**Rearrangement of Salt XIII to Form Amino Alcohol XIV.**—To a stirred solution of 0.06 mole of potassium amide in 300 ml. of liquid ammonia was added, during 10 min., 10.0 g. (0.021 mole) of salt XIII. After 6 hr., 10.2 g. (0.07 mole) of ammonium iodide was added, and the ammonia replaced by 250 ml. of ether. The ethereal suspension was filtered, and 20 ml. of 3 *N* hydrochloric acid was added dropwise to the filtrate. The resulting white precipitate was collected, and added to 150 ml. of 4 *N* sodium hydroxide. Ether (200 ml.) was added and the mixture stirred until all precipitate had dissolved. The ethereal solution was separated from the aqueous layer and the latter washed with 200 ml. of ether. The combined ether portions were dried over anhydrous magnesium sulfate and the solvent removed to give 5.2 g. (75%) of 2-methyl-3-dimethylaminomethyltriphenylcarbinol (XIV), m.p. 96–103°. A sample was recrystallized from hexane to a constant melting point of 102–104°.

*Anal.* Calcd. for $C_{23}H_{25}NO$: C, 83.34; H, 7.60; N, 4.23. Found: C, 83.27; H, 7.45; N, 4.09.

**Oxidation** of a 2-g. sample of the product was effected in 100 ml. of 1 *N* sodium hydroxide (refluxing) by adding potassium permanganate in 3-g. portions at 5-min. intervals until the purple color persisted. After refluxing overnight, the excess permanganate was destroyed with ethanol, and the manganese dioxide removed by filtration. The filtrate was acidified to precipitate 0.9 g. of crystalline product (XVII or XVIII), m.p. 190–203° and at 210–212° after recrystallization from ethanol–water.

*Anal.* Calcd. for $C_{21}H_{14}O_4$: C, 76.35; H, 4.27. Found: C, 76.17; H, 3.94.

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# Halogen–Metal Interchange of 2-, 3-, and 4-Bromobenzyldimethylamines with *n*-Butyllithium. Grignard Reagent of 2-Bromobenzyldimethylamine[1,2]

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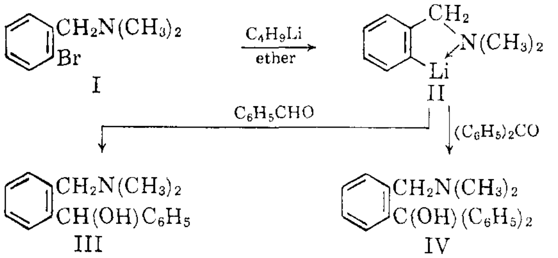
2-Bromobenzyldimethylamine underwent rapid halogen–metal interchange with *n*-butyllithium to form 2-lithiobenzyldimethylamine, which reacted with benzaldehyde and benzophenone to give the corresponding amino alcohols. 4-Bromobenzyldimethylamine also interchanged with butyllithium to give 4-lithiobenzyldimethylamine, which reacted with benzophenone to produce the amino alcohol. However, treatment of 3-bromobenzyldimethylamine with butyllithium gave a mixture of products. 2-Bromobenzyldimethylamine formed a Grignard reagent, but the other two isomers did not.

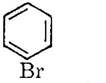
Although numerous aryl halides have been shown to undergo halogen–metal interchanges with *n*-butyllithium in ether,[3] reactions of 2-, 3-, and 4-bromobenzyldimethylamines appear not to have been studied previously with this reagent. We have found that the 2-bromo isomer I readily undergoes such an interchange with this reagent at room temperature to form II and presumably *n*-butyl bromide. This reaction was demonstrated by condensation of II with benzaldehyde and benzophenone to give amino alcohols III and IV in over-all yields of 68 and 80%, respectively (Scheme A).



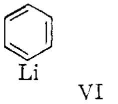
Scheme A

The melting point of amino alcohol III agreed with that reported for this compound by Bersch and Meyer,[4] who prepared it from 2-dimethylaminomethylbenzaldehyde and phenylmagnesium bromide. This structure was further supported by reduction of III with sodium and ethanol in liquid ammonia to form 2-benzylbenzyldimethylamine.[5] The structures of amino alcohols III and IV were confirmed by synthesis through the Grignard reagent of I (see next section). The infrared spectra of III and IV were consistent with the assigned structures.

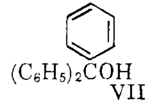
Similarly, 4-bromobenzyldimethylamine (V) underwent halogen–metal interchange with butyllithium in ether to form lithio derivative VI, which reacted with benzophenone to form presumably amino alcohol VII. This product was isolated as its methiodide in an over-all yield of 86%. Structure VII was supported by analysis of the methiodide and by its infrared spectrum.



