sharp-melting product.[16] A sample produced a wine-colored enol test with ethanolic ferric chloride. The infrared spectrum showed bands at 2.95 and 5.85–6.1 μ for the >NH and carbonyl groups, respectively. A thin layer chromatogram indicated a single component.

Anal. Calcd. for $C_{12}H_{12}ClNO_3$: C, 56.81; H, 4.77; Cl, 13.98; N, 5.52. Found: C, 57.01; H, 4.79; Cl, 14.08; N, 5.32.

Attempts to Acetylate Ethyl Phenylacetate and Phenylacetonitrile.—A mixture of 16.4 g. (0.1 mole) of ethyl phenylacetate, 40.8 g. (0.4 mole) of acetic anhydride, and 56.5 g. (0.3 mole) of BTDA was stirred at room temperature for 24 hr. The reaction mixture was decomposed with hot aqueous sodium acetate trihydrate. The resulting mixture was cooled, partially neutralized with solid sodium bicarbonate, and extracted with pentane. The organic extracts were washed with sodium bicarbonate solution, dried over sodium sulfate, and concentrated to afford 16.0 g. (97% recovery) of ethyl phenylacetate. The v.p.c. of the recovered ester showed no trace of the desired ethyl α-acetylphenylacetate.

A mixture of 11.7 g. (0.1 mole) of phenylacetonitrile and 40.8 g. (0.4 mole) of acetic anhydride in 150 ml. of 1,2-dichloroethane was cooled in an ice bath and saturated with gaseous boron trifluoride. After warming to room temperature and being stirred for 24 hr., the resulting orange solution was added to aqueous sodium acetate, and the 1,2-chloroethane was removed by distillation until the vapor temperature reached 90%. The residue was partially neutralized with solid sodium bicarbonate and extracted with ether. The ethereal extracts were washed with sodium bicarbonate solution, dried, and concentrated to afford 10.5 g. of an oil. A thin layer chromatogram of this oil indicated the presence of starting nitrile, traces of α-acetylphenylacetonitrile (IX), and α-acetylphenylacetamide (VII). A v.p.c. of this material indicated <10% of IX.

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[16] The wide melting range may indicate a mixture of crystalline forms of X or the presence of a mixture of X and one or more enol forms.

Metalations of Certain β-Phenylethyl- and γ-Phenylpropyldimethylamines with *n*-Butyllithium[1]

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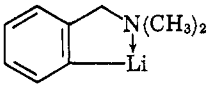
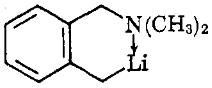
A study was made of metalation of amines of type $C_6H_5(CH_2)_nN(CH_3)_2$ (III) and $C_6H_5C(CH_3)_2CH_2N(CH_3)_2$ (V) with *n*-butyllithium, and of condensation of the resulting lithioamine with benzophenone. These reactions were realized with III (n = 3) and V but not with III (n = 2 or 4); with III (n = 2) dimethylamine was eliminated.

Benzyldimethylamine[2a] and 2-methylbenzyldimethylamine[2b] have recently been metalated with *n*-butyllithium in ether–hexane to form presumably I and II, in which lithium is coordinated with the unshared pair of electrons of nitrogen in five- and six-membered rings, respectively. The site of metalation was established by deuteration and by condensations with electrophilic compounds such as benzophenone.



I

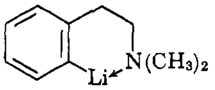


II

In view of these results it seemed possible that certain tertiary amines having the general formula III might undergo similar ring or side-chain metalation by *n*-butyllithium to form five- or six-atom coordination complexes. Thus, β-phenylethyldimethylamine (III, n = 2) might afford the six-atom coordination complex IV and, after addition of benzophenone, the corresponding condensation product. However, none of this product was isolated. Instead, hydrolysis of the reaction mixture afforded dimethylamine and neutral polymeric material. Apparently β-elimination of dimethylamine occurred (with or without prior metalation).

