# A STUDY OF THE ALKYLATION AND ARYLATION OF NITRILES WITH HALOGEN COMPOUNDS

Thesis for the Degree of M. S.
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Andrew A. Holzschuh
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A THESIS

Submitted to the School of Graduate Studies of Michigan
State College of Agriculture and Applied Science
in partial fulfillment of the requirements
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Department of Chemistry

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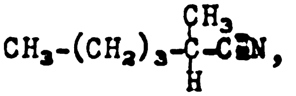
# ABSTRACT

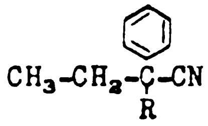
This investigation was begun as an attempt to phenylate propionitrile with bromobenzene using sodium hydride as a condensing agent. Much polymerization of the propionitrile occurred and no phenylated product was obtained.

Bergstrom and Agostinho (1) reported successful phenylation of propionitrile with chlorobenzene when they used potassium amide as a condensing agent. They obtained 43% of the mono-substituted product, hydratroponitrile, and some higher boiling material. This preparation was repeated as described by these authors. The first fraction, which would have contained the hydratroponitrile, boiled over a very wide range. It was not further investigated. If it had all been hydratroponitrile, it would have amounted to 27.7% yield. The second fraction boiled reasonably constant at 157° at 3 mm. pressure and it probably was 2-phenylhydratroponitrile. It amounted to 33.6% yield based on the propionitrile used. It was not further investigated.

One attempt was made to phenylate phenylacetonitrile with bromobenzene and sodium hydride. None of the phenylated product was obtained.

One attempt, also, was made to alkylate propionitrile with n-butyl bromide and sodium hydride. The monoalkylated product, 2-methylhexanenitrile,  $CH_3\text{-}(CH_2)_3\text{-}\overset{CH_3}{\underset{H}{C}}\text{-}C\equiv N$, was obtained in 23.6% yield based on the propionitrile used. Only a trace, if any, of the dialkylated product was obtained.

In order that the work would not get unduly extensive, at this point the objective was narrowed down to the preparation of the butyl substituted 2-phenylbutanenitriles,



from 2-phenylbutanenitrile and the butyl chlorides. The effect of the configuration of the isomer on the yield of product was to be determined. As a condensing agent both sodamide and sodium hydride were to be used and comparison of these obtained.

With sodamide as a condensing agent, this reaction gave good yields of alkylation product, when the n-butyl, s-butyl, and i-butyl chlorides were used as alkylating agents. The yields of 2-butyl-2-phenylbutanenitriles were: n-butyl, 87.3%; s-butyl, 91.7%; i-butyl, 90.1%; t-butyl, approximately, 7.7%.

With sodium hydride as a condensing agent the figures were: n-butyl, 73.0%; s-butyl, 80.7%; i-butyl, 79.3%. No preparation was attempted with t-butyl chloride and sodium hydride.

It was found impossible to hydrolyze these highly hindered nitriles for preparation of derivatives. However, they could be readily reduced to amines by the use of lithium aluminum hydride (2). This was done, and the amines were readily converted to suitable derivatives. The physical constants of the nitriles and the amines, and the melting points of the derivatives are shown in the accompanying table.

Infra-red spectra were obtained on the nitriles and the amines. The nitriles all showed the characteristic absorption band at 4.5 microns. In the spectra of the amines this band was no longer present.

## LITERATURE CITED

(1) F. W. Bergstrom and R. Agostinho, J. Am. Chem. Soc., 67, 2152 (1945).

(2) L. Amundsen and L. Nelson, J. Am. Chem. Soc., 73, 242 (1951).

## TABLE OF PROPERTIES

| Compound | B.p., °C. (5 mm.) | $D^{25}$ | $N_D^{25}$ |
|---|---|---|---|
| 2-Ethyl-2-phenylhexanenitrile | 126 | 0.9322 | 1.4971 |
| 2-Ethyl-3-methyl-2-phenylpentanenitrile | 126 | 0.9468 | 1.5038 |
| 2-Ethyl-4-methyl-2-phenylpentanenitrile | 119 | 0.9327 | 1.4976 |
| 2-Ethyl-3,3-dimethyl-2-phenylbutanenitrile [a] | 123-126 | 0.9571 | 1.5107 |
| 1-Amino-2-ethyl-2-phenylhexane [b] | 134 | 0.9283 | 1.5125 |
| 1-Amino-2-ethyl-3-methyl-2-phenylpentane [c] | 129.5 | 0.9471 | 1.5116 |
| 1-Amino-2-ethyl-4-methyl-2-phenylpentane [d] | 120.5 | 0.9279 | 1.5130 |

[a] This nitrile was obtained only in very small quantity and a derivatives was not made. However, it was a solid and melted at 57.2-58.0° after recrystallization.

[b] M. p. of phenylthiourea, 118.5-119°.

[c] M. p. of $\alpha$-napthylurea, 176-177°.

[d] M. p. of phenylthiourea, 140.3-141°.

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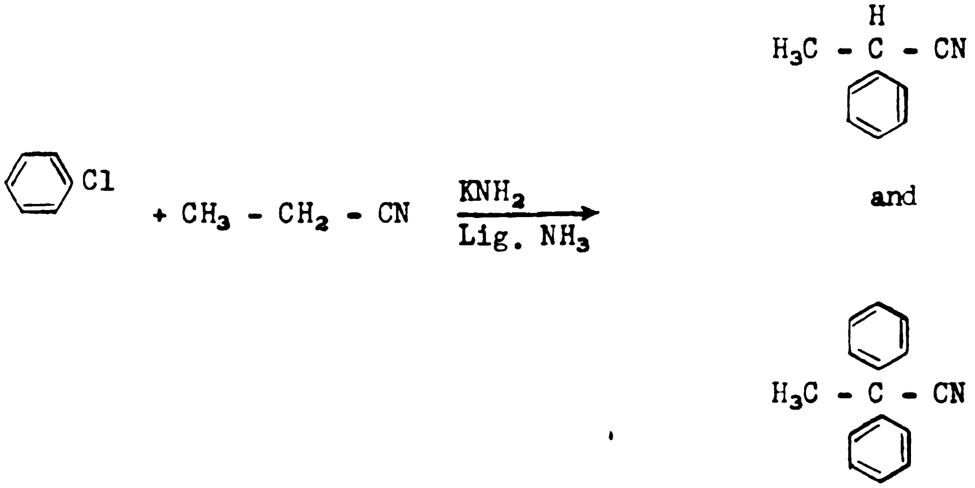
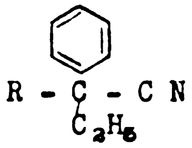
# INTRODUCTION

