[Contribution from the Chemical Laboratory of Iowa State College]

ORIENTATION IN THE METALATION OF AMINES

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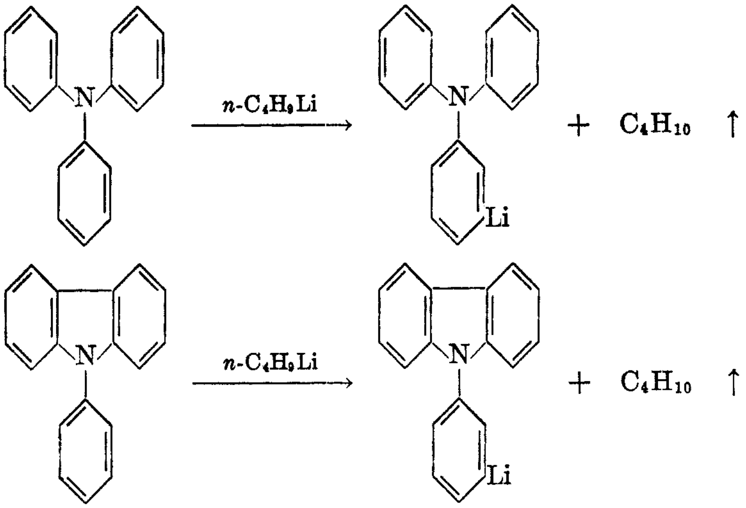
In nuclear metalations by organoalkali compounds, substitution occurs almost invariably *ortho* to the hetero element or to the group containing the hetero element (1). Among compounds in which the hetero element is nitrogen, the following have been found to conform to the rule: aniline (2), N-*n*-butylaniline (2), diphenylamine (2), N,N-dimethylaniline (3), carbazole (4), N-ethylcarbazole (4), and N-phenylcarbazole (5). This list comprises a variety of primary, secondary, and tertiary amines. The exception to this rule is the *meta* metalation (6) of triphenylamine, especially interesting because of the close chemical structure between this amine and N-phenylcarbazole (Chart I).

CHART I



It is unlikely that the electronegativity of the two phenyl groups in triphenylamine can account for the anomolous metalation of the remaining phenyl group, since diphenylamine metalates according to rule. In the latter molecule, the hydrogen atom and the phenyl group constitute the orienting factors, and the influence of the phenyl group must outweigh that of the hydrogen.

It is proposed here that the *meta* metalation of triphenylamine results from the steric hindrance of the large, free-rotating phenyl groups. Obviously, in triphenylamine, the three valence bonds of the nitrogen atom are equidistant from each other. However, in N-phenylcarbazole, this equidistance must conceivably be destroyed as a consequence of the union of two of the phenyl groups in the formation of the carbazole nucleus, thereby establishing less hindrance

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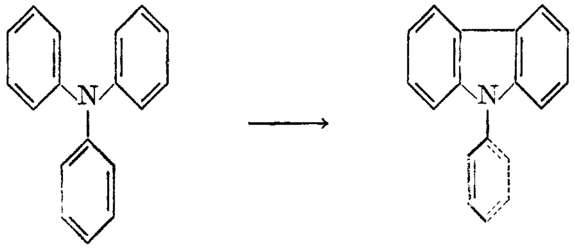
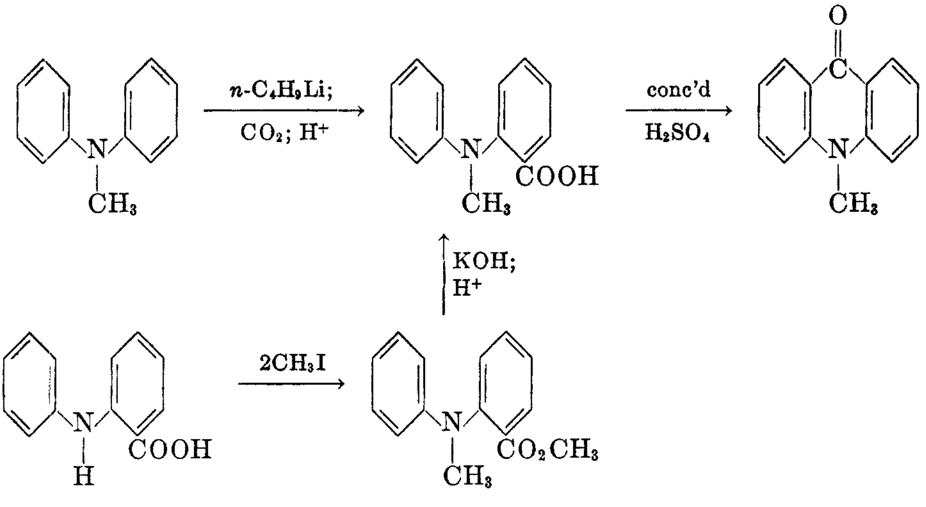
around the nitrogen valence bond attached to the remaining phenyl radical. For the purpose of illustration, the effect is exaggerated in equation 1. Also, the co-planarity induced on the two phenyl groups forming the carbazole moiety destroys the free rotation of these groups with an accompanying decrease in their steric influence. The net result of these structural changes spells more free space for the *ortho* hydrogen atoms of the phenyl radical, especially at the moment of plane perpendicularity between the phenyl and carbazole radicals (equation 1). It is this phenyl group which undergoes *ortho* metalation (5).

