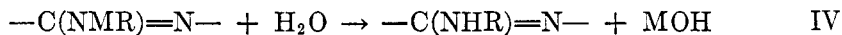
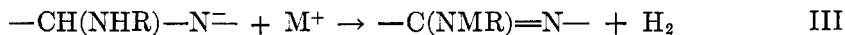
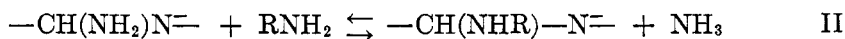


THE EQUILIBRIUM BETWEEN 2-AMINO- AND
2-ALKYLAMINO-QUINOLINES¹NYDIA G. LUTHY, F. W. BERGSTROM,² AND HARRY S. MOSHER*Received November 16, 1948*

It has been reported by Bergstrom *et al.* (1) that 2-alkylaminopyridines and 2-alkylaminoquinolines are obtained in fairly good yields by heating the eutectic mixture of sodium-potassium amide with pyridine or quinoline dissolved in a primary aliphatic amine. In this manner, for example, 2-cyclohexylaminoquinoline was obtained in 77% yield. A mechanism for this reaction was suggested:



Where M = an alkali metal

Equation II is an equilibrium reaction and therefore both amino- and alkyl-amino-quinolines should be obtained depending on conditions. Although this was implied by the authors, only the most readily isolated material was reported. From the yields (Table I) experimental evidence did indicate that the 2-alkyl-amino base was not the only product of the reaction.

The formation of 2-methylaminoquinoline was of especial interest since in the three experiments reported, the product was isolated only with difficulty and with some doubt as to its true identity. At one point (1) it has been stated that from the reaction of quinoline, sodium-potassium amide eutectic and excess methylamine in a heated autoclave, a 26% yield of 2-methylaminoquinoline was obtained with a melting point varying between 68 and 81°. This was attributed to two "crystalline modifications." Then too, Bergstrom (2) had observed that a sample of the lower-melting 2-methylaminoquinoline could be transformed to the higher-melting modification by treatment with potassium amide in liquid ammonia.

Since an attempt was being made in this laboratory to introduce the alkyl-amino group directly into the 2-position of quinoline through the use of lithium alkylamides without lithium amide as an intermediate, the above facts were of some significance. Therefore, it was decided to study the equilibrium suggested by equation II to see if both 2-amino- and 2-alkylamino-quinoline could not be isolated approaching the reaction from either direction as well as to search for the higher melting modification of 2-methylaminoquinoline.

¹ This paper is taken in part from a thesis submitted by N. G. L. to Stanford University in partial fulfillment of the Ph.D. degree, 1948.

² Deceased, March 29, 1946.

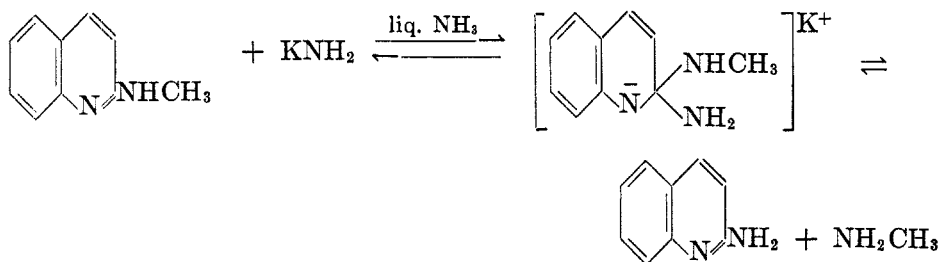
A pure sample of 2-methylaminoquinoline was prepared by treating 2-chloroquinoline with excess methylamine in a sealed tube at 100°. The product melted at 71.5° after purification. Other samples of 2-methylaminoquinoline prepared by treating quinoline-2-sulfonic acid or 2-methoxyquinoline with methylamine did not give a different melting point. 2-Methylaminoquinoline, m.p. 71.5°, was also obtained in good yield from the reaction of quinoline with lithium methylamide in anhydrous ether under nitrogen atmosphere. Extensive investigation both by this laboratory and Armour Research Foundation, Microscopy Section, of samples of 2-methylaminoquinoline obtained from various sources using the polarizing microscope and the methods of fusion analysis (3) revealed no other stable crystalline modification.

