

THE REACTION OF SODIUM BOROHYDRIDE
WITH N-ACYLANILINES

By

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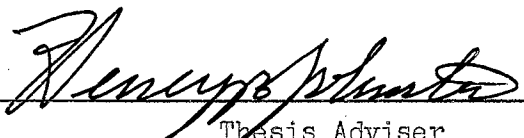
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Dean of the Graduate School

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INTRODUCTION

Sodium borohydride was discovered and identified as a result of investigations started in 1941 by Schlesinger, Brown and collaborators (2,3). It was prepared, along with other metallic borohydrides, as an intermediate for use in the preparation of uranium (IV) borohydride (27).

The synthesis of a compound, which at the time was given the formula $\text{Na}_2\text{B}_2\text{H}_6$ and called disodium diborane, was reported in 1936 by Stock and Laudenklos (35). In 1949 Kasper (12) found this compound to have a diffraction pattern identical with that of sodium borohydride as reported by Soldate in 1947 (34).

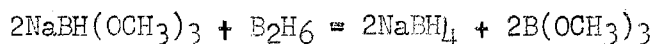
The first use of sodium borohydride as a reducing agent for organic compounds was in the reduction of acetone to isopropyl alcohol (28).

The purpose of the research carried out for this thesis was to investigate the reaction of sodium borohydride with various N-substituted amides.

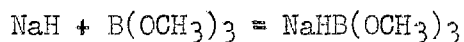
HISTORICAL

Preparation of Sodium Borohydride

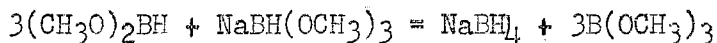
Sodium borohydride was prepared for the first time by the displacement of methyl borate from sodium trimethoxyborohydride with diborane (27).



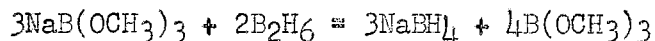
The sodium trimethoxyborohydride was prepared by the reaction of sodium hydride and methyl borate (25,27).



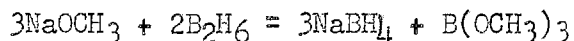
Dimethoxyborine was also found to react with sodium trimethoxyborohydride giving sodium borohydride and methyl borate (28).



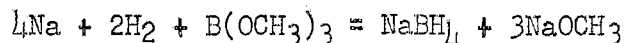
A similar synthesis of sodium borohydride was the displacement of methyl borate from tetramethoxyborohydride by diborane (24,28).



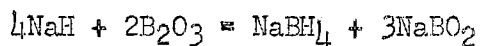
Sodium methoxide was found to react with diborane giving sodium borohydride, but this method is of no preparative value compared to the others (23,28).



A small yield of sodium borohydride was obtained from a reaction between methyl borate, sodium, and hydrogen (30).



A reaction between sodium hydride and boric oxide gave sodium borohydride as a product (30).



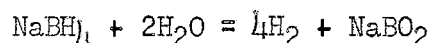
Physical properties

Sodium borohydride is a white crystalline solid which can be heated above 400° without decomposition (27). The crystal structure of sodium borohydride is based upon a face-centered cubic lattice with the unit cell containing four sodium and four boron atoms, as shown by x-ray studies. It is probable that the structure consists of borohydride ions and sodium ions (34). Sodium borohydride is soluble in cold water, liquid ammonia, and various amines (28). Many of its thermodynamic and other physical properties have been measured and can be found in the literature (6,7,8, 11,18,19,20).

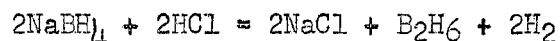
Chemical properties

The reactions of sodium borohydride can be divided into two classes: those in which it reacts with inorganic compounds, and those in which it reacts with organic compounds. In either case, the main function of the borohydride is that of a reducing agent.

Sodium borohydride is hydrolyzed by water, according to the following equation.

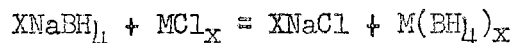


This reaction at lower temperatures is so slow, that the salt can be crystallized from cold water solutions in the form of the dihydrate (28,29). It reacts with hydrogen chloride producing diborane, sodium chloride, and hydrogen.



Sodium borohydride can be used to prepare other borohydrides

according to the following general equation.



Both aluminum and lithium borohydrides may be prepared in this way (31). The former is covalent while the latter is electrovalent.

Aqueous sodium borohydride is a good reducing agent for many metallic salts. The ions of silver, bismuth, mercury, arsenic, and antimony are reduced to the metal (22). Iron (III) is reduced to iron (II). Thallium (III) is reduced in alkaline solution to thallium (I). Vanadium (V), as the sulfate, is reduced in acid solution to vanadium (I). Manganese (VII) yields manganese (II), manganese (IV), and manganese (VI) in acid, neutral, and basic solution, respectively. Chromium (VI) is reduced to chromium (III) in acid or neutral solution, but does not react in alkaline solution. Molybdenum (VI) is reduced to molybdenum (V) in acid or neutral solution (21).

Sodium borohydride reacts quantitatively with boron fluoride etherate to liberate diborane (26,28).

It reacts rapidly with methanol at low temperatures to give sodium tetramethoxyborohydride and hydrogen (28).

Sodium borohydride is an excellent reducing agent for certain types of organic compounds. It reduces aldehydes and ketones to the corresponding alcohols. Unsaturated aldehydes and ketones are converted to unsaturated alcohols. The reduction occurs rapidly at room temperature in most cases. Water can be used as the solvent. The extent of the reaction is limited in many cases by the

difficulty encountered in hydrolyzing the alkyl borates formed as intermediates (4).