V



VI



VII

However, 3-bromobenzyldimethylamine produced a dark solution with butyllithium in ether (four hours), and addition of benzaldehyde or benzophenone afforded a complex mixture from which no crystalline product was isolated. This halogen–metal interchange might have been complicated by metalation at the position between the dimethylaminomethyl group and bromine atom,

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[1] Supported by the Army Research Office (Durham).

[2] For a Communication see F. N. Jones and C. R. Hauser, *J. Org. Chem.*, **27**, 701 (1962).

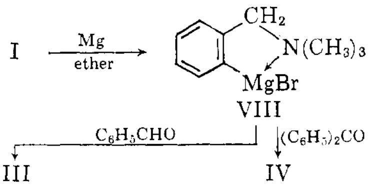
[3] See R. G. Jones and H. Gilman, *Org. Reactions*, **VI**, 339 (1951).

[4] H.-W. Bersch and R. Meyer, *Arch. Pharm.*, **287**, 613 (1954).

[5] S. W. Kantor and C. R. Hauser, *J. Am. Chem. Soc.*, **73**, 4122 (1951).

followed by elimination of lithium bromide and further reaction of the resulting benzyne product. The hydrogen at this *ortho* position would presumably be more active than that in benzyldimethylamine, which undergoes metalation at the *ortho* position with butyllithium in ether (ten hours).[2]

We treated 2-, 3-, and 4-bromobenzyldimethylamines with magnesium in ether, employing ethylene bromide as initiator. The 2-bromo isomer I was readily converted to its Grignard reagent (VIII), which was condensed with benzaldehyde and benzophenone to form amino alcohols III and IV in over-all yields of 80 and 85%, respectively (Scheme B). These products were shown to be identical to those obtained from lithium reagent II by the mixed melting point method and by comparison of their infrared spectra.



Scheme B

However, 3-, and 4-bromobenzyldimethylamines failed to be converted to Grignard reagents under similar conditions. Recently Mehta and Zupicich[6] reported that certain 2-bromobenzyldialkylamines form Grignard reagents, but that 3- and 4-bromobenzyldialkylamines do not.

Incidentally, we failed to obtain lithium reagent II on treatment of I with lithium in refluxing ether.

## Discussion

The halogen–metal interchange of the 2-bromo compound with butyllithium occurred rapidly, producing sufficient heat to boil the ethereal solution. Hydrolysis of a sample of the solution after ten minutes afforded benzyldimethylamine that was contaminated with only 3% of the starting halide I (see Experimental). However, the reaction of the 4-bromo compound V with butyllithium appeared to require three to four hours for maximum interchange.

The relatively rapid rate of interchange of the 2-bromo isomer seems ascribable to the co-ordinating capacity of the amino nitrogen. This capacity may take effect either by promoting interchange through a cyclic mechanism or by stabilizing the resulting lithio derivative II through internal coordination.

Also the formation of the Grignard reagent from the 2-bromo compound I but not from the 3- or 4-isomer appears ascribable to the stabilizing effect of internal coördination in the product. However, VIII is only one of several possible structures for this reagent.

The halogen–metal interchange between 4-bromobenzyldimethylamine (V) and butyllithium should be useful for the synthesis of various *para*-substituted derivatives, since this reaction appears to furnish the only known method of preparation of such an organometallic compound as VI. The halogen–metal interchange between 2-bromobenzyldimethylamine (I) and butyllithium to form II is not the most convenient method for preparation of II, since this lithium reagent may be prepared in excellent yield by direct metalation of benzyldimethylamine.[2] However, if amine I is on hand, the halogen–metal interchange is much faster than metalation. The Grignard reagent VIII may be useful for certain types of reaction that follow a different course with Grignard reagents than with the corresponding lithium reagent.[7]

## Experimental[8]

**Preparation of 2-, 3-, and 4-bromobenzyldimethylamines.**—The appropriate ring-substituted bromotoluene was brominated by the Wohl–Ziegler method,[9] using benzoyl peroxide as catalyst. The resulting dibromotoluene was then treated with a fourfold excess of dimethylamine in cold acetonitrile solution. The acetonitrile was removed *in vacuo*, and the residue was dissolved in 2 *N* hydrochloric acid. This solution was washed with ether and made basic with solid sodium hydroxide. The liberated amine was extracted with ether; the organic layer was dried over magnesium sulfate and fractionated.

2-Bromobenzyldimethylamine (I), b.p. 104–106° at 9 mm., $n^{22}D$ 1.5469–1.5472, was obtained in 62% over-all yield.

*Anal.* Calcd. for $C_9H_{12}BrN$: C, 50.48; H, 5.65; N, 6.45. Found: C, 50.69; H, 5.78; N, 6.39.

3-Bromobenzyldimethylamine b.p. 104.5–105.5° at 9.5 mm., $n^{25}D$ 1.5412, was obtained in 43% over-all yield.