This investigation was begun as a follow-up to some work reported by Bergstrom and Agostinho (1). They found that propionitrile could be arylated by chlorobenzene in liquid ammonia in the presence of potassium amide. The products obtained were the mono- and the diphenyl-substituted propionitriles. The reaction is



In this laboratory investigations have shown that the alkylation of nitriles can be carried out quite satisfactorily and conveniently using sodium hydride as the condensing agent with a toluene medium at somewhat elevated temperatures. Ring substituted phenylacetonitriles have been alkylated under these conditions with benzyl chloride and with butyl and amyl bromides. Initially the object of the work reported herein was to see if the use of sodium hydride could be extended to the phenylation of propionitrile. A number of attempts to do this resulted in failures. A number of variations of this plan were tried and it was found that alkylation of propionitrile with n-butyl bromide and sodium hydride could be accomplished with some success. In order not to get started on a more extensive investigation than was practical the objective was narrowed down to the preparation of the butyl-sutstituted 2-phenylbutanenitriles,



by the use of sodamide as a condensing agent, and to make a minimum investigation of the feasibility of the use of sodium hydride instead of the amide for the same reaction. The effect of the configuration of the butyl chloride on the yield of alkylation product was to be determined, as well as the effect of the nature of the condensing agent. In addition, characterization of the reaction products was to be carried out, since they have not been reported in the literature.

## HISTORICAL

The literature on the alkylation of nitriles has been quite extensively reviewed in a recent thesis by Workman (2). Therefore, only that work which seems most directly pertinent to this thesis will be reviewed here. Ramart (3) reported the successful benzylation of diethylacetonitrile, n-valeronitrile, and n-caprylic nitrile, using benzyl chloride and sodamide in ether medium. Ziegler and Ohlinger (4) reported that, after considerable difficulty with polymerization, they finally succeeded in the alkylation of butyronitrile using n-butyl chloride and sodamide. They claimed a 68% yield of alkylated product. Later Ziegler (5) reported the successful alkylation of isobutyronitrile with benzyl chloride and sodium hydride. The work of Bergstrom and Agostinho (1) on the phenylation of propionitrile by means of chlorobenzene and potassium amide was cited earlier.

Schuerch and Huntress (6) alkylated acetonitrile with ethyl bromide and sodamide in ether and obtained substantial yields of the mono- and diethylated products. Cristol and co-workers (7) investigated the reaction of sodium hydride with various alkyl halides at usual reaction conditions and found it to be inert. Workman (2) alkylated hydratroponitrile with the four isomeric butyl halides, using sodamide as the condensing agent. His yields were about 60%, except in the case of the t-butyl chloride. For the latter the yields were 0-12%.

## EXPERIMENTAL

### Chemicals

Propionitrile - Eastman practical grade material was redistilled. A small low boiling fraction was discarded and the remainder, which boiled at 95.5-96°, was the material used. A bromate-bromide titration showed that unsaturation was less than 0.01%.

Phenylacetonitrile - Eastman white label material was used as obtained.

2-Phenylbutanenitrile - This compound was prepared by the phosphorous oxychloride dehydration of Eastman practical grade $\alpha$-phenylbutyramide, by the method of Cram and Allinger (8). The product was fractionated through a column packed with helices. The fraction saved boiled at 110-111.5° at 9 mm. pressure and had a refractive index $N_D^{25}$ 1.5060. Reported values by the above authors are b.p. 122-124° at 16 mm. pressure and $N_D^{25}$ 1.5075.

Bromobenzene, chlorobenzene, and n-butyl bromide - These were Eastman white label grade materials and were used as obtained.

n-Butyl chloride - Eastman white label grade material was refractionated and a low boiling fraction of about 4% was discarded. The fraction used boiled constantly at 77°.

s-Butyl chloride - Eastman white label grade material was refractionated. The fraction saved boiled at 66-67°.

t-Butyl chloride - Refractionation of Eastman white label grade material gave a fraction which boiled at 50.5°.

i-Butyl chloride - Eastman white label grade material. On refractionation it was found difficult to get a material with a constant boiling point. The material used boiled at 67-70°.

Lithium aluminum hydride and sodium hydride - These compounds were used as obtained from Metallic Hydrides, Inc. They were repackaged into small bottles and stored in a desiccator.

Sodamide - This material was obtained from Farchan Laboratories. It had been in storage for several years in sealed bottles. It was good in appearance. It, also, was repackaged into small bottles and stored in a desiccator.

Toluene and absolute ether - These materials were obtained from the stockroom and were dried over sodium before use.

## General Information

In all the experiments, unless otherwise stated, the reactions were carried out in a 500 cc. three-necked flask, fitted with a stirrer, thermometer, dropping funnel, and reflux condenser. The reflux condenser was fitted with a soda lime drying tube. Fractional distillations were carried out in either of two columns. One was twelve inches long and packed with glass helices, the other was a fifteen inch long vacuum jacketed Vigreux column.

Halide conversion figures were obtained by titration of the aqueous layer by the Volhard method for halide ion.