Acid chlorides are reduced by use of a suspension of sodium borohydride in an inert solvent. The corresponding alcohols are formed. The reaction proceeds more easily with aliphatic acid chlorides than with aromatic acid chlorides (4).

Many polyhydroxy compounds and alpha-hydroxy acids form stable complexes with boric acid. Pyruvic acid and glucose, for example, are evidently reduced by sodium borohydride but form complexes from which boron-free products can not be isolated, as reported by Chaiken and Brown (4). However, the borohydride is reported by other investigators to be useful in reducing carbohydrates. Lindberg and Misiorny discuss the use of sodium borohydride as a quantitative tool in the determination of carbohydrates (17). The reduction of lactones is successful in many cases (13,15).

Oxo-steroids containing double carbon-nitrogen linkages are reduced by sodium borohydride to hydroxysteroids without reduction of the C-N double bonds (9).

The general equations for these reductions are shown below.

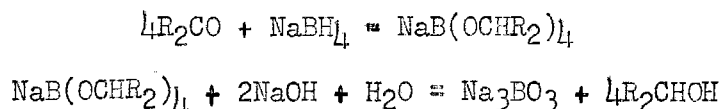


Table I gives several examples of these reduction reactions and the yields obtained.

Crotonyl chloride and cinnamoyl chloride evidently undergo some reaction at the carbon-carbon double bond (4), although in all

Table I
 Reductions Using Sodium Borohydride

Compound	Product	Yield %	Reference
Acetylacetone	2,5-Hexanediol	86	4
<u>n</u> -Butyraldehyde	1-Butanol	85	4
Diacetyl	2,3-Butanediol	62	4
Mesityl oxide	4-Methyl-3-pentenol-2	77	4
Methyl ethyl ketone	2-Butanol	87	4
Anisaldehyde	Anisyl alcohol	96	4
Benzil	Hydrobenzoin	89	4
<u>m</u> -Hydroxybenzaldehyde	<u>m</u> -Hydroxybenzyl alcohol	93	4
<u>m</u> -Nitrobenzaldehyde	<u>m</u> -Nitrobenzyl alcohol	82	4
<u>D</u> -lyxono- δ -lactone	<u>D</u> -xylose	--	36
Benzoyl chloride	Benzyl alcohol	76	4
Cinnamoyl chloride	Hydrocinnamyl alcohol	12	4
<u>n</u> -Butyryl chloride	1-Butanol	81	4

other known cases this type of double bond is unaffected.

Sodium borohydride does not affect nitriles, esters, or nitro groups. Acids and acid anhydrides show very little reduction after prolonged treatment (4).

It can be seen, therefore, that sodium borohydride is useful for the selective reduction of a few types of functional groups in the presence of many other functional groups.

EXPERIMENTAL

Purification of sodium borohydride

The crude sodium borohydride as obtained from Metal Hydrides Incorporated did not have the purity which was desired. Methods used previously for purification were recrystallization from cold water, isopropylamine, or liquid ammonia (1). A more convenient method, however, was discovered to be recrystallization from pyridine (16). This was accomplished by two methods.

Method 1. Crude sodium borohydride (20 grams) and anhydrous pyridine (500 ml.) were mixed and allowed to stand with frequent shaking for four hours. The pyridine solution was filtered by suction using a fine, fritted glass filter. The residue was washed with 100 ml. of pyridine, and the wash solution combined with the original filtrate. The pyridine was then distilled from the filtrate until approximately 50 ml. of solution remained. This distillation was accomplished with as little refluxing as possible. During the distillation, the solution usually developed an orange or red coloration which disappeared upon cooling. The solution which remained in the distillation flask was cooled and the sodium borohydride recrystallized. The sodium borohydride was filtered from the solution by suction using a fine, fritted glass filter. It was then placed in a drying pistol and dried at 15-25 mm. Hg and 100°, using a water aspirator with drying tube to obtain the vacuum. The drying was completed in four hours. During this time, the pistol was occasionally opened to remove pyridine which

condensed in the cold end of the apparatus. After the drying was completed, the pistol was taken to a dry box. The pure sodium borohydride was removed and ground in a mortar to a fine powder. It was then placed in weighing bottles and these were stored in a desiccator. The purity was found to be 98 per cent, by measuring the hydrogen evolution of a sample when reacted with aqueous acid.

Method 2. The crude sodium borohydride was extracted with pyridine and the solution filtered as in the first method. The sodium borohydride was precipitated by adding diethyl ether until no more precipitate separated. The sodium borohydride was collected by filtration, dried, and bottled as in the first method.

Reaction of sodium borohydride and acetanilide

In all of the experiments involving the use of sodium borohydride, it and the reactants were weighed in a dry box. The reactants were also mixed and placed in the reaction vessel while still in the dry box. The reaction vessel was stoppered, removed from the dry box, and not opened until immediately before being connected to the other apparatus used in the experiment.

