[Contribution from the Chemical Laboratories of Stanford University]

SOME POTASSIUM AMIDE-ACTIVATED PHENYLATIONS IN LIQUID AMMONIA (1)

PHILIP H. DIRSTINE and F. W. BERGSTROM

Received September 4, 1945

The phenyl halides react readily with strong bases such as the alkali amides in liquid ammonia and the alkali dialkylamides in ether (2) but fail to react within a period of a day or so with less basic compounds of the type of potassium anilide, potassium diphenylamide, and potassium quinaldyl. Reaction nevertheless does occur if potassium amide is added to a solution of any of the salts enumerated above, provided that a phenyl halide is also present. Wright and Bergstrom (3) thus prepared 2-benzylquinoline, 2-benzohydrylquinoline, and 2-triphenylmethylquinoline in accordance with the equations below.

$$\underset{\text{Quinaldine}}{C_9H_6NCH_3} \xrightarrow{KNH_2} C_9H_6NCH_2K \xrightarrow[KNH_2]{C_6H_5Cl} C_9H_6NCH_2C_6H_5 \qquad (I)$$

$$\xrightarrow{KNH_2} C_9H_6NCHKC_6H_5 \xrightarrow[KNH_2]{C_6H_5Cl} C_9H_6NCH(C_6H_5)_2 \xrightarrow{KNH_2}$$

$$C_9H_6NCK(C_6H_5)_2 \xrightarrow[KNH_2]{C_6H_5Cl} C_9H_6NC(C_6H_5)_3$$

The benzohydrylquinoline and triphenylmethylquinoline had the correct composition, but their structure was not definitely proved. It was for the purpose of orienting these compounds and of utilizing them in the preparation of free groups containing a quinoline nucleus that the present investigation was undertaken. Incidental to this a number of other catalytic phenylations have been studied.

The reactions of Wright and Bergstrom, shown in equation (I), have been confirmed. The 2-benzohydrylquinoline was oxidized to 2-quinolyldiphenylcarbinol, $C_9H_6NC(OH)(C_6H_5)_2$, which was found to be identical with the compound prepared by the action of an excess of phenylmagnesium bromide on ethyl quinaldate, thus proving its structure. Attempts to prepare 2-benzohydrylquinoline by reducing the carbinol, or by a Friedländer or Pfitzinger synthesis from 1,1-diphenylacetone, failed, as did also an attempt to make diphenyl-2-quinolylbromomethane from tribromoquinaldine, benzene, and aluminum chloride. It has not yet proved possible to synthesize 2-triphenylmethylquinoline. An interesting reduction of ω,ω,ω-tribromoquinaldine to ω,ω-dibromoquinaldine was effected by heating the former with concentrated sulfuric acid and a small amount of alcohol; presumably the reaction follows the equation,

$$C_9H_6NCBr_3 + C_2H_5OH = CH_3CHO + HBr + C_9H_6NCHBr_2 \qquad (II)$$

4-Methylquinoline (lepidine) forms alkali metal salts in liquid ammonia (4) which can be alkylated to give homologous 4-substituted quinolines. The potassium salt of lepidine can be catalytically phenylated with chlorobenzene and potassium amide to give 4-benzylquinoline and 4-benzohydrylquinoline; 4-triphenylmethylquinoline has not been isolated in any of our experiments. The 4-benzohydrylquinoline is readily oxidized to the 4-quinolyldiphenylcarbinol of Remfrey and Decker (5). Since 2,4-dimethylquinoline has two reactive methyl groups, its potassium salt is doubtless a mixture, and a catalytic phenylation gave several products, none of which could be isolated in a state of purity. 2-*n*-Propylquinoline could not be phenylated in accordance with the present method, even though it had previously been alkylated in ether (but not in liquid ammonia) (6). 9-Methylphenanthridine forms a potassium salt which is not very soluble in ammonia at −33°; it is apparently this factor that prevents its catalytic phenylation.

On the other hand, 2-methylpyridine is readily phenylated to give a mixture of 2-benzylpyridine, 2-benzohydrylpyridine, and 2-triphenylmethylpyridine in fairly good over-all yield, but 2,4-dimethylpyridine is converted largely to tars under the same conditions.

o-Tolunitrile may be regarded as a vinylene homolog of acetonitrile, and therefore might be expected to have an active hydrogen atom in the methyl group. This was found to be true, since the potassium salt of *o*-tolunitrile was phenylated to give *o*-benzylbenzonitrile and *o*-benzohydrylbenzonitrile (*o*-cyanotriphenylmethane).