*Anal.* Calcd. for $C_9H_{12}BrN$: C, 50.48; H, 5.65; N, 6.45. Found: C, 50.64; H, 5.83; N, 6.49.

4-Bromobenzyldimethylamine (VI), b.p. 104–105.5° at 9.5 mm., $n^{25}D$ 1.5408, reported b.p. 121–122° at 20 mm.,[10] $n^{25}D$ 1.5406,[10] was obtained in 48% over-all yield.

**Interchange of I with Butyllithium to Form II.**—*n*-Butyllithium was prepared from 11.7 g. (0.084 mole) of butyl bromide and 1.3 g. (0.19 g.-atom) of lithium in 150 ml. of anhydrous ether as described previously.[3] To the stirred solution was added 11.9 g. (0.056 mole) of 2-bromobenzyldimethylamine (I), causing spontaneous boiling for a few minutes.

A sample of the resulting solution of lithium reagent II was treated with water after 10 min. The crude amine product was isolated from the organic layer by extraction with acid and neutralization of the extract. Gas chromatography of this product showed that it contained about 97 mole % of benzyldimethylamine and only about 3% of start-

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[6] N. B. Mehta and J. Zupicich, Abstracts of Papers presented, Division of Organic Chemistry, 140th National Meeting of the American Chemical Society, Chicago, Ill., September, 1961, pp. 34Q–35Q.

[7] See, for example, G. F. Morris and C. R. Hauser, *J. Org. Chem.*, **27**, 465 (1962).

[8] Melting points and boiling points are uncorrected. Microanalyses were performed by Dr. Ing. Schoeller, Kronach, West Germany. Infrared spectra were recorded using a Perkin–Elmer Model 137 Infracord.

[9] See C. Djerassi, *Chem. Rev.*, **43**, 271 (1948).

[10] K. C. Dewhirst and D. J. Cram, *J. Am. Chem. Soc.*, **80**, 3155 (1958).

ing compound I. The infrared spectrum was essentially that of pure benzyldimethylamine; it showed only a trace of the strong peak of I at 751 cm.$^{-1}$.

However, in the reactions described below with carbonyl compounds, the ethereal solution of reagent II was allowed to stand for 1 hr. under nitrogen at room temperature before use.

**Reaction of II with Benzaldehyde.**—To the stirred solution of reagent II prepared as described above was slowly added a solution of 11 g. (0.1 mole) of benzyldehyde in anhydrous ether. The reaction mixture was stirred for 1 hr., and 150 ml. of water was added. The resulting mixture was stirred until all species were in solution. The layers were separated, the ether layer was extracted three times with 2 *N* hydrochloric acid,[11] and the acid extracts were poured immediately into excess aqueous sodium hydroxide. The resulting mixture was extracted three times with ether. The combined ethereal extract was dried over magnesium sulfate and concentrated. The residual solid was recrystallized from hexane to give 9.2 g. (68%) of 2-(dimethylaminomethyl)benzhydrol (III), m.p. 69.5–71°, reported m.p. 71°.[4] Recrystallization from hexane gave a sample melting at 72–72.5°. The infrared spectrum of III had a peak at 843 cm.$^{-1}$, characteristic of the aromatic dimethylaminomethyl group,[12] and peaks at 764, 754, 723, and 701 cm.$^{-1}$, consistent with a structure having aromatic rings bearing four and five adjacent hydrogens.[13]

*Anal.* Calcd. for $C_{16}H_{19}NO$: C, 79.65; H, 7.94; N, 5.81. Found: C, 79.52; H, 8.14; N, 5.81.

A sample of amino alcohol III was converted by ethanolic picric acid to its picrate. Recrystallization from 95% ethanol gave either of two crystal forms of the picrate of III, prisms melting at 128–129.5° or needles melting at 144.5–145.5°. The forms were interconverted by dissolving one in hot 95% ethanol and seeding the solution as it cooled with the other.

*Anal.* Calcd. for $C_{22}H_{22}N_4O_8$: C, 56.17; H, 4.71; N, 11.91. Found: C, 56.39; H, 4.98; N, 12.04.

**Reduction** of a 6.0-g. (0.025 mole) sample of III was effected with 2.8 g. (0.06 mole) of ethanol, 200 ml. of liquid ammonia, and 1.4 g. (0.06 g.-atom) of sodium, added in small pieces with stirring over a period of 45 min.[14] After 1 hr., 150 ml. of water was added and the reaction mixture was worked up to give 3.2 g. (57%) of 2-benzylbenzyldimethylamine, b.p. 125–131° at 0.7–1.0 mm., reported b.p. 189–191° at 33 mm.[5] The infrared spectra of this material and of an authentic sample prepared as described[5] were superimposable.