Experiment 1. Detection of volatile amines. Sodium borohydride (0.2826 grams, 0.0075 moles) and acetanilide (1.0457 grams, 0.0077 moles) were weighed out. The reactants were placed in an eight-inch test tube equipped with a side arm and mixed by shaking. The test tube was removed from the dry box and its sidearm connected to a funnel. The mouth of the funnel was held at the surface of 49.45 ml. of 0.1023 N hydrochloric acid solution. The test

tube was plunged into an oil bath which had previously been heated to 190°. Upon inserting the test tube into the bath, the solid first melted and then began to foam. Liquid was noted collecting on the sides of the test tube. When the mixture began to foam, gas was given off and forced through the hydrochloric acid solution. The temperature was allowed to drop to 185° where it was held until reaction ceased, as evidenced by the conclusion of gas evolution. At that time the test tube was removed from the apparatus and allowed to cool to room temperature. The hydrochloric acid was titrated and found to be unchanged as to acid concentration. The reaction mixture was extracted with 12 ml. of diethyl ether. The ether solution was evaporated leaving a yellow-brown solid. An oil film appeared to be covering the solid. The solid was recrystallized from hot water. Its melting point was 110-112°, and a sodium fusion test showed nitrogen to be present. Since acetanilide melts at 114° (13), a mixed melting point was run. The mixture melted at 112-114°, thus identifying the solid as acetanilide.

In order to detect the presence of unreacted sodium borohydride, the remainder of the reaction mixture, after the ether extraction, was extracted with water and then with 0.5 N hydrochloric acid. During water extraction the mixture bubbled slightly and was still evolving gas twelve hours later. This was presumed due to the slow reaction between water and sodium borohydride at room temperature. The hydrochloric acid solution gave an immediate gas evo-

lution, but this ceased after a few minutes.

Experiment 2. Detection of nonvolatile amines. Sodium borohydride (0.4232 grams, 0.0112 moles) and acetanilide (1.5225 grams, 0.0113 moles) were weighed out. The reactants were placed in an eight-inch test tube, mixed by shaking, and the test tube then connected to an apparatus for measuring gas volumes. The test tube was immersed in an oil bath which had been previously heated to 185°. The solid reactants immediately fused and then foamed up the sides of the tube. When the foaming began, gas was evolved. This gas evolution ceased after a very short time. The temperature of the bath was raised to 205° and a burner flame used to melt the foam from the sides of the reaction tube. After gas evolution had completely ceased, the oil bath and tube were allowed to cool to 100° before the tube was removed from the oil bath. The volume of gas evolved was 158 ml. at 33° and 737 mm. (0.0058 moles). The gas was passed through Tollens solution, which gave an inconclusive test.

The reaction mixture was extracted with 15 ml. of ether, and the ether extract was washed with an equal volume of water. On washing the ether extract with water, there was a rapid evolution of gas. The ether extract was evaporated to 100°, after which there remained an oily brown liquid. Upon immersing this brown residue in an ice bath, a solid crystallized out leaving a very small amount of brown oil. The mass as a whole appeared to be insoluble in water and soluble in 6 N hydrochloric acid. This resi-

due was then distilled and a small amount of yellow liquid was collected. It was insoluble in water and soluble in hydrochloric acid. Its boiling point was found to be in the region of 190-195°, as determined by a micro method.

The solid portion of the reaction mixture, which did not dissolve in ether, was identified as acetanilide by the same procedure used in experiment 1.

Experiment 3. Effect of rate of heating. Sodium borohydride (0.3476 grams, 0.0092 moles) and acetanilide (1.1317 grams, 0.0084 moles) were mixed and connected to the same apparatus as in experiment 2. The reaction tube was placed in an oil bath and heated slowly (over a period of 20-30 minutes) until it reached 205°, at which time charring began. After gas evolution ceased, the bath was allowed to cool to 100° and then the reaction tube was removed. The volume of gas collected was 138 ml. at 38° and 750 mm. (0.005 moles). Heating in this manner gave less trouble with the mixture foaming up in the tube above the oil bath.

The reaction mixture was extracted with ether, and the ether extract then washed with water. The evolution of gas upon washing the ether with water was again noticed. The ether solution was evaporated by means of vacuum at room temperature. An oily brown mixture remained as in experiment 2. Physical appearances would suggest that there is no difference in the outcome of the reaction due to the differences in the two methods of heating.

Experiment 4. Effect of ammonia on reaction. Sodium boro-

hydride (0.3295 grams, 0.0087 moles) and acetanilide (1.1793 grams, 0.0087 moles) were placed in an eight-inch test tube and mixed by stirring. Ammonia gas was passed over the mixture for about 15 minutes. During this time, no change was evident. A few drops of liquid ammonia were then added to the mixture. The mixture was allowed to warm up to room temperature, and then it was subjected to vacuum using a water aspirator. After a half hour of this vacuum treatment, a faint odor of ammonia was still evident.

The mixture was then heated slowly in a water bath. At 95° the mixture began melting. After 15 minutes at the boiling point of water, no sign of reaction was seen. The reaction tube was then transferred to an oil bath and the heating continued. At 125° reaction began, as evidenced by gas evolution. The temperature of the oil bath was held between 125 and 135° for one hour. It was cooled to room temperature and 20 ml. of 5 per cent hydrochloric acid was added. There was an immediate evolution of gas. When the solution was filtered, the acid filtrate was noted to be slightly pink.

Experiment 5. A series of runs was made in order to determine the minimum temperature at which reaction began.

Run 1. Sodium borohydride (0.2526 grams, 0.0067 moles) and acetanilide (0.9030 grams, 0.0067 moles) were mixed and treated with ammonia as in experiment 4. The mixture was then heated on a steam bath without first removing the excess ammonia. The mixture melted but showed little physical sign of reaction after two

hours of this treatment. After cooling the mixture, it was treated with 5 per cent hydrochloric acid which gave an immediate evolution of a large quantity of gas.

