinoline, in the manner of the equation

$$2C_9H_7N + Ba(NH_2)_2 = (C_9H_6NNH)_2Ba + H_2 \quad (1)$$
$$(C_9H_6NNH)_2Ba + 2H_2O = Ba(OH)_2 + 2C_9H_6NNH_2$$

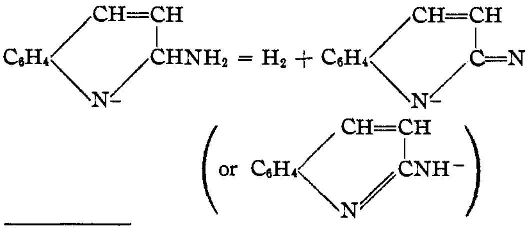
The same reaction occurs, irrespective of whether the quinoline or the barium amide is in excess, and in one experiment (III, 3) the hydrogen was formed in approximate agreement with equation (1). The mechanism of the reaction is probably the following.

The amide ion adds to the α carbon atom of quinoline,



(2)

The addition compound loses hydrogen to give the anion of a salt of 2-aminoquinoline[10] [the presence of barium (or strontium) seems to be necessary].



(3)

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(9) *Cf.* Bergstrom, THIS JOURNAL, **53**, 3031 4067–4071, (1931).

(10) One can also interpret this reaction by assuming that hydrogen is removed from the addition compound of (2) as H^-, this react ing with ammonia to form NH_2^- and H_2. This corresponds to the mechanism proposed by Ziegler and Zeiser [*Ber.*, **63B**, 1848 (1930)] for the sodium amide pyridine reaction, in which sodium hydride is assumed to be split off.

The latter reaction is accelerated by soluble salts of barium, as well as by a number of nitrates (see Table III). The nitrate ion appears ineffective in the absence of barium, since 2-aminoquinoline is not formed by the action of sodium amide and sodium nitrate on quinoline (reaction mixture hydrolyzed with water).

The Action of Salts on Quinoline in Liquid Ammonia.—The observation of Chichibabin[2] to the effect that potassium anilide, C_6H_5NHK, reacts with pyridine under an inert hydrocarbon to give 2-anilinopyridine, suggests that salts containing very weak anions other than NH_2^- might react with quinoline in liquid ammonia in the approximate sense of equations (2) and (3). With the exception of potassium ammonobarate, $Ba{=}NK{\cdot}2NH_3$, none of the salts examined reacted with quinoline in the expected manner. It is suggested that potassium ammonobarate is very slightly dissociated in liquid ammonia into potassium amide and barium amide, the latter of which reacts with quinoline in accordance with equation (1).

Catalysis in the Formation of 2-Aminoquinoline.—From the results of Table III, it is evident that barium thiocyanate[11] and barium nitrate exert the greatest catalytic effect, the reaction of equation (1) being as complete in one day at 20° as in a week or two with no catalyst. The slightly soluble barium bromide is without catalytic activity. The activity of the nitrates may in part be due to a decrease in the size of the crystals of the sparingly soluble reaction product, which therefore has less tendency to form an adherent coating over the barium amide.

The catalytic action of barium nitrate and barium thiocyanate is not due to the formation of an ammonia soluble ammonobasic salt, since the addition of a small quantity of potassium amide to a liquid ammonia solution of either of the above salts gives an immediate and permanent precipitate of barium amide.

Summary

1. The alkali amides in liquid ammonia, *n*-butylamine or triethylamine, convert quinoline to thick liquids or resinous substances. In the presence of metallic mercury, 5–11% of the theoretical amount of 2-aminoquinoline is formed.

2. 2-Aminoquinoline and hydrogen are formed in good yield by the action of barium amide on quinoline in liquid ammonia at room temperatures. Strontium amide attacks quinoline to a very slight extent, but calcium amide is unreactive.

3. The reaction between barium amide and quinoline is markedly accelerated by barium nitrate, barium thiocyanate, lithium nitrate and strontium nitrate. Sparingly soluble salts of barium have very little effect on the rate of the reaction. Thiocyanates of the alkali metals are not positive catalysts.

4. Of a number of salts containing weak anions, potassium ammonobarate is the only one that reacts with quinoline to form hydrogen and 2-aminoquinoline. It is suggested that potassium ammonobarate is slightly dissociated in liquid ammonia into the amides of potassium and barium.

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[11] A solution of barium thiocyanate alone in liquid ammonia does not attack quinoline (Table II).

The Methane Fermentation of Organic Acids and Carbohydrates[1,2]

BY D. TARVIN AND A. M. BUSWELL

Previous papers[3,4] from this Laboratory have reported investigations of the degradation of fatty acids, carbohydrates and other aliphatic compounds. Practically all of these were converted to carbon dioxide and methane with complete recovery of the carbon fed as gas. Carbon dioxide and hydrogen were shown to be converted into methane and water by bacteria and a general equation was formulated for the decomposition of compounds containing carbon, hydrogen and oxygen.

Production of fatty acids as intermediates in the fermentation had been noted by various workers[3,4,5] and an alpha oxidation was believed to be indicated in fatty acid decomposition, in contrast to Knoop's theory of beta oxidation in

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[1] An abstract of a thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry in the Graduate School of the University of Illinois, 1933.

[2] Presented before the Division of Biological Chemistry at the 86th meeting of the American Chemical Society, Chicago, Illinois, September 10–15, 1933.

[3] Neave and Buswell, THIS JOURNAL, **52**, 3308 (1930).

[4] Symons and Buswell, *ibid.*, **55**, 2028 (1933).

[5] Fischer, Lieske and Winzer, *Biochem. Z.*, **245**, 2 (1932).