TABLE I

REACTIONS OF PYRIDINE AND QUINOLINE WITH Na-K EUTECTIC IN ALKYLAMINES (1)

BASE	AMINE	YIELD
Quinoline	Cyclohexylamine	77% 2-Cyclohexylaminoquinoline
Pyridine	"	34% 2-Cyclohexylaminopyridine
Quinoline	<i>n</i> -Butylamine	40% 2- <i>n</i> -Butylaminoquinoline
Pyridine	"	50-64% 2- <i>n</i> -Butylaminopyridine
Pyridine	<i>n</i> -Heptylamine	21% 2- <i>n</i> -Heptylaminopyridine
Pyridine	Methylamine	73% 2-Methylaminopyridine

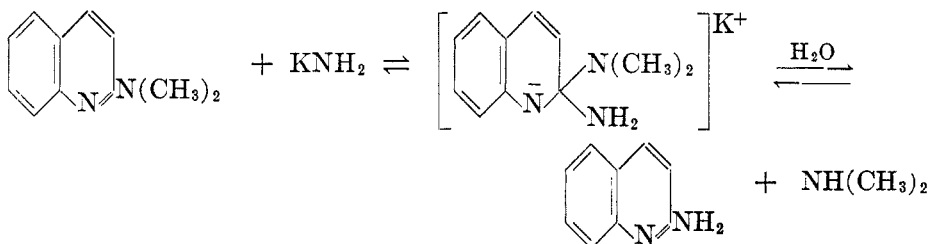
When 2-methylaminoquinoline was allowed to react with potassium amide or a mixture of sodium and potassium amide in liquid ammonia at room temperature, both 2-amino- and 2-methylamino-quinoline were isolated:



This was an approach from the right-hand side of the equilibrium in equation II. The presence of an addition compound which is implied by equation I in the forward reaction was substantiated by a brilliant yellow color when the reactants were mixed in liquid ammonia. It was shown that neither 2-methylaminoquinoline nor potassium amide alone give this characteristic color in liquid ammonia; the colored addition compound persists even when exposed to air and does not disappear until hydrolysis is complete.

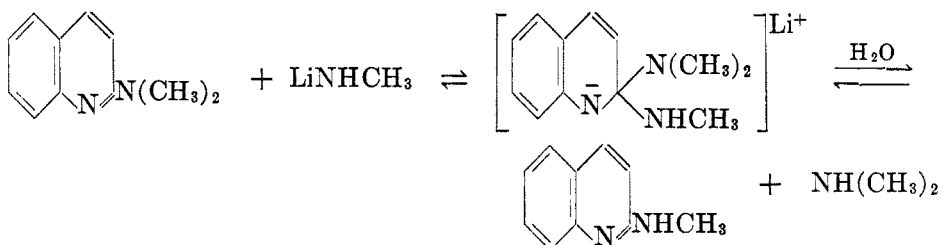
Furthermore, when 2-dimethylaminoquinoline was combined with potassium amide in liquid ammonia at room temperature for eighteen hours, 2-amino-

line was readily isolated by fractional recrystallization. This was a much shorter time than that necessary for the previous experiment.



That the equilibrium favored the formation of 2-aminoquinoline was not surprising since 2-dimethylaminoquinoline could not be obtained from the reaction of quinoline with potassium dimethylamide in excess dimethylamine nor with lithium dimethylamide in ether solution and nitrogen atmosphere.

Finally when 2-dimethylaminoquinoline was allowed to react with lithium methylamide in anhydrous ether and inert atmosphere, 2-methylaminoquinoline was isolated.



The separation and isolation of the two products from any one of the reactions presented a difficult problem. While 2-aminoquinoline melted at 129–130°, 2-methyl- and 2-dimethyl-aminoquinoline both melted at approximately 70° and all three had very similar solubilities in most organic solvents. Therefore, more sensitive methods were needed for identification and separation of the two components of an equilibrium mixture. Observation of the optical properties through use of the polarizing microscope combined with the methods of chromatographic adsorption analysis (4, 5) were successfully employed.

Between the crossed nicols of a polarizing microscope it was shown that 2-amino- and 2-methylamino-quinoline have easily recognizable crystalline characteristics and form a eutectic when allowed to approach each other as they crystallize from the melt. Then too, by taking a series of melting points in capillaries using varying compositions of the two compounds, a phase diagram was obtained which indicated a eutectic at approximately 23% 2-methylaminoquinoline and 77% 2-aminoquinoline.

The anomalous melting point reported by Bergstrom and Sturz (1) for 2-methylaminoquinoline probably indicates that their product was a mixture of 2-amino- and 2-methylamino-quinoline melting at about 80°. This mixture could result as indicated in the equilibrium by the action of the excess amide ion used in the preparation.