Run 2. Sodium borohydride (0.2295 grams, 0.0061 moles) and acetanilide (0.8263 grams, 0.0061 moles) were mixed and reacted in the same manner as in run 1 except that an oil bath was used. The temperature was held at 115° for two hours and again no sign of reaction was evident.

Run 3. Sodium borohydride (0.2896 grams, 0.0077 moles) and acetanilide (1.0314 grams, 0.0076 moles) were mixed and treated with ammonia as in run 1. The mixture was then heated to 127° using an oil bath. At the end of one hour of heating, the mixture began to turn brown and foam. After two and one-half hours at this temperature, the reactants had become very dark and reaction appeared to have ceased.

The reaction mixture was then extracted with 6 N hydrochloric acid. The acid solution upon standing became pink. This solution was then extracted with ether; however, the acid solution still remained colored. The acid solution was then made basic using 5 per cent potassium hydroxide. At first it became cloudy as if a precipitate were forming, but it cleared up on shaking until a very small amount of the precipitate remained. So little precipitate remained that it could not be separated. After standing for twenty-four hours, the basic solution turned dark blue.

The ether extract was evaporated in an oil bath to 90°, at

which time only a few drops of liquid remained. This residue solidified on cooling but seemed covered with oil. The residue was purified and identified as acetanilide as in experiment 1.

Run 4. Isoamyl alcohol was refined to obtain a liquid that boiled at 123°. The alcohol (500 ml.) was placed in a 5-liter three-neck flask. In one neck of the flask, a reflux condenser was placed. In the other small neck a thermometer was placed. The reaction vessel, an eight-inch test tube, was placed in the center neck of the flask. The reaction tube was connected to a gas-measuring burette and also to a small burette to be used for making liquid additions to the reaction mixture.

Sodium borohydride (3.0277 grams, 0.080 moles) and acetanilide (10.7041 grams, 0.079 moles) were placed in the test tube. Liquid ammonia was added and then allowed to evaporate at room temperature. The tube was then connected to the apparatus and the alcohol refluxed to heat it. There was an immediate evolution of gas as the apparatus was heated to 100°. It was assumed to be ammonia since no evidence of reaction could be seen.

Shortly after the temperature reached 125°, the mixture began to foam and gas was given off. Three hours later the foaming began to decrease and that solid which had collected on the side of the tube began to fall to the bottom of the tube.

Five and one-half hours after the reaction started, 1300 ml. of gas had been given off.

Eight hours after the start of reaction, the mixture was a-

llowed to cool and the final volume of gas was determined to be 1320 ml. at 31° and 747 mm. Hg (0.050 moles).

Although gas no longer was being liberated, the mixture had not turned brown.

By means of the small burette that was connected to the reaction tube, 50 ml. of 5 per cent hydrochloric acid was added. This caused an evolution of 2970 ml. of gas at 27° and 745 mm. Hg (0.1140 moles). The total recovery of hydrogen was 0.164 moles.

The reaction tube, which now contained hydrochloric acid, separated into several layers. There was a white solid layer, a yellow solid layer, and a liquid layer.

The white solid was identified as acetanilide. The yellow solid was acetanilide which was coated with a yellow oil.

The acid solution was made basic with solid potassium hydroxide, and an oil separated. An infrared spectrogram was made from this oil. It was tentatively identified as methylaniline, or ethylaniline, or a mixture of both.

Run 5. Sodium borohydride (3.3631 grams, 0.0889 moles) and acetanilide (6.0045 grams, 0.0444 moles) were mixed and treated with liquid ammonia. The ammonia was allowed to evaporate off at room temperature. This was then heated at 125° for two hours. The volume of gas evolved was 175 ml. at 28° and 749 mm. Hg (0.0067 moles).

None of this gas was absorbed by a saturated barium hydroxide solution, indicating the absence of carbon dioxide. An attempt to burn the gas, using a standard combustion pipette, was unsuccessful.

Experiment 6. In order to determine the best mole ratio of reactants to be used, a series of runs was made using various mole ratios. None of these mixtures was treated with ammonia and all were heated at 180-200° using an oil bath. A standard combustion pipette was used in the attempts to burn the gas. To determine the amount of unreacted sodium borohydride, 5 per cent hydrochloric acid was added after the reaction was complete--until hydrogen was no longer being liberated and the volume of this hydrogen was measured.

Run 1. Sodium borohydride (0.5012 grams, 0.0132 moles) and acetanilide (0.8917 grams, 0.0066 moles) were heated for one hour. The volume of gas given off was 151.2 ml. at 25.5° and 749 mm. Hg (0.0059 moles). The combustion pipette broke and that part of the run was lost. Upon adding the acid, 565 ml. of gas was evolved at 25.5° and 749 mm. Hg (0.0220 moles).

Run 2. Sodium borohydride (0.4883 grams, 0.0129 moles) and acetanilide (0.5748 grams, 0.0043 moles) were reacted. This reaction gave 126 ml. of gas at 26° and 752 mm. Hg (0.0049 moles). The gas did not burn, nor was it absorbed in barium hydroxide solution before or after the combustion attempt. When hydrochloric acid was added to the reaction mixture, 730 ml. of gas was given off at 26° and 752 mm. Hg (0.0284 moles).