1.



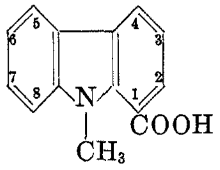
Conversely, if steric hindrance accounts for the abnormal behavior of triphenylamine towards *n*-butyllithium, then replacement of one of the phenyl groups by a much smaller one, such as the methyl radical, should effect resumption of orthodox metalation. Such is actually the case. The position of *ortho* metalation in N-methyldiphenylamine was ascertained in two ways: (a) by ring closure of the N-methyl-N-phenylanthranilic acid to N-methylacridone, and (b) by N-methylation of authentic N-phenylanthranilic acid (Chart II).

CHART II

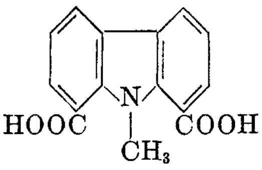


Retention of *meta* metalation is to be expected in a compound in which the phenyl group of triphenylamine is replaced by another large group, such as possibly the cyclohexyl, *tert*-butyl, or isobutyl. Unfortunately, the small quantity of gummy acid obtained from the metalation of cyclohexyldiphenylamine could not be purified for identification. Interestingly, the amine, obtained by the N-phenylation of N-cyclohexylaniline, could not be prepared by cyclohexylation of either diphenylamine or sodium diphenylamide.

Metalation of N-methylcarbazole yields, subsequent to carbonation, both a mono- and a dibasic acid. The cumulative evidence for the *ortho* metalation of a large variety of aromatic amines, in which the groups attached to the nitrogen are H-H, H-alkyl, H-aryl, alkyl-alkyl, and alkyl-aryl, suggests very strongly that the carboxyl groups are located in the 1- and 8-positions (I, II). The isolation of the dibasic acid is especially interesting because N-ethylcarbazole undergoes only monometalation, in the *ortho* position, even with a large excess of metalating agent (4). These facts conform with the theory of steric hindrance applied to the metalation of amines. The larger ethyl group[2] makes dimetalation more difficult. Possibly related is the failure of N-ethyldiphenylamine to metalate (7) in contrast to the behavior of N-methyldiphenylamine. Also, the difference in behavior between N-ethyldiphenylamine and N-ethylcarbazole is noteworthy. It is very likely that the joining of the two phenyl groups to form the carbazole nucleus reduces the hindrance present in the former molecule. In all the above cases, it is possible that steric factors may influence not only the initial metalation, but also the subsequent reaction (in these examples, carbonation) in which the metalation product is derivatized. For example, it is conceivable that triphenylamine may be metalated to a small extent in the *ortho* position, but that the *o*-lithio compound reacts so slowly with carbon dioxide that no recognizable amount of the *o*-acid is formed.



I



II

The scope of these reactions is being examined.

EXPERIMENTAL

Metalation of N-methyldiphenylamine. (*a*) A 50-cc. ethereal solution of 18.3 g. (0.1 mole) of freshly distilled methyldiphenylamine was added to 0.126 mole of *n*-butyllithium in 175 cc. of ether. After 24 hours of reflux, the colorless solution was carbonated in an ethereal slush of Dry Ice. Acidification of the aqueous, alkaline layer yielded an oil, from which a green crystalline material precipitated after extended cooling. Recrystallized from ethanol, the pale green acid melted at 102.5–103.5°. The yield was 1.0 g. (4.4%).