**Reaction of II with Benzophenone.**—To a stirred solution of reagent II prepared from 2.14 g. (0.010 mole) of I and 0.03 mole of butyllithium in ether was added a solution of excess benzophenone in ether. After stirring for 1 hr., water was added; the 2-(dimethylaminomethyl)triphenylcarbinol (IV) was just slightly soluble in ether and crystallized from the mixture during hydrolysis. The resulting mixture was filtered; the filtrate was washed with hexane, leaving 2.93 g. of IV, m.p. 141–144°. Recrystallization of this product from absolute ethanol gave 2.54 g. (80%) of IV in two crops of m.p. 153.5–154° and 154–155°. The infrared spectrum (potassium bromide disk) of IV had strong peaks at 844, 769, 763, and 700 cm.$^{-1}$, consistent with the proposed structure.[12,13]

*Anal.* Calcd. for $C_{22}H_{23}NO$: C, 83.24; H, 7.30; N, 4.41. Found: C, 83.30; H, 7.47; N, 4.36.

The picrate of a sample of IV, recrystallized twice from 95% ethanol, melted at 168–169°.

*Anal.* Calcd. for $C_{28}H_{26}N_4O_8$: C, 61.53; H, 4.80; N, 10.25. Found: C, 61.42; H, 4.99; N, 10.47.

**Interchange of V with Butyllithium to Form VI. Reaction with Benzophenone.** To a stirred solution of 0.03 mole of *n*-butyllithium in 50 ml. of ether was added 2.14 g. (0.010 mole) of 4-bromobenzyldimethylamine (V). The resulting solution was allowed to stand under nitrogen at room temperature for 4 hr. Then the solution was stirred as a solution of 6 g. (0.033 mole) of benzophenone in ether was added. After 1 hr., the reaction mixture was worked up as described above for amino alcohol III to give 3.09 g. of noncrystalline 4-(dimethylaminomethyl)triphenylcarbinol (VII). A solution of this oil in 20 ml. of acetone was treated with excess methyl iodide to precipitate immediately 3.95 g. (85% based on amine V) of the methiodide of VII, m.p. 227–228°. A sample, recrystallized twice from acetonitrile, melted at 229–230°. The infrared spectrum had strong peaks at 822 cm.$^{-1}$, ascribable to the presence of two adjacent aromatic hydrogens,[13] and at 765 and 701 cm.$^{-1}$, indicating the presence of five adjacent aromatic hydrogens.

*Anal.* Calcd. for $C_{23}H_{26}INO$: C, 60.12; H, 5.70; N, 3.05. Found: C, 60.14; H, 5.14; N, 2.95.

**Conversion of I to Grignard Reagent VIII.**—In the usual Grignard reagent apparatus was placed 3 g. (0.13 g.-atom) of magnesium. A solution of 1 g. (5 mmoles) of ethylene bromide in 25 ml. of anhydrous ether was added; as the resulting reaction subsided, slow addition of a solution of 21.4 g. (0.10 mole) of I in 150 ml. of anhydrous ether was started. The Grignard reagent began to form immediately. When addition was complete, the reaction mixture was stirred for 1 hr. at room temperature before usage.

**Reaction of VIII with Benzaldehyde.**—To a stirred solution of the Grignard reagent prepared as described above was added a solution of 12 g. (0.11 mole) of benzaldehyde in ether. The reaction mixture was stirred for 1 hr., hydrolyzed with water, and worked up essentially as described above for isolation of amino alcohol III to give 19.3 g. (80%) of III, m.p. 71–72°, picrate m.p. 145–145.5°. Mixed melting points of these compounds with amino alcohol III and its picrate obtained from lithium reagent II were undepressed. The infrared spectra of III from the two sources were superimposable.

**Reaction of VIII with Benzophenone.**—Similarly, 20 g. (0.11 mole) of benzophenone in ether solution was added to a stirred solution of VIII prepared as described above. The reaction mixture was stirred for 1 hr. and hydrolyzed with water. To the resulting mixture was added 600 ml. of warm benzene to dissolve the product IV which had crystallized. The mixture was filtered, the aqueous layer was separated, and the organic layer was concentrated to give semicrystalline VI. This material was washed with hexane, and the solid that remained was recrystallized from absolute ethanol to give 25.3 g. (85%) of amino alcohol IV, m.p. 152–153°, picrate m.p. 168–169°. Mixed melting points of these compounds with amino alcohol IV and its picrate obtained from lithium reagent II were undepressed. The infrared spectra of IV from the two sources were superimposable.

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[11] After acid extraction, the ether layer contained *n*-butylphenylcarbinol which resulted from reaction of the excess *n*-butyllithium with benzaldehyde.

[12] W. Q. Beard, Jr., and C. R. Hauser, *J. Org. Chem.*, **25**, 334 (1960).

[13] L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed., John Wiley & Sons, Inc., New York, N. Y., 1958, pp. 76–78.

[14] See A. J. Birch, *J. Chem. Soc.*, 809 (1945).