Run 3. Sodium borohydride (0.4739 grams, 0.0125 moles) and acetanilide (0.4235 grams, 0.0031 moles) were used. The gas evolved was 109 ml. at 26° and 752 mm. Hg (0.0042 moles). The gas failed to react as in run 2. The acid treatment gave 750 ml. of gas at

26° and 752 mm. Hg (0.0284 moles).

Run 4. Sodium borohydride (0.5677 grams, 0.0150 moles) and acetanilide (0.3415 grams, 0.0025 moles) were used. There were 122 ml. of gas given off at 25° and 749 mm. Hg (0.0047 moles). The gas did not burn nor was it absorbed by the barium hydroxide solution. Upon adding acid to the reaction mixture, 930 ml. of gas was evolved at 25° and 749 mm. Hg (0.0362 moles).

Run 5. Sodium borohydride (0.4556 grams, 0.0120 moles) and acetanilide (0.1629 grams, 0.0012 moles) were used. The gas volume was 82.2 ml. at 25° and 749 mm. Hg (0.0032 moles). This gas reacted in the usual manner. Reaction with acid produced 780 ml. of gas at 25° and 749 mm. Hg (0.0303 moles).

Run 6. Sodium borohydride (0.1062 grams, 0.0028 moles) and acetanilide (1.1381 grams, 0.0084 moles) were reacted. This gave 65.2 ml. of gas at 24° and 751 mm. Hg (0.0025 moles). The gas reacted as before. Addition of acid liberated only 8 ml. of gas at 24° and 751 mm. Hg (0.0003 moles).

Run 7. Sodium borohydride (0.1472 grams, 0.0039 moles) and acetanilide (2.6179 grams, 0.0194 moles) were used. The volume of gas was 120 ml. at 25° and 751 mm. Hg (0.0047 moles). The acid treatment produced no gas.

During runs 2, 3, 4, and 5, a small amount of white smoke was given off during the reaction. This smoke settled out on the sides of the gas delivery tube giving a white film.

Table II gives a summary of these experiments. The table shows

that, at mole ratios of less than three moles of acetanilide per mole of sodium borohydride, hydrogen is released upon addition of acid.

In order to use all the hydrogen available in the borohydride, the following experiments were carried out using a mole ratio of more than 3 moles of acetanilide to one mole of sodium borohydride.

Experiment 7. A series of runs was carried out at temperatures above 150°, for the purposes of bringing about complete reaction and to facilitate the recovery of reaction products.

Run 1. Sodium borohydride (5.1822 grams, 0.1369 moles) and acetanilide (75.3303 grams, 0.5573 moles) were mixed in a one-liter three-neck flask. One neck was stoppered, one contained a thermometer, and the other was used to pipe off the gas evolved by the reaction. The flask was filled with a heating mantle.

Reaction started at 150°. At 180° the heating mantle was removed but not in time to save the reaction. The foaming was too great for the volume of the flask. The reaction mixture forced out the stoppers and was lost.

Run 2. A different method for carrying out the reaction was attempted. A three-neck flask was equipped with a thermometer, take-off condenser, and a dropping funnel. The dropping funnel had an eightmillimeter bore.

Enough acetanilide was placed in the flask to make it about one-third full. The flask was then heated to 220° and sodium borohydride was added a little at a time through the dropping funnel until further addition caused no more reaction.

Table II

The Effect of Varying the Mole Ratio of the Reactants

Run number	1	2	3	4	5	6	7
Moles sodium borohydride	0.0132	0.0129	0.0125	0.0150	0.0120	0.0028	0.0039
Moles acetanilide	0.0066	0.0043	0.0031	0.0025	0.0012	0.0084	0.0194
Mole ratio of reactants	0.5000	0.3333	0.2480	0.1667	0.1000	3.0000	4.9744
Moles gas evolved	0.0059	0.0049	0.0042	0.0047	0.0032	0.0025	0.0047
Moles gas per mole borohydride	0.4470	0.3798	0.3360	0.3133	0.2667	0.8929	1.2051
Moles gas evolved by acid	0.0220	0.0284	0.0284	0.0362	0.0303	0.0003	0.0000
Total moles gas recovered	0.0279	0.0333	0.0326	0.0409	0.0335	0.0028	0.0047

No products were driven over and collected by the condenser. Further attempts to isolate products were not made.

Run 3. This run was identical to the second run except that the temperature was held at 250° . This also failed to give products by way of the condenser. The reaction did not foam and left a tarry, brown mass at completion.

The reaction mixture was extracted with ether. The ether extract was extracted in turn with concentrated hydrochloric acid. The acid was kept cool in an ice bath and made basic by the addition of solid potassium hydroxide.

A heavy dark brown liquid separated. This liquid was washed with water. It was then distilled using a Todd column.

The first fraction came over at 90° and separated into two layers. This was probably due to incomplete fractionation.

The second fraction came over at 180° . This was light yellow and had an amine odor. The acetyl derivative melted at 113° as compared to 114° for acetanilide (18). Thus it was identified as aniline, the boiling point of which is 184.4° (19).

The remainder could not be forced through the column. All attempts made to purify it failed.

Run 4. An apparatus was constructed for the purpose of taking the liquid products from the reaction mixture as they were formed. This consisted of a 500-ml. round-bottom flask on which a side arm was placed. The tube was joined to the side of the flask midway between top and bottom. The tube was equipped with a u-trap in such

a manner that the tube could be kept submerged in the oil bath, except for a small bend to get it over the side of the bath.