All reported melting points were taken in capillary tubes and are those obtained after the material had been recrystallized repeatedly until the melting point increased only slightly or not at all. The final values were determined with standardized thermometers graduated in one-fifth degree divisions and immersed as marked.

All yield figures were calculated on the basis of the reactant nitrile used.

# I. STUDIES OF THE ARYLATION OF NITRILES

## A. Attempt to Arylate Propionitrile in the Presence of Sodium Hydride

Four different attempts as described below were made in an effort to arylate propionitrile with bromobenzene in the presence of sodium hydride.

To the apparatus described above (see General Information) was added a mixture of 25.7 g. (0.467 mole) propionitrile and 38 g. bromobenzene. A suspension of 11.2 g. (0.467 mole) sodium hydride in 38 g. bromobenzene was placed in the dropping funnel. Enough more bromobenzene was used for rinsing to make a total of 150 g. (0.96 mole). About one-third of the sodium hydride was added at once. A mild gas evolution was observed. When the mixture was slowly warmed to 100° it turned brown and gummy. It was cooled to 70° and the rest of the sodium hydride was added during a few minutes. The reaction mass, which soon became so sticky that it was difficult to agitate, was heated at 110-120° for one hour. It was cooled and treated with a little alcohol (to react with any remaining sodium hydride) and then with water. An insoluble slimy impurity was removed by filtration. The layers were separated and the oil layer was washed once with 50 cc. water. The water layer was analyzed by the Volhard method and found to contain 0.185 mole bromide ion. This corresponds to 40.5% conversion based on the nitrile used. The oil layer was fractionated and approximately 6 g. low boiling (up to the boiling point of bromobenzene, 154°)

material were obtained. Next an undetermined amount of bromobenzene was distilled over. After that only a few drops of material could be distilled even at 2 mm. pressure. The material remaining in the distillation flask became very thick and sticky on cooling. It was discarded.

In the second attempt toluene was used as a diluent and solvent. The preparation was made with 0.67 mole of each reactant. The sodium hydride was added with the aid of toluene (100 cc.) because the bromobenzene has such a high specific gravity that it floats the hydride and makes it difficult to feed to the reaction flask. The reaction mixture was heated to 65-70° and the hydride was added in one hour at this temperature. The batch was then warmed slowly. At 90° it reacted with considerable evolution of heat. This mixture was heated another half hour at about 100° and became very sticky and balled up. The batch was discarded at this point.

Since the nitrile appeared to have been polymerizing, a little of it was treated with sodium hydride in a test tube. Only moderate reaction took place at room temperature. When warmed up it reacted more and more until, at 75-85° it became yellow and sticky. The first reaction product may have coated the hydride and thereby slowed the reaction. Heating could then dissolve or otherwise remove this layer and permit the reaction to continue. A review of the literature revealed that the formation of dimeric and trimeric condensation products of acetonitrile and propionitrile can be effected by the alkali metals (9,10,11,12,19). The two forms are both soluble in acid. Since the desired product is acid-insoluble, in the following runs the product layer was acid washed to remove any of the polymers that might be formed.

In the third preparation, 34.4 g. (0.60 mole) propionitrile, 15.0 g. (0.625 mole) sodium hydride, and 120 g. (0.76 mole) bromobenzene in 50 cc. toluene were permitted to react. The sodium hydride was added during 15 minutes at room temperature and the mixture stirred for one-half hour. No noticeable reaction took place. No reaction was observed as the mixture was heated to 62° during one and one-half hours. The addition of a few drops of alcohol had no effect. When the mixture was heated to 70°, reaction occurred and the temperature rose rapidly to 90°. It became very sticky and the agitator set up. The mixture was heated to 118°, then cooled and alcohol and water were added. Considerable reaction took place on addition of the alcohol. The layers were separated and analysis of the aqueous layer showed 9.2% bromide conversion. The oil layer was washed once with water, twice with acid, and again with water. After removal of the excess bromobenzene there remained about 4 or 5 g. of high boiling material which could not be distilled at reduced pressure without decomposition. This material was discarded.

In the final experiment in this series, an attempt was made to avoid a high concentration of nitrile at any time. It was hoped that in a highly diluted state, with a high concentration of bromobenzene present, the nitrile would be phenylated rather than undergoing polymerization. The sodium hydride (15.4 g., 0.643 mole) and bromobenzene (188 g., 1.2 moles) were loaded into the reaction flask, and heated to 90-100°. A solution of 33 g. (0.60 mole) propionitrile in 100 cc. toluene was added over a period of three hours. The mixture became very sticky as previously observed. It was heated an additional hour at 120-125° and then cooled. On addition of alcohol considerable reaction took place. This may be a decomposition of the sodio derivative of the polymer. The water layer showed 39% bromide conversion. The oil layer was acid washed as before. This time the acid wash separated from the oil layer was made alkaline and about 20 g. of a sticky oily material separated from it. This amount of polymer corresponds to about 60% of the starting nitrile. After removal of the toluene and bromobenzene from the oil layer, very little material was left. When it was attempted to distill this material at 2 mm. pressure it began to decompose and some material froze in the reflux head. The distillation was discontinued and the material was discarded.

### B. Arylation of Propionitrile in the Presence of Potassium Amide

This reaction was carried out according to the procedure of Bergstrom and Agostinho (1). The potassium amide was prepared by the addition of metallic potassium to liquid ammonia in the presence of ferric oxide catalyst. This was similar to the preparation of sodamide in liquid ammonia, and in addition all the precautions for the handling of metallic potassium were observed.