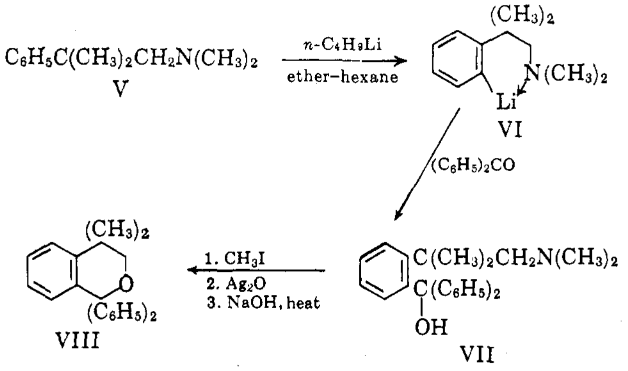
$C_6H_5(CH_2)_nN(CH_3)_2$

III



IV

SCHEME I



It then seemed plausible that the β-phenylethyl type of amine V, which has no β-hydrogens, might undergo metalation to form complex VI and subsequent condensation with benzophenone to afford VII (Scheme I). This was realized, VII being obtained in 17% yield. No appreciable side reaction occurred, and 73% of the starting amine V was recovered.

Structure VII was supported by analysis and absorption spectra. The infrared spectrum showed a band at 3497 cm.$^{-1}$ attributed to the hydroxyl group.[3] This peak was small and almost obliterated by the broad peaks around 3000 cm.$^{-1}$, which were due to the carbon–hydrogen absorption of the methyl groups. The spectrum of VII also showed peaks in the 770–730 and 710–690-cm.$^{-1}$ regions for five adjacent aromatic hydrogens.[4] The n.m.r. spectrum of VII in carbon tetrachloride exhibited no fine splitting either

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

[2] (a) F. N. Jones, R. L. Vaulx, and C. R. Hauser, *J. Org. Chem.*, **28**, 3461 (1963); (b) R. L. Vaulx, F. N. Jones, and C. R. Hauser, *ibid.*, **29**, 1387 (1964).

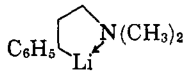
[3] L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 96.

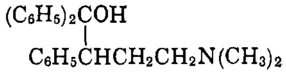
[4] See ref. 3, pp. 76–78.

in the aromatic or alkyl regions. The spectrum showed singlets at −73 ± 1, −127 ± 1, and −146 ± 1 c.p.s., which were assigned to the C-methyl groups, the N-methyl groups, and the methylene, respectively. The singlets for the N- and C-methyl groups were of approximately equal intensity while the methylene singlet had about one-third the intensity of each of the methyl singlets.

Structure VII was confirmed by cyclization of its methiodide to give isochroman VIII in 42% yield (see Scheme I). Structure VIII was supported by analysis and absorption spectra. The infrared spectrum shows strong absorption at 1074 cm.$^{-1}$ indicating a cyclic ether.[5] Peaks at 766, 754, and 703 cm.$^{-1}$ were attributed to four and five adjacent aromatic hydrogens.[4] The n.m.r. spectrum of VIII in carbon tetrachloride showed singlets at −80 ± 1 and −207 ± 1 c.p.s. which were attributed to the methyl groups and methylene, respectively. An aromatic multiplet appeared at approximately −434 c.p.s. The area ratios were CH_3/CH_2 = 3.05 (calculated 3.00) and aromatic hydrogen/CH_2 = 7.00 (calculated 7.00).

Next, amine III (n = 3) was metalated and condensed with benzophenone. Evidently this amine underwent side-chain metalation to form the five-membered ring coordination complex IX, since condensation product X was obtained in 57% yield.

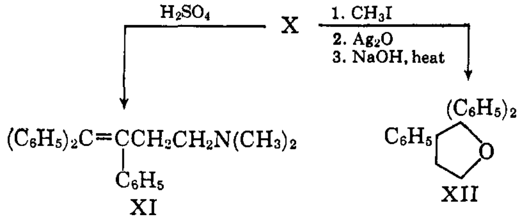

IX


$$\begin{array}{c}(C_6H_5)_2COH\\ |\\ C_6H_5CHCH_2CH_2N(CH_3)_2\end{array}$$
X

Structure X was supported by analysis and infrared spectrum, which showed a band at 3425 cm.$^{-1}$ attributed to the hydroxyl group[3] and at 744 and 702 cm.$^{-1}$ for five adjacent aromatic hydrogens.[4]

Structure X was confirmed by dehydration to amino olefin XI and cyclization through its methiodide to tetrahydrofuran XII (Scheme II). The structures of XI and XII were supported by analyses and infrared spectra. The spectrum of XI did not show a peak for a hydroxyl group; bands at 760, 710, and 700 cm.$^{-1}$ indicated five adjacent aromatic hydrogens.[4] The infrared spectrum of tetrahydrofuran XII showed a strong peak at 1032 cm.$^{-1}$ attributed to the cyclic ether.[5] Peaks indicating the appropriate aromatic substitution were present in the spectrum.