A relatively large quantity of acetanilide (about 100 grams) was placed in the flask. It was then heated to 215--220°. Sodium borohydride was added in very small quantities through a dropping funnel. Each portion was allowed to react completely before another was added. The products that were distilled from the mixture were collected in a tube surrounded by an ice bath. The total reaction time was about two hours. During this time, about 5 ml. of product was collected.

The products were fractionated using a Todd column.

The first fraction came over at 183-185°, amounting to 1.2 ml. This was identified as aniline by boiling point and the acetyl derivative, as in run 3.

Between 185° and 202°, 0.3 ml. came over. No attempt was made to identify this fraction.

The next fraction consisted of 3 ml. and came over at 202-204°. This was identified as N-ethylaniline by boiling point and the acetyl derivative, which melted at 53° as compared with the literature value of 54° (33).

About 1 ml. of residue was left in the distillation flask.

A second run was made using the same procedure. It gave essentially the same results except a little more product was collected. Fractionation of the product gave the same fractions as in the previous run.

Experiment 8. This experiment was an attempt to liquefy the gas given off by the reaction. The experiment was performed in the same manner as run 4, experiment 7, except that the gas was led through a liquid air trap. The trap did not condense any of the gas given off by the reaction.

Experiment 9. The following general procedure was used for five replicate reactions, for the purpose of establishing a quantitative relation between the reactants and the products.

Sodium borohydride (2 grams, 0.0528 moles) and acetanilide (50 grams, 0.3699 moles) were mixed in a 250-ml. round-bottom flask. The flask was connected through a reflux condenser to a gas burette. It was then immersed in an oil bath, which had been preheated to 200°, and allowed to remain there for one half hour. This was ample time for the reaction to go to completion as evidenced by gas evolution. The volume of gas evolved by the reaction, its temperature, and the atmospheric pressure were measured.

When the reaction mixture cooled to room temperature, it was extracted with 350 ml. of C.P. anhydrous acetone. The acetone dissolved the unreacted acetanilide and the amine products but left a small amount of insoluble residue.

The residue from the acetone extraction was filtered from the solution using a fine, fritted glass filter. It was dried under vacuum at 100° and weighed.

The acetone was removed from its solution by distillation. The residue from the acetone distillation was then extracted with

400 mL. of 1 N hydrochloric acid. This treatment dissolved the amine products but not very much of the unreacted acetanilide. The acid solution was then neutralized to pH 7 with 6 N sodium hydroxide, and steam distilled. The organic layer was separated from the distillate and dried over calcium chloride.

The organic layer was fractionated using a Todd column.

The first fraction came over at 183-5°. The acetyl derivative melted at 113-4°. The benzoyl derivative melted at 159-60°. The boiling point for aniline was noted to be 184.4° (14), the melting point of acetanilide 114° (13), and the melting point of benzanilide 160° (32).

A small amount of material distilled between 185 and 200°. Identification of this fraction was not attempted.

Between 200 and 203° a fraction came over and was identified as N-ethylaniline, boiling point 204° (15), by its acetyl derivative which melted at 52-53° as compared with the literature value of 54° (33), and benzoyl derivative which melted at 60°, the same as the literature value (33).

The results of this experiment have been condensed into Table III. Owing to mistakes, parts of the various runs were lost and thus there are omissions from the table.

Experiment 10. Using the method described in Daniels, Williams, and Mathews (5), the molecular weight of the gas evolved by the reaction between sodium borohydride and acetanilide was determined.

Five determinations gave individual values of 2.45, 3.29, 2.39,

Table III

Products of the Sodium Borohydride-Acetanilide Reaction

Moles sodium borohydride used	0.0528	0.0528	0.0528	0.0528	0.0528
Moles acetanilide used	0.3699	0.3699	0.3699	0.3699	0.3699
Mole ratio of reactants	7.0000	7.0000	7.0000	7.0000	7.0000
Moles gas evolved	-----	0.0836	0.0826	0.0825	0.0825
Moles gas per mole of borohydride	-----	1.5800	1.5600	1.5600	1.5600
Grams acetone-insoluble residue	3.9900	3.9100	3.9900	4.5300	5.1500
Moles product					
183-5° (aniline)	-----	0.0250	0.0190	0.0330	-----
185-200°	-----	0.0060	0.0080	0.0120	-----
200-3° (N-ethylaniline)	-----	0.0370	0.0380	0.0250	-----
Total moles of product	-----	0.0680	0.0650	0.0700	-----
Moles product per mole of borohydride					
Aniline	-----	0.4700	0.3600	0.6300	-----
N-ethylaniline	-----	0.7000	0.7200	0.4700	-----

2.89, and 4.14. The average of these values is 3.0.

A sample of the gas was sent to the Mass Spectrometer Laboratory of the Texas A. and M. Research Foundation for analysis. The results are shown in Table IV (10).

Table IV

Gas Analysis by Mass Spectrograph

Air	1.6%
Ethanol	0.9%
Hydrogen	97.5%
Oxides of Nitrogen	< 0.1%
Carbon Dioxide	< 0.06%
Carbon Monoxide	Negligible

Experiment 11. Qualitative detection of ethyl alcohol. A one-gram sample of the residue remaining after the acetone extraction in experiment 9 was placed in a small distillation flask. About 20 ml. of 10 per cent sodium hydroxide was added. The mixture was heated to just below its boiling point for about two hours. It was then slowly distilled until about 10 ml. of distillate was collected. The distillate gave a positive iodoform test and a negative Schiff's test.