Potassium metal (7.8 g., 0.20 mole) was converted to the amide in about 400 cc. liquid ammonia in a 1-l. three-necked reaction flask. Another portion of potassium amide was made in a 500 cc. flask from 15.6 g. (0.40 mole) potassium in about 200 cc. liquid ammonia. To the former was added 11 g. (0.20 mole) propionitrile, followed by 45 g. (0.40 mole) chlorobenzene during a few minutes time. Very little, if any, visible reaction occurred. The second portion of amide was pressured slowly over into the reaction flask during a period of 20 minutes. A violent reaction ensued and the mixture turned dark brown. After 45 minutes of stirring, 20 g. ammonium bromide was added to neutralize any remaining potassium amide. Then 150 cc. water was added very slowly. The mixture was acidified with dilute hydrochloric acid. One hundred cubic centimeters toluene was added and the layers were separated. The oil layer was washed four times with water and fractionated at 20 mm. pressure. Two fractions were collected. The first (7.3 g.) distilled at 116-140° at 20 mm. pressure (not constant anywhere), $N_D^{25}$ 1.5124. If calculated as monoarylated product this corresponds to 27.7% yield. The second fraction (13.9 g.) distilled at 140° at 20 mm. pressure to 162° at 3 mm. pressure (mostly at 157° at 3 mm.), $N_D^{25}$ 1.5700. If calculated as the diarylated product this corresponds to 33.6% yield. Bergstrom and Agostinho (1) report only that they obtained 43% yield of the monoarylated product (b.p. 105-112° at 8 mm.) and some higher boiling material. Workman (2) gives for hydratroponitrile a boiling point of 82° at 3 mm. pressure, $N_D^{20}$ 1.5120.

### C. Attempted Arylation of Phenylacetonitrile in Presence of Sodium Hydride

Eighty grams (0.683 mole) phenylacetonitrile and 150 g. (0.95 mole) bromobenzene were loaded into the reaction flask. To this mixture was added 16.4 g. (0.683 mole) sodium hydride in 100 cc. toluene over a period of two hours while the temperature was maintained at 90-110°. The batch was very thick so 50 cc. more toluene was added. After the mixture had been stirred at 95-105° for 22 hours it was quite thin and reddish colored. It was treated with alcohol and then with water (ammonia evolution). It was filtered and the layers were separated. The water layer showed 22.7% bromide conversion.

The oil layer was washed twice with water, twice with acid, and again twice with water. After the bromobenzene had been removed there remained about 14 g. material, which could not be distilled at 2 mm. pressure. It was discarded.

## II. ALKYLATION OF PROPIONITRILE IN PRESENCE OF SODIUM HYDRIDE

To a mixture of 36.6 g. (0.666 mole) propionitrile and 100 g. (0.73 mole) n-butyl bromide at 30°, was added 16 g. (0.666 mole) sodium hydride in 100 cc. toluene during one-half hour. No noticeable reaction occurred. The mixture was gradually heated to 50° and held at this temperature for 21 hours. At the end of this time it still was a thin gray slurry much like it was at the start. Over a period of six hours it was heated gradually to 112° and held there for two hours. The only evidences of reaction were that the reflux temperature had increased from 98° to 112° and that the gray color had changed to almost white. The mixture was treated with alcohol (reaction), followed with water. After filtration and separation the water layer showed 64.3% bromide conversion.

The oil layer was acid washed and then water washed. The acid wash liberated about 18 g. oil when it was made alkaline. This is evidence of considerable polymerization of the nitrile. After the toluene and butyl bromide had been removed the oil layer was fractionated and two fractions were collected. The first (17.5 g.) distilled at 70-93° (mostly 78-80°) at 30 mm. pressure, $N_D^{25}$ 1.4070, $D^{25}$ 0.7985. This corresponds to a 23.6% yield of 2-methylhexane nitrile. The second fraction (2.5 g.) distilled at 100-126°, $N_D^{25}$ 1.4255. 2-Methylhexanenitrile has a reported boiling point of 43-50° at 9 mm., $D^{25}$ 0.797 (20).

One gram of the suspected 2-methylhexanenitrile (first fraction above) was converted to the corresponding amide by heating with 5 g. of

75% sulfuric acid on the steam bath for 20 minutes. It was poured into ice water; the crystals which formed melted at 64-67°. Recrystallization from benzene raised the m.p. to 68.5-69.0°. The amide of 2-methylhexanenitrile is reported to melt at 66° (20) and at 70-72.5° (21).

## III. THE ALKYLATION OF 2-PHENYLBUTANENITRILE WITH THE BUTYL CHLORIDES USING SODAMIDE

The same procedure was used for all the alkylations in this series. All alkylations were run in duplicate. The reactants were used in the ratio of one mole sodamide, 0.81 mole nitrile, and 0.94 mole butyl chloride. Approximately 0.4 mole sodamide was used in each preparation.

The 2-phenylbutanenitrile, the butyl chloride, and 50 cc. toluene were charged into the 500 cc. reaction flask. The sodamide in another 50 cc. toluene was added from the dropping funnel at a temperature sufficiently high to make the reaction proceed readily and at a rate which permitted good control of the temperature. The time of addition was from one-half to one hour and could have been shortened considerably by use of more cooling. The temperature of addition was 65-80° in the cases of the n-butyl, s-butyl, and i-butyl isomers. For the t-butyl isomer it was 55-65°. The batch was then heated to reflux temperature which was 118-120° for all except the t-butyl isomer, for which it was 112-116°. As will be seen later, in this latter case the starting nitrile reacted to only a small degree, and, since it has a lower boiling point than the expected product, it is reasonable that it should raise the reflux temperature of the toluene a lesser amount.

One further variation was instituted in the case of the t-butyl chloride runs. It was expected that isobutylene might likely be formed as a by-product. The top of the reflux condenser was connected to a bubbler trap containing 15% sulfuric acid and the outlet from the trap was connected to a dry ice trap. In both runs a quantity of material was collected in the dry ice trap, which was sufficient to account for about 70% yield if it were all isobutylene. The material was readily flammable. Most of it boiled between -10° and +10°, and the remainder over the range up to 40°. It appeared to be mostly isobutylene, contaminated with a little t-butyl chloride.