SCHEME II



Finally, it seemed possible that amine III (n = 4) could be metalated similarly on the side chain by n-butyllithium to form the six-atom coordination complex corresponding to the five-atom complex IX. However, addition of benzophenone to the reaction mixture failed to afford the condensation product, and the starting amine was recovered. In side-chain metalation of amines of type III, the six-atom coordination complex appears to form less readily than the five.

Experimental[6]

Preparation of Amines.—N,N-dimethyl-β-phenylethylamine (III, n = 2) was prepared by allowing a solution of 172 g. (0.93 mole) of β-phenylethyl bromide and 120 g. (2.7 moles) of anhydrous dimethylamine in 600 ml. of absolute ethanol to stand at room temperature (25–30°) for 5 days. The ethanol was removed and the residue was dissolved in 2 M hydrochloric acid. The acid solution was washed with ether, cooled, and made basic with sodium hydroxide pellets. The liberated amine was taken up in ether and dried over anhydrous magnesium sulfate. Removal of the solvent left an oil which was distilled to give 93.3 g. (67%) of III (n = 2) b.p. 82.5–85° at 8 mm., lit.[7] b.p. 205° (predicted b.p. at 8 mm., 87°).

N,N-Dimethyl(β-phenylisobutyl)amine (V) was prepared as described previously[8,9] from β-methylallyldimethylamine and benzene in the presence of aluminum chloride. The boiling point (89–91° at 9.7 mm.) and refractive index (1.4980) of V agree with the physical constants reported previously.[9]

N,N-Dimethyl-γ-phenylpropylamine (III, n = 3) was prepared from 86.3 g. (0.43 mole) of 3-(bromopropyl)benzene and 100 g. of anhydrous dimethylamine in 250 ml. of absolute ethanol as described above for the preparation of III (n = 2). Distillation of the residual oil afforded 70.8 g. (83%) of III (n = 3), b.p. 82–83° at 5 mm., lit.[10] b.p. 225° (predicted b.p. at 5 mm., 82°).

N,N-Dimethyl-δ-phenylbutylamine (III, n = 4), was prepared by treatment of 17.73 g. (0.135 mole) of dimethylaminomethyl n-butyl ether[11] with 0.15 mole of γ-phenylpropylmagnesium bromide as described previously for a related compound.[12] The reaction mixture was poured onto crushed ice and 0.2 mole of ammonium chloride. The organic layer was combined with an ether extract of the aqueous layer and extracted three times with 100-ml. portions of 2 M hydrochloric acid. The combined acid extracts were cooled and made basic with 6 M sodium hydroxide. The liberated amine was taken up in ether and dried over anhydrous magnesium sulfate. Removal of the solvent afforded an oil which was distilled to give 15.22 g. (64%) of III (n = 4), b.p. 94–95° at 3.5 mm., lit.[13] b.p. 70–71° at 0.9 mm. (predicted 92–93° at 3.5 mm.).

Treatment of III (n = 2) with n-Butyllithium and Benzophenone.—To 7.45 g. (0.05 mole) of III (n = 2) was added 40 ml. (0.06 mole) of 1.5 M n-butyllithium. The flask was filled with anhydrous ether and stirred at room temperature for 24 hr. The red metalation mixture was poured into a boiling ethereal solution of 12.76 g. (0.07 mole) of benzophenone. After standing 7 hr., the mixture was hydrolyzed and a considerable amount of a basic gas was evolved. On working up the reaction mixture as described below for amine V, no crystalline product was isolated; much neutral polymeric material was obtained.

In a separate experiment, water was added dropwise to the red metalation mixture, which was prepared as described above. The evolved gas was bubbled through 20 ml. of saturated ethanolic picric acid to afford a yellow precipitate which was collected and recrystallized from 95% ethanol. There was obtained the picrate of dimethylamine, m.p. 159–161°, undepressed on admixture with an authentic sample.

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(5) See ref. 3, p. 119.

(6) Melting points and boiling points are uncorrected. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were produced on a Perkin-Elmer Model 21 spectrophotometer and a Perkin-Elmer Infracord Model 137. n-Butyllithium in hexane was obtained from Foote Mineral Co., New Johnsonville, Tenn. N.m.r. spectra were produced on a Varian A-60 n.m.r. spectrometer using solutions with a tetramethylsilane internal reference.