The foregoing procedure was repeated substituting 6 N sulfuric acid in place of the sodium hydroxide. The distillate gave a very definite iodoform test and a negative Schiff's test. An attempt to fractionate this liquid showed some indication of a liquid boiling at about 80° but so little was present that it could not be separated.

A sample of the residue was tested for nitrogen by the sodium fusion method. The test was negative. A Dumas combustion was run and gave a positive test for nitrogen.

Experiment 12. In order to establish some basis for the reaction between sodium borohydride and acetanilide by which free hydrogen is produced, an attempt was made to show the existence of a compound of the type $\text{NaB}(\text{N}(\text{O})\text{COCH}_3)$. An experiment was run in the usual manner using 1 gram of sodium borohydride (0.0264 moles) and 25 grams of acetanilide (0.1850 moles). The reaction mixture was cooled to ice temperature and extracted with 25 ml. of cold water. The water solution was washed with diethyl ether.

Solid sodium hydroxide was carefully added to the water solution, and the mixture refluxed for about one hour. At the end of this treatment, the water solution was cloudy and the odor of aniline was present.

A small amount of benzoyl chloride was added to the solution. There was a small immediate reaction. The solution was cooled in an ice bath and the precipitate removed. It melted at $158-60^\circ$ as compared to benzanilide which melts at 160° (20).

Reaction of sodium borohydride and formanilide

Sodium borohydride (2 grams, 0.0528 moles) and formanilide (40 grams, 0.3302 moles) were mixed in a 250 ml. round-bottom flask. The flask was connected to a gas burette and heated in a water bath.

Reaction started very slowly at 55° . At 70° the mixture began rapid foaming. The temperature was held at 75° for about 10 minutes,

after which the reaction subsided, and then heated to 100° for 15 minutes. The volume of gas evolved was 1170 ml. at 33° and 744 mm. Hg (0.0433 moles). This represented 0.82 moles of hydrogen per mole of borohydride.

The reaction mixture was cooled to room temperature and then extracted with 300 ml. of anhydrous acetone. The residue from the acetone extraction was dried under vacuum at 100° and its weight was recorded as 6.5834 grams. The acetone was removed by distillation.

The residue after the removal of the acetone was fractionated, using a Todd column. A drop of liquid came over at 85° but was not identified. The fractionation was continued under vacuum. Material (10 ml.) came over between 45° and 55° at 5 mm. This fraction was then carefully refractionated and 8 ml. was collected at 46-7° and 5 mm. Hg. A small amount of material was lost by column hold up. The acetyl derivative was prepared and found to melt at 112-3°. This compared with the melting point of acetanilide which is 114° (18). The benzoyl derivative melted at 158-9°. It was noted that benzanilide melts at 160° (20).

An attempt to burn the gas evolved by the reaction, using an ordinary combustion pipette, was not successful.

DISCUSSION

Prior to this work, the reduction of organic compounds by sodium borohydride has utilized water as a reactant for the purpose of hydrolyzing a postulated complex (4). It is now evident that the use of water is not necessary for the production of products from the reaction between sodium borohydride and acylanilines. The conclusion is that the mechanism of the reaction studied is not the same as that of the reaction studied by earlier investigators.

The reaction of sodium borohydride and acetanilide is fairly reproducible. Its course is not affected substantially by either rapid or slow heating.

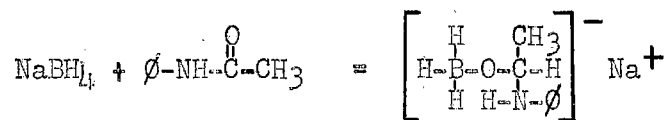
The use of liquid ammonia for the purpose of dissolving the reactants, thus forming an intimate mixture before heating, gave no indication of being valuable.

The time required for complete reaction varied little, if at all, when the temperature used was above 150°. Reaction at lower temperatures required a much longer period.

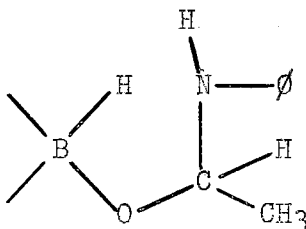
Three major products from this reaction were identified. They were hydrogen, aniline, and N-ethylaniline. In addition, ethanol was identified as a minor part of the gas evolved, and a fairly good case for the presence of the ethoxide radical was found.

There are two points on the acetanilide molecule which would presumably be attacked preferentially by the borohydride. These are the oxygen atom, or carbonyl group, and the nitrogen atom, the hydrogen of which is fairly acidic.

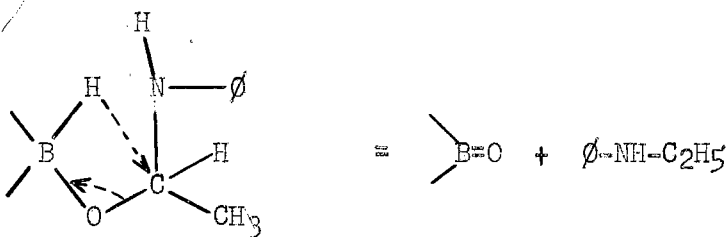
The attack at the carbonyl group would be in the same manner as indicated by previous investigators, i.e., the formation of a complex as shown below.