The fact that all three compounds, 2-amino-, 2-methylamino-, and 2-dimethylamino-quinoline fluoresce in ultraviolet light made separation of any one component of the mixture (resulting from an equilibrium reaction) on a column of activated alumina an easy task. The compounds were adsorbed from a solution of petroleum ether (35–65°) and developed by washing with a 5% acetone-petroleum ether solution. They were eluted in the predicted order; 2-dimethylaminoquinoline was most readily displaced followed by 2-methylaminoquinoline, and 2-aminoquinoline could be washed down best with the addition of 1% alcohol to the acetone-petroleum ether solvent.

Thus, through quantitative separation and identification of the products of the experiments the existence of the equilibria was established.

EXPERIMENTAL

Treatment of 2-methylaminoquinoline with sodium-potassium amide in liquid ammonia. Into a long combustion-type tube contained in a Dry Ice-acetone bath was placed a small porcelain boat containing 0.2 g. of pure 2-methylaminoquinoline. An excess of a mixture of sodium and potassium amide, 1.5 g., was added and 30 ml. of ammonia distilled into the tube which was then sealed. At once an intense yellow solution formed which did not change color on standing. The contents of the tube were shaken occasionally because the slightly soluble amides tended to settle to the bottom.

After five days the tube was opened and the excess ammonia evaporated into the hood, but the yellow color (addition compound ?) persisted and did not finally disappear until hydrolysis was completed. Hydrolysis was accomplished through the cautious addition of moist benzene at first, followed by a mixture of benzene and water. The benzene layer was separated and dried over sodium hydroxide; finally it was filtered and concentrated so that only a brown oil remained. This oil was extracted four times with petroleum ether (55–85°) using 80 ml. of the solvent. Upon standing, the residue solidified to a few brown crystals, m.p. 125–129° (the melting point of 2-aminoquinoline is 129–130°).

The picrate recrystallized from alcohol, m.p. 250–253°, did not lower the melting point of the picrate of a known sample of 2-aminoquinoline. The petroleum ether extracts yielded fractions containing varying compositions of 2-methylamino- and 2-amino-quinoline melting from 58–70°.

The experiment was repeated using twelve, twenty-four, and forty-eight hours, but much lower yields were obtained than when 5–7 days were allowed in which approximately 15% yield of 2-aminoquinoline was obtained.

The various fractions were investigated between the crossed nicols of the polarizing microscope. By repeated recrystallization from the melt, the two components were concentrated, each with its own characteristic habit. Slides were made up with known mixtures of 2-amino- and 2-methylamino-quinoline and compared with the products of the equilibrium experiments whose existence could readily be recognized.

Separation by chromatographic adsorption. A 48-cm. Pyrex glass column was filled with 32 cm. of activated alumina, grade F-20, 80–200 mesh, activity 2–3 on the Brockman scale. An aliquot sample of the product from the 7-day equilibrium reaction was dissolved in 50 ml. of petroleum ether (35–65°) and poured on the activated alumina. Gentle suction was used to speed the liquid so that the drops were collected at the rate of 30–40 per minute. In a dark room when a G.E. BH-4, 100-watt mercury arc lamp was used as a source of ultraviolet illumination, it was noted that all the material was adsorbed in the first few centimeters of the column and fluoresced a beautiful violet color. Development with 5% acetone-petroleum ether solution caused separation into two bands which soon had 8–10 cm. distance between them. The material comprising the two bands was collected and separated by further development.

Evaporation of the solvent yielded white crystalline materials, and the first fraction was

identified as 2-methylaminoquinoline by its melting point, 70–71°, and by the fact that it did not lower the melting point of a known sample of the compound. The second fraction was similarly identified as 2-aminoquinoline.

Treatment of 2-dimethylaminoquinoline with sodium amide in liquid ammonia. Into a long combustion-type tube was placed a small porcelain boat containing 0.026 g. of 2-dimethylaminoquinoline, m.p. 71–72°, which had previously been prepared from 2-chloroquinoline and dimethylamine in a sealed tube reaction. Another porcelain boat was used to insert 1 g. of sodium amide, and 30 ml. of ammonia were distilled in after which the cooled tube was sealed and allowed to stand at room temperature for eighteen hours. The familiar bright yellow color developed although not as bright as with 2-methylaminoquinoline.

After the tube was opened and the ammonia evaporated, the yellow-colored mass was hydrolyzed by several small additions of benzene and water. The benzene layer was separated and dried, the excess solvent removed under reduced pressure, and the remaining light brown oil solidified on standing. After three extractions using petroleum ether (35–65°), a light brown crystalline material was obtained, m.p. 125–128°. The first crystals which came out of the petroleum ether extracts were filtered, m.p. 123–125°. A mixture melting point with a known sample of 2-aminoquinoline (m.p. 129–130°) was 127–129°. The picrate of the product melted from 253–256° and did not lower the melting point of the picrate of a known sample of 2-aminoquinoline.