Anal. Calc'd for $C_{14}H_{13}NO_2$: Neut. equiv., 226.2; N, 6.16.

Found: Neut. equiv., 230.5, 231.0; N, 6.06, 6.28.[3]

(*b*) Treatment of 0.1 mole of N-methyldiphenylamine with 0.2 mole of *n*-butyllithium for 40 hours increased the yield of crude acid (m.p. 96–101°) to 3.2 g. (14.1%). Twice re-

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[2] Adams and Stewart, *J. Am. Chem. Soc.*, **63**, 2859 (1941), demonstrated the markedly increased steric effect of the ethyl radical over the methyl in racemization studies on arylamines.

[3] Nitrogen analysis by Mr. A. L. Dittman.

crystallized from petroleum ether (b.p. 60–68°), the crystals melted at 103–104°, and the yield of pure product was 1.8 g. (7.9%).

Cyclization of N-methyl-N-phenylanthranilic acid. One gram of the acid, isolated from the metalation and carbonation of methyldiphenylamine, was dissolved in 10 cc. of cold, concentrated sulfuric acid, and warmed on a water bath for 1½ hours. The solution turned red-brown with a marked blue-green fluorescence. After careful dilution with water, the precipitate was filtered off, washed, digested in boiling dilute alkali, filtered once more, and crystallized from ethanol. The pale yellow crystals melted at 198–199°, and a mixture melting point with authentic N-methylacridone, prepared by the procedure of Bergmann and Blum-Bergmann (8), showed no depression. The yield was 0.7 g. (76.4%).

N-Methylation of N-phenylanthranilic acid. N-Phenylanthranilic acid (3 g., 0.014 mole), 5 g. (0.035 mole) of methyl iodide, and 0.6 g. (0.015 mole) of sodium hydroxide in 13.0 cc. of water were refluxed for 24 hours. Then 20 cc. of a 20% solution of sodium hydroxide was added and the mixture was boiled for an additional hour to destroy excess methyl iodide and to hydrolyze the methyl ester. When a clear, homogeneous solution was formed, the contents were diluted with 200 cc. of water and acidified with conc'd hydrochloric acid. The yield of crude N-methyl-N-phenylanthranilic acid, melting at 92–97°, was 3.0 g. (94.4%).

After recrystallization from an ether-petroleum ether (b.p. 60–68°) mixture, the pale green needles were obtained in a yield of 1.6 g. (50.3%). The acid melted at 104–104.5°, and admixed with the acid obtained from the metalation of N-methyldiphenylamine, it melted at 103–104°.

N-Cyclohexylaniline. This amine, distilling at 150–151°/16 mm., was obtained in 46.4% yield from the reaction between 1.3 moles of aniline and 0.4 mole of cyclohexyl bromide (9).

N-Cyclohexyldiphenylamine. (*a*). N-Cyclohexylaniline (17.5 g., 0.1 mole), 22.4 g. (0.11 mole) of iodobenzene, 8.3 g. (0.06 mole) of potassium carbonate, and 3.0 g. of copper powder were heated in a metal bath at 220–240° for 48 hours. After cooling, the crystalline mass was dissolved in ether and the copper was removed by filtration. The ethereal filtrate was dried over Drierite, filtered, and the ether removed by distillation. The oily residue was distilled under a vacuum. The yellow fraction, boiling at 156–160°/3–4 mm., solidified on cooling. Twice recrystallized from an ethanol-ethyl ether mixture, the large white crystals melted at 74–75.5°. The yield was 11.6 g. (46%).

In a preliminary run conducted at 180–200° for 18 hours, the yield was 13.1%.

Anal. Calc'd for $C_{18}H_{21}N$:[4] C, 86.0; H, 8.44; N, 5.57.

Found: C 85.9; H, 8.34; N, 5.73.

(*b*). A mixture of 33.8 g. (0.2 mole) of diphenylamine, 46.0 g. (0.29 mole) of cyclohexyl bromide, 16.4 g. (0.2 mole) of powdered, anhydrous sodium acetate, and 0.3 g. of iodine was heated in an oil-bath at 140° for 30 hours. The contents were poured into ice-water and the oil which separated solidified after a short while. The recovery of crude diphenylamine was almost quantitative.