EXPERIMENTAL

The experimental method has been partly described in previous articles (7). Briefly, the apparatus consists of a 500-ml. 3-necked flask and a 1000-ml. 3-necked flask, so arranged that the contents of the former could be siphoned into the latter, which was fitted with a good mechanical stirrer. Potassium amide (from 6 g. or 0.15 atom of metallic potassium, with an iron oxide catalyst) was prepared in about 500 ml. of liquid ammonia in the larger flask, and to this was added an equivalent of quinaldine, lepidine or other compound whose potassium salt it was desired to form. Chlorobenzene (26–28 g., about 0.25 mole) was then introduced, and potassium amide solution (from 6 g. potassium, 0.15 atom) was forced over from the smaller flask with good stirring. Ammonium chloride equivalent to the potassium used (about 16 g.) was added at the end of about an hour to stop the reaction, and the ammonia was allowed to evaporate. Water was introduced to dissolve inorganic salts, and then benzene (100–150 ml.) to dissolve organic material. The treatment of the benzene solution depended upon the nature of the products that were formed; bases were generally removed by shaking with strong hydrochloric acid, and both the acid and the benzene solutions were worked up, as described later.

Phenylation of quinaldine. The catalytic phenylation of quinaldine gives 2-benzylquinoline, 2-benzohydrylquinoline, and 2-triphenylmethylquinoline in agreement with the work of Wright and Bergstrom (3). The relative amount of the triphenylmethylquinoline appeared to be increased by alternate addition of the chlorobenzene and the potassium amide to the solution of the potassium quinaldyl.

2-Benzohydrylquinoline (0.5 g.) was dissolved in 5 ml. of glacial acetic acid and the solution gently heated. Chromic anhydride was slowly added in small quantities until the brown color of the anhydride no longer changed to the green of the chromic ion. Half of the solvent was evaporated under suction and the solution cooled in ice. The needles that separated were crystallized from a 50–50 mixture of benzene and acetone; m.p. 188.5–189.5° corr.

Anal. Calc'd for $C_{22}H_{17}NO$: C, 84.88; H, 5.50; N, 4.50.
Found: C, 84.90; H, 5.93; N, 4.47.

Melting points of mixtures with the 2-quinolyldiphenylcarbinol prepared by the action of phenylmagnesium bromide on ethyl quinaldate were the same.

Ethyl quinaldate was prepared by refluxing for six hours a solution of quinaldic acid (80 g., 0.46 mole) in absolute ethanol (400 ml.) to which 50 cc. of conc'd sulfuric acid had been slowly added. The alcohol was distilled until a fairly viscous solution remained; this was poured into water and neutralized with ammonia. The heavy oil that separated was washed with water, dried, and distilled *in vacuo*; b.p. 180°/14 mm.; yield, 47 g., or 51%. Kindler (8) previously prepared this ester by the hydrochloric acid method, and gives the boiling point 186–188°/13 mm. (prob. corr.).

Phenylmagnesium bromide (0.50 mole) was prepared in 500 ml. of absolute ether in a 2-liter 3-necked flask fitted with reflux condenser, mercury sealed stirrer, and a dropping-funnel. Ethyl quinaldate (0.23 mole, 46.2 g.), dissolved in 200 ml. of absolute ether, was added over a period of an hour with stirring. At the end of this time the mixture was cautiously treated with dil. sulfuric acid (20 ml. in 300 ml. water). The white crystals that separated were filtered and washed with water, dried, and crystallized from a 50–50 acetone-benzene mixture. The melting point was 188.5–189.5°, and the yield was 47.3 g. (66%). The hydrochloride, prepared by passing dry hydrochloric acid gas through a solution of the carbinol in warmed benzene, melted, after crystallization from this solvent, at 178–179°, dec. It was sparingly soluble in hot benzene, and could not be crystallized from alcohol without hydrolysis to the carbinol.

Anal. Calc'd for $C_{22}H_{17}NO \cdot HCl$: C, 75.96; H, 5.22; Cl, 10.19.
Found: C, 76.04; H, 5.10; Cl, 9.71.

Phenylation of lepidine. The standard procedure was followed, except that in some of the experiments the amount of potassium amide added from the small flask was increased to 0.20–0.24 mole. The benzene solution of the reaction product was shaken for some time with 8 *N* hydrochloric acid in a thick-walled stoppered Erlenmeyer flask. The benzene and the aqueous acid solution were decanted from the tarry crystals of 4-benzohydrylquinoline hydrochloride, and the latter washed with 8 *N* hydrochloric acid. The benzene layer was separated and discarded (only tarry materials were obtained from it), the aqueous solution filtered to remove some benzohydryl quinoline hydrochloride, and then made basic with sodium hydroxide. The resulting oil was extracted with benzene, and the latter distilled; 4-benzylquinoline came over at 220–225° (uncor.) at 19 mm., or 180–190° at about 2 mm. The combined precipitates of benzohydrylquinoline hydrochloride were washed with a little acetone to remove tar, and either crystallized from water or dilute alcohol containing a little hydrochloric acid, or else converted to the free base by boiling with dilute sodium hydroxide solution. The benzohydrylquinoline was crystallized from 75% ethanol with the use of decolorizing carbon if necessary.