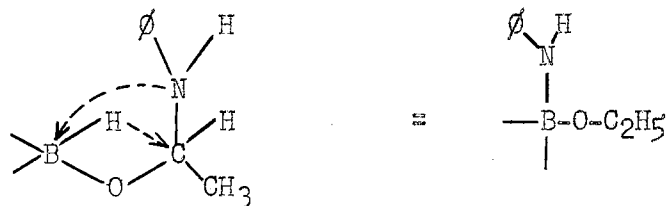
Due to the bond angles, one of the hydrogen atoms bonded to the boron atom could be very near the carbon atom in the carbonyl group, as shown below.



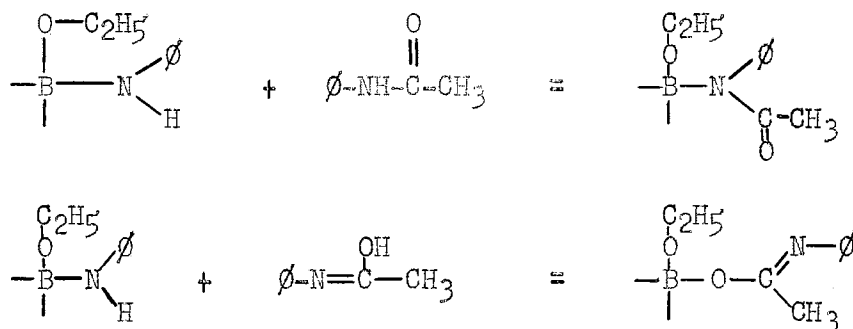
The above complex could then undergo rearrangement in two ways. One rearrangement would be the migration of the hydrogen atom and the splitting of the carbon-oxygen bond. This would give N-ethyl-aniline as a product.



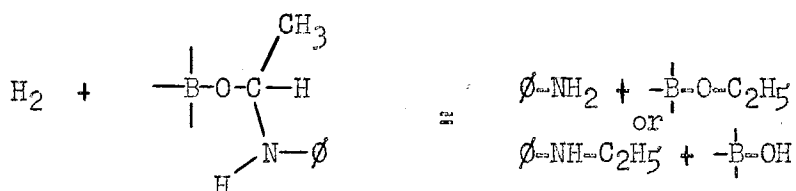
Another possibility would be the migration of the hydrogen atom to the carbonyl carbon and the splitting of the nitrogen-carbon bond, the nitrogen then migrating to form a boron-nitrogen bond.



The complex thus formed could be broken by reaction with another molecule of acetanilide. The acetanilide could give up a hydrogen atom to the aniline radical and displace it from the complex forming aniline. The displacement could proceed via the keto or enol form of acetanilide. The equations below show these two possibilities.

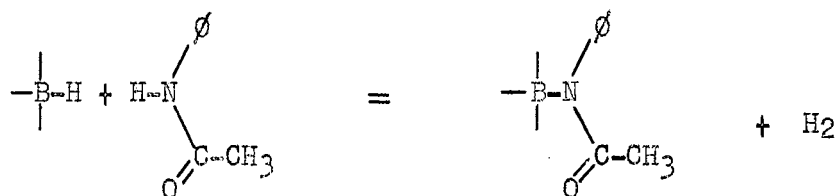


On the other hand, the borohydride-acetanilide complex could undergo hydrogenolysis, in the presence of free hydrogen, to form either aniline or N-ethylaniline, depending on which bond is broken.

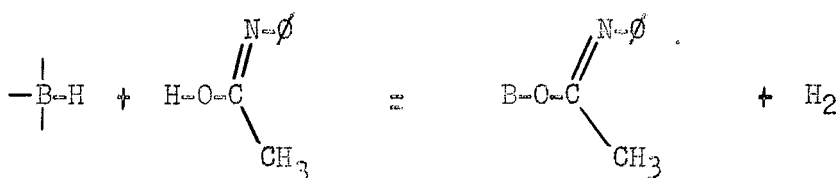


To account for the presence of free hydrogen the attack of the borohydride at the nitrogen atom seems reasonable. A direct reaction at the nitrogen atom forming a boron-nitrogen bond would liberate

one mole of hydrogen. The equation below illustrates this possibility.



A similar reaction can be written involving the enol form of acetanilide.



The ultimate proof of the postulates presented in this discussion is left as a proposal for future work. Whether it is possible, in view of the complex mixtures formed, ever actually to isolate and identify the intermediates postulated, is doubted. A study of the reaction of sodium borohydride with other amides (amides that contain groups which would affect the acidity of the hydrogen bonded to the nitrogen atom) would appear to be helpful.

Some future work might also be done on the use of solvents in these reactions.

Concerning the reaction between sodium borohydride and formamide, the same postulates as in the reaction with acetanilide may be adopted. The conclusion is that one process merely takes precedence over the other.

SUMMARY

The reaction between sodium borohydride and acetanilide was studied under a variety of conditions. The products that were isolated and identified were hydrogen, aniline, and N-ethylaniline.

The total reaction evidently involves several different reactions which take place simultaneously. This makes analysis of the products difficult and in some cases perhaps impossible.

Mechanisms have been postulated to explain the formation of the products obtained. While these postulates are open for criticism, they do explain the data which is presented.

The only organic product isolated from the reaction of sodium borohydride with formylanilide was aniline. It is supposed that this reaction proceeds in the same manner as the formation of aniline from acetanilide.

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