(*c*). Cyclohexyl bromide (16.3 g., 0.1 mole) and an equivalent of sodium diphenylamide, prepared from *n*-butylsodium and diphenylamine, failed to react after being heated and stirred for 20 hours in a nitrogen atmosphere. After hydrolysis and working up in a customary manner, the diphenylamine was recovered.

Metalation of N-cyclohexyldiphenylamine. A solution of 8.8 g. (0.035 mole) of the amine and 0.05 mole of *n*-butyllithium in 90 cc. of ether were kept under reflux for 23 hours. At the end of this time, color test I (10) was positive and color test IIa (11) negative. After carbonation and hydrolysis, the alkaline layer yielded a gummy acid, which could not be purified for identification. The yield of crude acid was 0.3 g.

N-Methylcarbazole. This compound has already been prepared in excellent yield (12). However, a procedure used for the N-ethylation of 2,8-dibromocarbazole was preferred (13), since it eliminates direct, personal handling of the poisonous methyl sulfate. To a hot solution of 45 g. (0.27 mole) of carbazole in 225–250 cc. of acetone was added in one portion 60 g. (0.48 mole) of practical methyl sulfate (hood!). A solution of 45 g. sodium hydroxide in 30 cc. of water was added dropwise over a 20-minute period to the hot, agitated solution

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[4] Carbon and hydrogen analyses by Dr. R. V. Christian.

of carbazole in acetone. Stirring under reflux was continued for 2 hours and the contents then were poured into ice-water. Crude N-methylcarbazole (m.p. 85–87°) precipitated out in almost quantitative yield. Recrystallized from 95% ethanol in beautiful, nacreous crystals, the compound melted at 88–89°. The yield was 44 g. (90.5%).

Metalation of N-methylcarbazole. A solution of 14.5 g. (0.08 mole) of N-methylcarbazole and 0.1 mole of *n*-butyllithium in 180 cc. of ethyl ether was refluxed and stirred for 24 hours, at the end of which time the dark red solution gave a positive color test I and a negative color test IIa. After carbonation and hydrolysis, the emulsion was broken up by acidification, followed by addition of dilute alkali. The aqueous alkaline layer was filtered, boiled with Norit, and refiltered. The cooled filtrate was acidified with dilute mineral acid to yield 5.5 g. of crude mixed acids.

From the ether layer, 8 g. (55%) of N-methylcarbazole was recovered.

The crude acid was digested in 100 cc. of refluxing benzene for 15 minutes and filtered through a steam-funnel. The residue was washed with 5–10 cc. of hot benzene and the washings discarded. The residue, recrystallized in small white needles from hot ethanol, melted at 252–254° with evolution of gas. Since the neutral equivalent showed that the compound was a dicarboxylic acid of N-methylcarbazole, the yield of 0.8 g. was 3.4% of the theoretical.

Anal. Calc'd for $C_{15}H_{11}NO_4$:[5] Neut. equiv., 134.5; C, 66.94; H, 4.12.
Found: Neut. equiv., 138.2; C, 67.07; H, 4.09.

The benzene extract was concentrated to about one-half of the original volume and cooled; the crude monobasic acid which precipitated out melted at 176–179°. Recrystallized from ethanol, the pale tan crystals of N-methylcarbazole-(1)-carboxylic acid melted at 185°. Further recrystallization did not raise the melting point. The yield was 2.2 g. (12.2%).

Anal. Calc'd for $C_{14}H_{11}NO_2$: Neut. equiv., 225.2; N, 6.22.
Found: Neut. equiv., 226.6; N, 6.07.

SUMMARY

The rule of orientation in the metalation of aromatic amines by organoalkali compounds is that the metal enters the ring *ortho* to the nitrogen atom. Steric factors may well account for exceptions to this rule. The inability of N-ethyldiphenylamine to metalate whereas N-methyldiphenylamine does, the ability of N-methylcarbazole to di-metalate whereas N-ethylcarbazole does not, and the *meta* metalation of triphenylamine contrasting with the *ortho* metalation of N-phenylcarbazole, fit in with the steric aspects of the metalation of amines.

AMES, IOWA

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[5] Carbon and hydrogen analyses by Dr. J. Ziffer.