After the reaction was completed it was cooled and water and a little filtercel were added. After filtration the layers were separated and the water layer was analyzed for chloride ion. The oil layer was washed further, in some cases only with water, in others with salt water, and in still others with acid followed by water. The purpose of the acid wash was to remove polymeric nitriles. Apparently in this series none of these were formed, as no difference was noted in the amount of distillation residue as a result of the acid wash. Salt water in place of plain water served only to make the layers separate faster. It was not necessary.

After distillation of the toluene the residual product was fractionated thru the Vigreux or the helices-packed column at 5 mm. pressure. Fractions were taken and the refractive index observed for each and recorded as shown in Table I for 2-ethyl-3-methyl-2-phenylbutanenitrile. The boiling points and refractive indices followed the same pattern of variation quite closely for all the successful runs. In all the runs a negligible amount of distillation residue remained. In the two runs with t-butyl chloride about 80% of the starting nitrile was recovered.

The high boiling fractions from the two runs were combined and refractionated. The boiling range was narrowed down to about 6°, however, a constant boiling fraction was not obtained. That fraction which had the least variation in boiling point was used for determination of physical constants. Three of the fractions solidified. These were combined, pressed out, and recrystallized from ligroin and again from methanol, m.p. 57.2-58.0°.

The yields, chloride conversions, physical constants, and nitrogen contents are summarized in Table II. The nitrogen analyses and all other chemical analyses of the prepared compounds reported herein were done by the Micro-Tech Laboratories, Skokie, Illinois.

In a typical run, 48.1 g. (0.332 mole) 2-phenylbutanenitrile, 35.6 g. (0.386 mole) s-butyl chloride, and 50 cc. toluene were charged into the reaction flask. A suspension of 15.9 g. (0.408 mole) sodamide in 50 cc. toluene was placed in the dropping funnel. The flask was heated and the amide added at such a rate that the temperature was maintained at 70-85°. After the addition of the amide, the mixture was heated at reflux temperature (118-120°) for one hour. It was cooled and 100 cc. water and a little filtercel were added. After filtration and separation of the layers, the water layer was analyzed and found to contain 0.332 mole chloride ion, which corresponds to 100% chloride conversion, based on the nitrile used. The oil layer was washed once with salt water, twice with acid, and once more with salt water. After most of the toluene had been distilled at atmospheric pressure, the remaining product was fractionated at 5 mm. pressure. The distillation data and the refractive indices of the fractions taken are shown in Table I.

### TABLE I

### DISTILLATION OF 2-ETHYL-3-METHYL-2-PHENYLPENTANENITRILE

| Fraction | B.p., °C. (5 mm.) | Weight, Grams | $N_D^{25}$ |
|---|---|---|---|
| 1 | 82-105 | 0.8 | 1.5005 |
| 2 | 105-127 | 1.6 | 1.5039 |
| 3 | 127-127.5 | 8.8 | 1.5038 |
| 4 | 127.5 | 9.9 | 1.5037 |
| 5 | 127.5 | 14.5 | 1.5039 |
| 6 | 127.5 | 10.0 | 1.5037 |
| 7 | 127.5-128 | 12.0 | 1.5037 |
| 8 | 128-132 | 5.4 | 1.5040 |

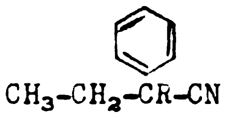
The residue and column holdup amounted to about one gram. The density of fraction five was determined at 25° with a pycnometer and found to be 0.9466. The total weight of all the cuts, except the first, was 62.2 g. This corresponds to a yield of 93.3% based on the starting nitrile.

## IV. THE ALKYLATION OF 2-PHENYLBUTANENITRILE WITH THE BUTYL CHLORIDES USING SODIUM HYDRIDE

In this series the mole ratios of the reagents were the same as were used in the sodamide series, namely, one mole sodium hydride, 0.94 mole butyl chloride, and 0.81 mole nitrile. The batch size was considerably smaller, 0.186 mole sodium hydride. The procedure used was substantially the same as that described in Section III. It was found that the sodium hydride could be added practically all at once at any temperature below the initial reflux temperature of 105°. In about one hour the reflux temperature would increase to 113° and remain there while it was stirred for an additional hour. After the reaction was complete a little alcohol was added to get rid of any sodium hydride before the addition of the water. Only the n-butyl, s-butyl and i-butyl derivatives were prepared and only one run was made of each. The data is summarized in Table II. The distillation residues again were negligible. Sufficient low boiling material (mainly the starting nitrile) was recovered to account for about 10-15% of the yield. In the case of the i-butyl isomer about 4% of high boiling material was obtained, which was not further investigated.

## TABLE II

## YIELDS AND PHYSICAL CONSTANTS FOR THE 2-BUTYL-2-PHENYLBUTANENITRILES



$CH_3-CH_2-CR-CN$

| R | Chloride Conversion % | Yield, % | B.p., °C. (5 mm.) | $D^{25}$ | $N^{25}_D$ | N,%[a] |
|---|---|---|---|---|---|---|
| n-Butyl | 100.0 | 87.8 | 127.5 | 0.9320 | 1.4971 | 6.90 |
| n-Butyl | 98.8 | 87.0 | 125.0 | 0.9325 | 1.4971 | |
| n-Butyl[b] | 77.0 | 73.0 | 128.0 | | 1.4973 | |
| s-Butyl | 100.0 | 93.3 | 127.5 | 0.9466 | 1.5038 | 6.91 |
| s-Butyl | 93.5 | 90.2 | 125.0 | 0.9470 | 1.5039 | |
| s-Butyl[b] | 92.0 | 80.7 | 123.0 | | 1.5038 | |
| i-Butyl | 91.0 | 89.6 | 120.0 | 0.9329 | 1.4977 | 7.02 |
| i-Butyl | 89.3 | 91.1 | 118.0 | 0.9326 | 1.4976 | |
| i-Butyl[b] | 93.0 | 79.3 | 118.0 | | 1.4976 | |
| t-Butyl | 75.2 | 79.0[c] | | | | |
| t-Butyl | 77.2 | 80.0[c] | | | | |
| t-Butyl[d] | | ca. 7.7 | 123-126 | 0.9571 | 1.5107 | 6.86 |

[a] Calculated for $C_{14}H_{19}N$; N, 6.96.