Alternately, the benzene extract of the reaction mixture was directly distilled, finally *in vacuo* to obtain 4-benzylquinoline (flask heated in an oil-bath). The tarry residue that did not distil was removed from the flask with warm acetone, and the latter almost entirely removed by distillation. Several volumes of ligroin were stirred in, giving crystals of benzohydrylquinoline, which were recrystallized from 75% alcohol with the use of Norit.

The yields were variable. In two experiments, the yield of 4-benzylquinoline was 37%, and that of 4-benzohydrylquinoline about 3%; in another experiment, 20.6% of crude benzohydrylquinoline hydrochloride was obtained, with only a small amount of 4-benzylquinoline.

4-Benzohydrylquinoline hydrochloride melts with decomposition at some temperature between 260° and 290° (rate of heating is important). For analysis it was crystallized several times from alcohol and dried at 100°.

Anal. Calc'd for $C_{22}H_{17}N \cdot HCl$: C, 79.62; H, 5.47; N, 4.22.
Found: C, 79.68, 79.61; H, 5.43, 5.51; N, 4.43, 4.39.

4-Benzohydrylquinoline melts at 146–147°, uncor.; for analysis it was crystallized several times from 80% alcohol.

Anal. Calc'd for $C_{22}H_{17}N$: C, 89.45; H, 5.80; N, 4.74.
Found: C, 89.33, 89.24; H, 5.90, 5.82; N, 4.85, 4.89.

The 4-benzylquinoline was identified by conversion to the picrate, m.p. 177–178° [literature (9), 178°]. 4-Benzohydrylquinoline was oxidized by chromic anhydride to the known (5) 4-quinolyldiphenylcarbinol, m.p. 247° (literature, 247.5°), following the directions for the preparation of 2-quinolyldiphenylcarbinol.

Phenylation of 2,4-dimethylquinoline. The phenylation of the potassium salt of 2,4-dimethylquinoline gave a complex mixture from which it was difficult to separate chemical individuals. One crystalline fraction (soluble in acetone but not in ether) melted at 163–165°; another fraction, m.p. 200–222°, was insoluble in both acetone and ether. One of the distilled fractions gave a picrate of the composition of a picrate of a methyl benzylquinoline.

Phenylation of 2-picoline. 2-Picoline (0.1 mole) was phenylated according to the standard procedure. The insoluble crystalline material from the benzene-water hydrolysate was filtered, the benzene layer evaporated, and finally heated under slightly reduced pressure to remove all solvent, 2-picoline, and chlorobenzene. A second crop of crystals separated from the cooled liquid. The total yield of material, crystallized from benzene and melting at 241° uncor., was 5.8 g., including the 2 g. recovered below (18%). This is undoubtedly the unknown triphenyl-2-pyridylmethane.

Anal. Calc'd for $C_{24}H_{19}N$: C, 89.68; H, 5.96; N, 4.36.
Found: C, 89.46; H, 5.96; N, 4.50.

The liquid separated from the second crop was extracted with 8 *N* hydrochloric acid, the latter made basic with sodium hydroxide, and in turn extracted with benzene. These extracts were distilled, finally at 12 mm., to obtain three fractions: 133–137° (5 cc.); 186–189° (5 cc.) and 210–215° (2 g.). The last fraction was crystallized from alcohol and proved to be triphenylpyridylmethane. The first two fractions were redistilled at 1 mm. to obtain 4.1 g. of an oil boiling at 93–94° (24%; 2-benzylpyridine) and 4.3 g. boiling at 163–164° (18%; 2-benzohydrylpyridine). The latter crystallized on standing and then melted at 62–63°, in agreement with the value given by Chichibabin and Benevolenskaya (10).

Anal. Calc'd for $C_{18}H_{15}N$: C, 88.13; H, 6.16; N, 5.71.
Found: C, 88.12; H, 6.30; N, 6.25.

The oil boiling at 93–94°/1 mm. gave a picrate melting at 139°; 2-benzylpyridine picrate melts at 140° (11).

Phenylation of o-tolunitrile. The benzene solution of the reaction product was shaken with 8 *N* hydrochloric acid in a separatory funnel to remove aniline and other bases, and distilled, first at 760 mm. to remove solvent, and then at 2 mm. *o*-Benzylbenzonitrile came over at 158–160°, and was converted to *o*-benzylbenzoic acid m.p. 117° [literature, 117° (12)], by heating for 18 hrs. with methyl alcoholic sodium hydroxide, and acidifying with dil. sulfuric acid. *o*-Benzohydrylbenzonitrile came over as an oil at 200–210°; crystallizations from alcohol gave crystals melting at 88°. Drory (13) reports the melting point 89°.