From the weight of 2-dimethylaminoquinoline recovered and the 2-aminoquinoline obtained, the ratio was found to be 3:1. Separation by chromatographic adsorption as in the first experiment on a column of activated alumina gave two bands, the first being identified as 2-dimethylaminoquinoline and the second 2-aminoquinoline.

Treatment of 2-dimethylaminoquinoline with lithium methylamide in ether. Phenyllithium was prepared by adding 4.5 g. (0.028 mole) bromobenzene dropwise to 200 ml. of anhydrous ether in which was suspended 0.3 g. (0.428 mole) of freshly cut, thin slices of lithium. The whole was contained in a 500-ml., 3-necked flask in the bottom of which was sealed a three-way stopcock. After the bromobenzene had been converted to phenyllithium as evidenced by warming of the flask and development of a pale purple color, the sludge of oxides and minute pieces of excess lithium was drained and then the stopcock turned so that the solution flowed by gravity into a second three-necked flask. The second round bottom flask contained an ether solution of anhydrous methylamine and as the phenyllithium flowed in, lithium methylamide was formed with some evolution of heat and formation of a creamy precipitate. An ether solution of 1.12 g. of 2-dimethylaminoquinoline was added and the mixture was refluxed for six hours, then kept at room temperature for forty hours. At all times nitrogen atmosphere was maintained throughout the system. The now familiar yellow color of the addition complex developed not unlike those in the previous experiments.

After hydrolysis using benzene and water, the ether-benzene layer was dried and finally evaporated almost to dryness. The yellow-brown oil that remained was taken up in 1:1 hydrochloric acid and extracted with ether in order to free the quinoline bases from unreacted bromobenzene and small amounts of diphenyl which might have formed in the reaction. The base was regenerated with aqueous ammonia and extracted with benzene which was dried and concentrated. Petroleum ether (35–65°) was added and the solution subjected to chromatographic adsorption analysis on activated alumina. The column was developed as before and two bands were seen to fluoresce in the presence of ultraviolet illumination. The wider band was collected and after evaporation of the solvent a white crystalline material was obtained, m.p. 69–71°, which did not lower the melting point of a known sample of 2-dimethylaminoquinoline. The second band (Fraction 2) representing a yield of approximately 2%, was a pale yellow oil which did not readily solidify. A milligram of this oil was used to form a picrate which was washed by decantation after centrifuging using a 1-ml. tube. The melting point of the picrate was approximately 226° and did not lower the melting point of the picrate of a known sample of 2-methylaminoquinoline.

The remainder of the material was dissolved in ethyl alcohol and its adsorption spectrum found using the Beckman spectrophotometer.

Fraction 2: max. 244 mu; min. 305 mu; max. 340 mu.

2-Methylaminoquinoline: max. 244 mu; min. 300 mu; max. 340 mu.

2-Dimethylaminoquinoline: max. 250 mu; min. 296 mu; max. 350 mu.

A sample of the 2-dimethylaminoquinoline used as starting material was also subjected to chromatographic adsorption to detect any impurity which might have been present. Only one fluorescent band was observed when the column was illuminated with ultraviolet light. In view of the sensitivity of the method, it was concluded that the original compound was pure and had contained no trace of 2-methylaminoquinoline previous to the experiment.

SUMMARY

1. When either 2-methylamino- or 2-dimethylamino-quinoline was treated with a mixture of sodium-potassium amide or alkali amide alone, in liquid ammonia at room temperature a bright yellow solution of an addition complex was formed which upon hydrolysis gave a mixture from which 2-aminoquinoline could be isolated. The 2-dimethylamino group was the more easily replaced by the amino group. Treatment of 2-dimethylaminoquinoline with lithium methylamide in ether solution gave a small yield of 2-methylaminoquinoline.

2. These facts substantiated the equilibrium mechanism proposed for the reaction of quinoline with alkali amides or alkylamides in liquid ammonia and perhaps other solvents in which it is proposed that there is the formation of an intermediate complex.

3. It was shown that 2-amino-, 2-methylamino-, and 2-dimethylamino-quinoline fluoresce when adsorbed on a column of activated alumina and subjected to ultraviolet light. The separation of the products of the equilibrium experiments was accomplished quantitatively by chromatographic adsorption analysis and further confirmed by melting points, mixed melting points, investigation of optical properties, and comparison of adsorption curves with the pure known compounds.

4. Using the methods of fusion analysis and the polarizing microscope, it was shown that no stable isomorphous form of 2-methylaminoquinoline having an 80° melting point exists as has previously been claimed in the literature.

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