[b] Sodium hydride was used as condensing agent. Sodamide was used in the others.

[c] Recovered 2-phenylbutanenitrile.

[d] Based on the refractionation of the combined high boiling fractions from the two preceding runs. The solid melted at 57.2-58°.

# V. PREPARATION OF DERIVATIVES

## A. Attempted Hydrolysis of Nitriles

Reports in the literature state quite clearly that the hydrolysis of highly sterically hindered nitriles is very difficult (2,13,14,15,16). In the extreme cases the nitrile is converted to the amide or the sodium salt of the acid by treatment with alkali in a high boiling solvent such as glycerine or diethylene glycol, or to the amide by treatment with sulfuric acid. The amide may be converted to the acid by treatment with butyl nitrite and sulfuric acid.

Both alkaline and acid hydrolyses of these nitriles were attempted. The product made from the t-butyl chloride was available in only a very small amount, and no preparation of a derivative of it was attempted. In Tables III and IV are listed the attempts at hydrolysis by alkali and by acid, respectively. In the alkaline hydrolyses no reaction could be observed, except, in a few cases, for the evolution of a trace of ammonia. In all cases an insoluble oil was recovered when the reaction mixture was poured into water. The water soluble material which was obtained in the 90% sulfuric acid hydrolyses was assumed to be sulfonated product.

## TABLE III

## ATTEMPTED ALKALINE HYDROLYSIS OF THE 2-BUTYL-2-PHENYLBUTANENITRILES

| R | Reagents | Time, hours | Temperature, °C. | Results and remarks |
|---|---|---|---|---|
| n-Butyl | Butylene glycol, KOH | 4.0 | 190 | Complete miscibility. Results, negative. |
| n-Butyl<br>s-Butyl<br>i-Butyl | Ethylene glycol, KOH | 16.0 | 190-210 | Not miscible, frequent shaking, negative. |
| n-Butyl | Tripropylene glycol monomethyl ether, KOH | 0.5 | 190-240 | Negative |
| n-Butyl | Benzyl alcohol, KOH | 0.5 | 200-210 | Negative |
| n-Butyl | Butylene glycol LiOH | 0.5 | 190 | Negative |
| n-Butyl | Glycerine, LiOH | 0.5 | to 240 | Negative |
| n-Butyl | Tripropylene glycol, KOH | 0.5 | to 240 | Negative |
| n-Butyl | Tripropylene glycol, glycerine, KOH | 0.5 | to 240 | Negative |
| n-Butyl | Tripropylene glycol, NaOH | 0.5 | to 240 | Negative |
| n-Butyl | 60% KOH (fused) | 1.0 | 153-240 | Mechanical stirring, Results, negative. |

## TABLE IV

## ATTEMPTED ACID HYDROLYSIS OF THE 2-BUTYL-2-PHENYLBUTANENITRILES

| R | Reagents | Time, hours | Temperature, °C. | Results and remarks |
|---|---|---|---|---|
| n-Butyl | 90% Sulfuric acid, sodium nitrite (16) | 1.0<br>0.5 | 100-130 | Negative |
| i-Butyl | 95% Sulfuric acid | 0.5 | 80 | Sulfonated, negative |
| i-Butyl | Conc. HCl | 2.0 | 120-140 | Sealed tube, negative |
| s-Butyl | 75% Sulfuric acid | 0.5 | 140-190 | Negative |
| s-Butyl | 95% Sulfuric acid | 1.25 | 80 | Sulfonated, negative |
| n-Butyl | 75% Sulfuric acid, salt | 0.5 | 170-190 | Negative |
| n-Butyl | 95% Sulfuric acid | 0.25 | 80 | Sulfonated, negative |
| n-Butyl | Conc. HCl, dioxane | 2.0 | 80 | Negative |

## B. Reduction of Nitriles and Preparation of Derivatives

Work going on in this laboratory on another project showed that nitriles similar to these could be readily reduced to amines by use of lithium aluminum hydride and that the amines could be converted into substituted thioureas with isothiocyanates. The work was now directed towards use of this method for characterization of the new nitriles.

The reduction was carried out according to the procedure of Amundsen and Nelson (17). Four grams lithium aluminum hydride and 100 cc. dry ether were loaded into the reaction flask (the same apparatus as was used for the alkylations). About 10 g. nitrile in another 100 cc. dry ether was added during a few minutes at room temperature. After refluxing for about 45 minutes the mixture was cooled and 4 cc. water was added dropwise. This was followed by 3 cc. 20% sodium hydroxide and 14 cc. more water. Apparently these quantities were so chosen that the inorganic phase would come out solid and the separation of gelatinous aluminum hydroxide is avoided. The ether solution was filtered from the solid and the latter washed twice with fresh ether. After evaporation of the ether the oil was distilled at 5 mm. pressure without a fractionating column. The amines were practically water-white before distillation. The weights of the fractions taken and their boiling points are listed in Table V.

The second cuts were used for determination of the physical constants and the preparation of derivatives. The substituted urea and thioureas were prepared by mixing equal parts of the amine and $\alpha$-naphthylisocyanate or phenylisothiocyanate according to the usual procedure. Reaction took place readily with evolution of heat.