(7) J. von Braun, *Ber.*, **43**, 3209 (1910).

(8) A. W. Weston, A. W. Ruddy, and C. M. Suter, *J. Am. Chem. Soc.*, **65**, 674 (1943).

(9) A. C. Cope, T. T. Foster, and P. H. Towle, *ibid.*, **71**, 3929 (1949).

(10) L. Senfter and J. Tafel, *Ber.*, **27**, 2309 (1894).

(11) This compound (b.p. 137–140°) was prepared from dimethylamine, formalin, and n-butyl alcohol as described previously for the preparation of diethylaminomethyl n-butyl ether: G. M. Robinson and R. Robinson, *J. Chem. Soc.*, 532 (1923).

(12) A. T. Stewart, Jr., and C. R. Hauser, *J. Am. Chem. Soc.*, **77**, 1098 (1955), procedure B.

(13) G. C. Jones and C. R. Hauser, *J. Org. Chem.*, **27**, 3572 (1962).

An additional 100 ml. of water was added to the decomposed metalation mixture, and the organic layer was extracted with 100-ml. portions of 1 *M* hydrochloric acid. The combined acid extracts were cooled, made basic with 6 *M* sodium hydroxide, and extracted with ether. After drying over anhydrous magnesium sulfate, the ether was removed to afford 0.90 g. of a light yellow oil. A vapor phase chromatogram of this oil indicated that it was mainly recovered starting amine (12%).

The ether solution remaining after the acid extraction was dried and the solvent was removed to afford a thick red oil. A vapor phase chromatogram indicated that this oil consisted of a mixture of approximately nine components. No styrene was present in the mixture.

Metalation of Amine V and Condensation with Benzophenone.—A solution of 8.86 g. (0.05 mole) of amine V and 80 ml. (0.12 mole) of 1.5 *M* *n*-butyllithium in 150 ml. of anhydrous ether was stoppered and allowed to stand at room temperature for 5 days. The dark red metalation mixture was poured into a boiling ethereal solution of 23.7 g. (0.13 mole) of benzophenone. The mixture was stoppered and allowed to stand at room temperature for 4 days. The mixture was hydrolyzed by cautious addition of water, and the ether layer was extracted with three 80-ml. portions of 1 *M* hydrochloric acid. The acid extracts along with the white precipitate that had formed during the extraction were combined and made basic with 6 *M* sodium hydroxide. The liberated amine was taken up in ether and the combined ethereal extracts were dried over anhydrous magnesium sulfate. Removal of the solvent afforded a light yellow oil which crystallized on addition of hexane. The crystals were collected and dried to afford 3.00 g. (17%) of *o*-(α-dimethylaminomethylisopropyl) triphenylcarbinol (VII), m.p 162–165° after recrystallization from hexane–absolute ethanol. The analytical sample melted at 165–166.5°.

Anal. Calcd. for $C_{25}H_{29}NO$: C, 83.52; H, 8.13; N, 3.98. Found: C, 83.52; H, 8.23; N, 4.08.

The hexane solution remaining after VII was collected was concentrated to afford a yellow oil which was distilled to give 6.45 g. (73%) of V, b.p. 89–92° at 9.5 mm. The refractive index was identical to that of the starting material.

When the metalation time was 72 hr. and the condensation period 12 hr., the yield of VII was 9%. When the metalation mixture was refluxed under nitrogen for 48 hr. and the condensation mixture refluxed 7 hr., the yield of VII was 8%, 75% of V being recovered.

The methiodide of VII was prepared by refluxing 4.0 g. (0.011 mole) of VII with 24 ml. (0.4 mole) of methyl iodide in 100 ml. of absolute ethanol for 8 hr. The solution was cooled in ice as 400 ml. of anhydrous ether was added dropwise. The resulting white crystals were collected and dried to afford 5.1 g. (92%) of methiodide which melted at 233–235° dec. when placed in a block preheated to 225°.

Cyclization of the methiodide of VII to VIII was accomplished by treating a suspension of 5.1 g. (0.01 mole) of methiodide in 400 ml. of water with 9.2 g. (0.04 mole) of silver oxide as described previously for a related cyclization.[14] Removal of the solvent, after reaction and work-up, afforded an oil which crystallized when cooled in an equal volume of absolute ethanol. The white crystals were collected and dried to afford 3.14 g. (42%) of 1,1-diphenyl-4,4-dimethylisochroman (VIII), m.p. 114–115.5°. This melting point was not changed by further recrystallization from absolute ethanol.