Anal. Calc'd for $C_{20}H_{15}N$: C, 89.18; H, 5.61.
Found: C, 89.48; H, 5.87.

The yield of benzylbenzonitrile was 8.2 g. from 0.13 mole of *o*-tolunitrile (32%), and of *o*-benzohydrylbenzonitrile 3.1 g., or 8.8%.

ω,ω-Dibromoquinaldine. Tribromoquinaldine (18.9 g., 0.05 mole), ethyl alcohol (20 cc. of 95%), and conc'd sulfuric acid (5 cc.) were heated in a 100-cc. flask with take off of distillate. When the temperature (thermometer in the liquid) reached 102–105°, a brisk evolution of gas (mostly HBr) was observed, and the solid phase slowly dissolved. When the gas evolution had ceased, heating was continued for a few minutes to drive off dissolved hydrobromic acid, but was discontinued at the first sign of darkening of the liquid. After cooling, the product was poured into 500 cc. of cold water, and the flask rinsed out with the same solvent. The mixture was stirred for some time, and then filtered to remove dibromoquinaldine, which was crystallized from ethanol; yield, 14.7 g., or 98%; m.p. 119–120°. Hammick (14) reports the melting point as 120°.

Anal. Calc'd for $C_9H_6NCHBr_2$: Br, 53.0. Found: Br, 52.9.

Methyl alcohol, *n*-propyl alcohol, and isopropyl alcohol did not replace the ethanol in this preparation. Only with the two latter (and at about 130°) was dibromoquinaldine obtained, but there was much charring. Some acetal was also formed in the reaction with ethanol.

SUMMARY

1. 2-Picoline, quinaldine, lepidine, and *o*-tolunitrile are phenylated by adding potassium amide to a solution of their potassium salts and chlorobenzene in liquid ammonia. The following compounds were prepared in this manner: 2-Benzylpyridine, 2-benzohydrylpyridine, 2-triphenylmethylpyridine, 2-benzylquinoline, 2-benzohydrylquinoline, 2-triphenylmethylquinoline, 4-benzylquinoline, 4-benzohydrylquinoline, *o*-benzylbenzonitrile, *o*-benzohydrylbenzonitrile.

2. The structure of the 2-benzohydrylquinoline prepared by Wright and Bergstrom was confirmed by oxidizing it to diphenyl-2-quinolylcarbinol, which was also synthesized by the action of phenylmagnesium bromide on ethyl quinaldate.

3. 2-*n*-Propylquinoline, 2,4-dimethylquinoline, 2,4-dimethylpyridine, and 9-methylphenanthridine were not successfully phenylated by this method.

STANFORD UNIVERSITY, CALIF.

REFERENCES

(1) DIRSTINE, PHILIP H. Doctorate thesis, Stanford University.
(2) BERGSTROM, WRIGHT, CHANDLER, AND GILKEY, *J. Org. Chem.*, **1**, 170 (1936).
HORNING, C. H. Thesis, Stanford University 1939.
GILMAN AND AVAKIAN, *J. Am. Chem. Soc.*, **67**, 349 (1945).
(3) WRIGHT AND BERGSTROM, *J. Org. Chem.* **1**, 179 (1936).
(4) BERGSTROM, *J. Am. Chem. Soc.*, **53**, 4071, 4076 (1931).
(5) REMFREY AND DECKER, *Ber.*, **41**, 1008 (1908).
(6) BERGSTROM, *J. Am. Chem. Soc.*, **53**, 4075 (1931) and unpublished work.
(7) SEIBERT AND BERGSTROM, *J. Org. Chem.*, **10**, 544 (1945).
URNER AND BERGSTROM, *J. Am. Chem. Soc.*, **67**, 2108 (1945).
(8) KINDLER, *Ber.*, **69**, 2798, 2806 (1936).
(9) RABE AND PASTERNACK, *Ber.*, **46**, 1029 (1913).
(10) CHICHIBABIN AND BENEVOLENSKAYA, *Ber.*, **61**, 551 (1928).
(11) CHICHIBABIN, *J. Russ. Phys.-Chem. Soc.*, **33**, 249 (1901); *Chem. Zentr.*, **1901**, 2, 128.
(12) CASSIRER, *Ber.*, **25**, 3022 (1892).
(13) DRORY, *Ber.*, **24**, 2572 (1883).
(14) HAMMICK, *J. Chem. Soc.*, 1302 (1926).