### TABLE V

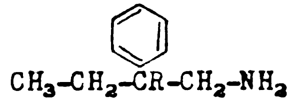
### DISTILLATION DATA FOR THE 1-AMINO-2-BUTYL-2-PHENYLBUTANES

| Fraction | n-Butyl | s-Butyl | i-Butyl |
|---|---|---|---|
| 1 | 133-134°<br>1.3 g. | 126-129.5°<br>1.4 g. | 115.5-119.5°<br>1.7 g. |
| 2 | 134°<br>5.4 g. | 129.5°<br>5.3 g. | 120.5-121°<br>5.2 g. |
| Residue and holdup | 0.8 g. | 1.3 g. | 1.5 g. |

The mixtures were warmed a little and then permitted to cool and crystallize. The solids were recrystallized from methanol. Phenylisothiocyanate was used for the n-butyl and the i-butyl isomers. However, it would not give a solid product with the s-butyl isomer so $\alpha$-napthylisocyanate was used to prepare a derivative. The properties of these amines are listed in Table VI.

## TABLE VI

### PROPERTIES OF THE 1-AMINO-2-BUTYL-2-PHENYLBUTANES



$$CH_3\text{-}CH_2\text{-}\overset{C_6H_5}{C}R\text{-}CH_2\text{-}NH_2$$

| R | B.p., °C. (5 mm.) | $D^{25}$ | $N_D^{25}$ | N,[a] % | Phenylthioureas<br>M.p., °C.[d] | <br>N,[b] % | <br>S,[b] % |
|---|---|---|---|---|---|---|---|
| n-Butyl | 134.0 | 0.9283 | 1.5725 | 6.51 | 118.5-119. | 8.04 | 9.53 |
| s-Butyl | 129.5 | 0.9471 | 1.5716 | 6.62 | 176-[c] 177 | 7.57[c] | |
| i-Butyl | 120.5 | 0.9279 | 1.5130 | 7.06 | 140.5-141 | 8.06 | 9.30 |

[a] Calculated for $C_{14}H_{23}N$: N, 6.82.

[b] Calculated for $C_{21}H_{28}N_2S$: N, 8.23; S, 9.42.

[c] α-Naphthylurea. Calculated for $C_{25}N_{30}N_2O$: N, 7.48.

[d] Melting points are corrected.

# DISCUSSION

The literature indicates quite definitely that the simple nitriles (9,10,11,12) polymerize easily with the alkali metals and with strong bases. The experiments with propionitrile and sodium hydride show that this polymerization is readily effected by sodium hydride also, and in fact, to such a degree that alkylation and arylation are practically impossible.

Sodamide apparently is such a mild reagent that it does not cause polymerization, but still is active enough to effect condensation with alkyl halides. However, Ziegler and Ohlinger (4) claimed that they did get some polymerization of propionitrile when they tried to alkylate it with sodamide. Bergstrom and Agostinho (1) did their work with chlorobenzene, potassium amide, and propionitrile, in liquid ammonia, and in addition thet used a second very large portion of potassium amide. They offered very little explanation of why this was necessary. It was noticed in this investigation that the addition of this second portion of amide caused a violent reaction while the addition of the first amide caused little noticeable reaction. The work of Ziegler and Ohlinger was done above room temperature.

The experiment with n-butyl bromide, propionitrile, and sodium hydride showed that with a more active halide some alkylation could be accomplished. This observation is in general agreement with earlier work in this laboratory which showed that ring substituted phenylacetonitriles could be alkylated with butyl and amyl bromides and with benzyl chloride using sodium hydride. In this latter case the nitrile being rather highly substituted would be less sensitive to polymerization.

The preparation from propionitrile, chlorobenzene, and potassium amide checked the results of Bergstrom and Agostinho (1) only approximately. They reported a fair yield of monophenylated product and did not isolate the diphenylated material. In the present work the lower boiling material was obtained in only a small quantity and boiled over such a wide range that it was not further investigated. However, the higher boiling fraction boiled at least reasonably constant and was probably the diphenylated product. However, this point was not proven. Only one experiment was run here and judging from the published information the above authors also ran only one experiment, so the information must be considered as being very meager.

The results obtained in the alkylation of 2-phenylbutanenitrile were in good agreement with past experience with nitriles of similar structure. The 2-phenylbutanenitrile is a quite highly substituted compound and would not be expected to be very susceptible to polymerization. The aliphatic halides are at least moderately active and thereby alkylation should be favored. It is interesting that the n-butyl chloride gives a lower yield of alkylated product than do the s-butyl and the i-butyl chlorides. This observation is in agreement with some present work in this laboratory with the isomeric amyl halides and also with the findings of Workman (2) in his work on the alkylation of hydratroponitrile with butyl halides and sodamide. He obtained about a 60% yield with the n-butyl isomers and about 70% yields with the s-butyl and i-butyl isomers. On the other hand Tilford and co-workers (22) alkylated cyclohexyl cyanide with amyl and butyl bromides using sodamide as a condensing agent, and found that in both cases the n-alkyl bromide gave about 20% more yield than the i-alkyl bromide. The fact that t-butyl chloride gave almost no yield of alkylated product was in agreement with the results of both Tilford (22) and Workman (2). It should be mentioned that with the other factors favorable, sodium hydride can be used as a condensing agent with fair results. The use of this condensing agent was investigated to only a minimum degree and it is very probable that the yields by this method could be increased with further study of the variables.

It might be worthy of mention here that the attraction for sodium hydride was the fact that it could be purchased and stored safely and the preparation of sodamide could be omitted from the experimental work. This objection to sodamide may no longer be serious. The material used in this work was purchased in the dry state, kept in storage for several years, and was found to be in very good condition. Older experience as reported is that the material often deteriorated in storage and became hazardous due to the formation of sodium nitrite due to air oxidation in the presence of moisture.