Anal. Calcd. for $C_{23}H_{22}O$: C, 87.86; H, 7.05. Found: C, 87.60; H, 7.10.

Metalation of Amine III (n = 3) and Condensation with Benzophenone.—To 16.3 g. (0.1 mole) of III (n = 3) was added 135 ml. (0.2 mole) of 1.5 *M* *n*-butyllithium in hexane and 200 ml. of anhydrous ether. The solution was stirred and refluxed under nitrogen for 24 hr.; anhydrous ether was added occasionally to replace that lost in the stream of nitrogen. To the stirred metalation mixture was added slowly 40 g. (0.22 mole) of benzophenone in 200 ml. of anhydrous ether. The resulting mixture was stirred and refluxed 4 hr., then decomposed with 150 ml. of cold water. The layers were separated and the ether layer was dried over anhydrous magnesium sulfate. Removal of the solvent afforded 19.8 g. (57%) of 4-dimethylamino-1,1,2-triphenyl-*n*-butanol (X), m.p. 127–130°. After three recrystallizations from absolute ethanol, a sample melted at 133–133.5°.

Anal. Calcd. for $C_{24}H_{27}NO$: C, 83.44; H, 7.88; N, 4.05. Found: C, 83.29; H, 7.93; N, 4.19.

The picrate of X melted at 168–169° after three recrystallizations from 95% ethanol.

Anal. Calcd. for $C_{30}H_{30}N_4O_8$: C, 62.71; H, 5.26; N, 9.75. Found: C, 62.72; H, 5.28; N, 9.69.

The methiodide of X, prepared in 89% yield by refluxing X with excess methyl iodide in acetonitrile followed by addition of anhydrous ether to the cold mixture, melted at 244–245° after three recrystallizations from acetonitrile.

Anal. Calcd. for $C_{25}H_{30}INO$: C, 61.62; H, 6.20; N, 2.87. Found: C, 61.35; H, 6.18; N, 2.72.

Dehydration of amino alcohol X was effected by refluxing 3.30 g. (0.01 mole) of X in 100 ml. of 20% sulfuric acid for 16 hr. The resulting mixture was cooled and made basic with 6 *M* sodium hydroxide. The liberated amino olefin was taken up in ether and the ethereal solution was dried over anhydrous magnesium sulfate. Removal of the solvent afforded 2.66 g. (83%) of 4-dimethylamino-1,1,2-triphenylbutene-1 (XI), m.p. 106–109°. Recrystallization from hexane gave an analytical sample of XI, m.p. 111–111.5°.

Anal. Calcd. for $C_{24}H_{25}N$: C, 88.03; H, 7.70; N, 4.28. Found: C, 87.62; H, 7.56; N, 4.18.

Cyclization of the Methiodide of X to Tetrahydrofuran XII.—This cyclization was accomplished using 4.87 g. (0.01 mole) of methiodide as indicated above for the cyclization of VII. Removal of the solvent afforded 2.9 g. (96%) of 2,2,3-triphenyltetrahydrofuran (XII), m.p. 113–116°. Recrystallization from 95% ethanol gave a sample melting at 114–116°.

Anal. Calcd. for $C_{22}H_{20}O$: C, 87.96; H, 6.71. Found: C, 87.67; H, 6.79.

Treatment of III (n = 4) with *n*-Butyllithium.—A solution of 7.09 g. (0.04 mole) of III (n = 4), 80 ml. (0.12 mole) of 1.5 *M* *n*-butyllithium, and 200 ml. of anhydrous ether was treated for 48 hr. as described above for III (n = 3). To the orange metalation mixture was added 23.7 g. (0.13 mole) of benzophenone in 100 ml. of anhydrous ether. After stirring and refluxing for 5 hr., the mixture was poured into 150 g. of ice and worked up as described for the metalation and condensation of V. Removal of the solvent gave a yellow oil, which was distilled to afford 6.11 g. (86%) of the starting amine III (n = 4), b.p. 97–99° at 4.0 mm. The refractive index agreed with that of the starting amine.

When the metalation was performed at 0° for 48 hr. and the condensation at room temperature for 7 hr., 93% of the starting amine was recovered.

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[14] H. W. Bersch, R. Meyer, A. V. Mletzko, and K. H. Fischer, *Arch. Pharm.*, **291**, 85 (1958).