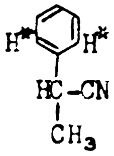
In connection with the difficulty encountered in the attempts to hydrolyze these nitriles it is interesting to examine them from the standpoint of the *six-number* concept advanced by Newman (23). He made a study of the rates of esterification of a number of acids having varying degrees of steric hindrance and found that the rate decreases as the *six-number* increases. His *six-number* is defined as the number of atoms within the molecule which occupy a six position if the carbonyl oxygen is counted as one. In Figure I are shown the configurations of the nitriles made by Workman (2) (I through V) and of those made in this investigation by alkylation of 2-phenylbutanenitrile (VI through IX). Each sixth atom from the nitrogen atom is starred (*). The *six-numbers* are shown for each nitrile in parenthesis. Nitrile I could be hydrolyzed readily by heating it with sulfuric acid (75%) for fifteen minutes on the steam bath. II and III could not be hydrolyzed by any of the more moderate methods. However, by heating with potassium hydroxide and amyl alcohol at reflux for ten hours, hydrolysis was finally accomplished. These two nitriles have a *six-number* of 5. IV and V with *six-numbers* of 8 and 11 respectively could not be hydrolyzed in any manner by Workman (2). The experience with the nitriles VI through IX, which could not be hydrolyzed, has already been described in an earlier Section of this thesis. From the standpoint of their *six-numbers* this non-reactivity is just what would be expected.

For some reason the steric factors which prevent hydrolysis do not interfere with the reduction to amines.

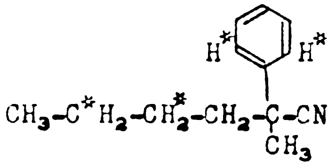
FIGURE I

Six-numbers of Sterically Hindered Nitriles

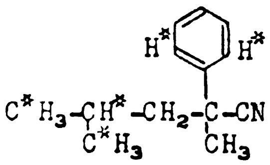
I (2)



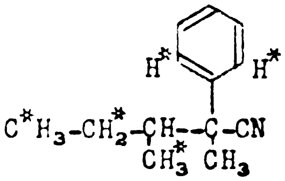
II (5)



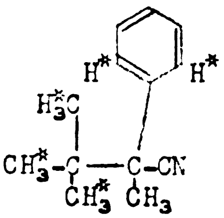
III (5)



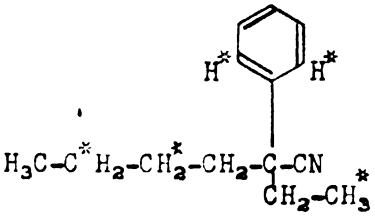
IV (8)



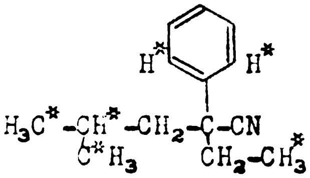
V (11)



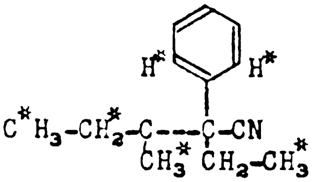
VI (8)



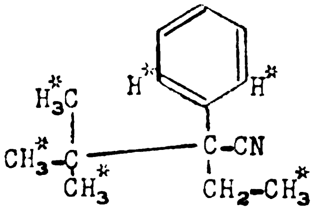
VII (8)



VIII (11)



IX (14)



# SUMMARY

1. Attempts to arylate propionitrile with bromobenzene using sodium hydride as a condensing agent were unsuccessful. Much polymerisation of the nitrile occurred.

2. Propionitrile was arylated in approximately 60% yield by the use of potassium amide according to the special procedure of Bergstrom and Agostinho (1).

3. One attempt to alkylate propionitrile with n-butyl bromide and sodium hydride resulted in 23.6% yield of monoalkylated product.

4. One attempt to arylate phenylacetonitrile with bromobenzene and sodium hydride was unsuccessful.

5. Alkylation of 2-phenylbutanenitrile with the four isomeric butyl chlorides and sodamide was successful with the n-butyl, s-butyl and i-butyl chlorides, but unsuccessful in the case of the t-butyl chloride. In the latter case about 8% yield was obtained. The n-butyl isomer gave about an 88% yield, while the s-butyl and the i-butyl isomers gave yields of about 90-91%.

6. It was found that 2-phenylbutanenitrile could be alkylated with butyl chloride when sodium hydride was used as a condensing agent. The yields from the n-butyl, s-butyl, and i-butyl chlorides were about 12% lower than the yields when sodamide was used and were in the same order. No run was made with t-butyl chloride in this series.

7. Many attempts were made to hydrolyze the 2-butyl-2-phenylbutanenitriles for the purpose of characterization. These were all unsuccessful. It was found that these nitriles could be reduced quite easily with lithium aluminum hydride to the corresponding amines. Derivatives were prepared from the amines. Physical constants of the nitriles and the amines were determined.

8. The resistance to hydrolysis of these nitriles and of the 2-butyl-2-phenylpropanenitriles prepared by Workman (2) was shown to correlate with the <u>six-number</u> concept advanced by Newman (23).

## SUGGESTIONS FOR FURTHER WORK

1. The reaction of propionitrile with chlorobenzene in liquid ammonia with potassium amide as a condensing agent would be an interesting subject for further study. It is the only example, as carried out by Bergstrom and Agostinho (1), of a successful arylation of a nitrile to be found in the literature. Investigations could be made to see how generally applicable this technique is, to try to get more information regarding the intrinsic nature of the reaction and why the second addition of amide is needed, to see if other media besides liquid ammonia can be used, and perhaps to determine whether sodamide will work equally well, since there are definite advantages in working with sodamide rather than with potassium amide.

2. In the experiments with sodium hydride, bromobenzene, and propionitrile a substantial degree of bromide conversion was obtained. It would be interesting to find out what happens to the bromobenzene and what conditions are required to make it happen. Information such as this would very likely provide some clues as to how to vary the conditions of the alkylation in such a manner as to improve the yields.

3. Obviously the alkylation of 2-phenylbutanenitrile with t-butyl chloride could stand some further study. Variations in temperature of reaction, working in a different medium, e.g. liquid ammonia, and the use of other condensing agents would provide subjects for further study.

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