Metalations of Benzyldimethylamine and Related Amines with *n*-Butyllithium in Ether. Deuteration to Form Ring and Side-chain Derivatives[1]

Frank N. Jones, Mary F. Zinn, and Charles R. Hauser

Department of Chemistry, Duke University, Durham, North Carolina

Received August 13, 1962

Benzyl-type tertiary amines were treated with *n*-butyllithium in ether, and the resulting metalated intermediates were treated with deuterium oxide to show the site of metalation. Benzyldimethylamine and dibenzylmethylamine afforded *ortho*-deuterated products, whereas 2-methyl- and 2,3-dimethylbenzyldimethylamines gave *ortho*-methyl (side-chain) deuterated products. N,N-Dimethyl-3-phenylpropylamine was presumably metalated at the position alpha to the benzene ring. In all cases, the site of metalation was such that the amino nitrogen could coordinate with the lithium of the metalated intermediate through a five- or six-membered ring. The formation of such a ring is thought to be an important factor.

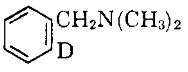
Although numerous aromatic compounds have been metalated by alkyllithium reagents,[2] metalations of benzyldimethylamine and related tertiary amines appear not to have been reported previously.

We have effected metalations of such amines with *n*-butyllithium in ether and have determined the probable structures of the resulting lithio intermediates by deuteration with deuterium oxide. The results are summarized in Table I.

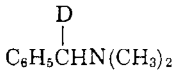
Metalation of benzyldimethylamine (I) followed by deuteration gave the ring-deuterated amine IIa, not the possible isomer IIb.

$C_6H_5CH_2N(CH_3)_2$

I



IIa



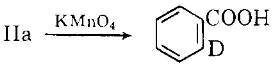
$C_6H_5\overset{D}{C}HN(CH_3)_2$

IIb

That the product contained deuterium in the aromatic ring as in IIa, not IIb, was indicated by its nuclear magnetic resonance (n.m.r.) spectrum in deuteriochloroform solution. This spectrum showed unsplit peaks at $\delta = 2.21$ (methyl hydrogen) and $\delta = 3.39$ (methylene hydrogen) and a multiplet centering at $\delta = 7.26$ (aromatic hydrogen) p.p.m. from an internal tetramethylsilane standard. These peaks had the approximate area ratios 6.0:2.2:4.0, respectively.

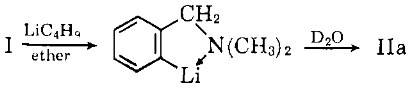
That the ring of IIa contained deuterium in the *ortho*-position was supported by its infrared spectrum (see Table II). It is known that substitution of deuterium for hydrogen in an aromatic ring affects the spectrum of the compound in the 850–690-cm.$^{-1}$ region as would substitution of any other group.[3] The presence of a strong peak in the 770–730-cm.$^{-1}$ region and of a second strong peak near 700 cm.$^{-1}$ indicates the presence of five adjacent aromatic hydrogens; this is exemplified by the spectra of toluene and benzyldimethylamine (I). The presence of one or two peaks in the 770–735-cm.$^{-1}$ region and none near 700 cm.$^{-1}$ indicates the presence of four adjacent aromatic hydrogens.[4] The spectra of toluene-2*d* and of amine IIa fit the latter pattern, indicating *ortho*-deuteration of amine IIa. It is also noteworthy that the strong peak in the spectrum of I at 849 cm.$^{-1}$, which has been assigned to a group vibration of the aryl dimethylaminomethyl group,[5] is unaltered in the spectrum of IIa.

The structure of the product was confirmed as IIa by oxidation to form benzoic acid-2*d* (III), the deuterium content of which was essentially the same (0.93 D atom/molecule) as that of the deuterioamine (equation 1). The infrared spectrum of this acid was identical with that reported for III (see Table II).



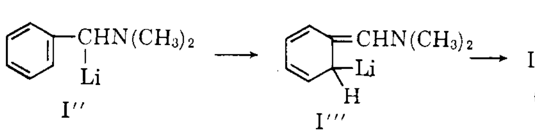
III (1)

The formation of the ring-deuterated amine IIa may be represented by equation 2, in which I′ is the lithio intermediate.



I′ (2)

Lithio intermediate I′ may have been formed either by direct *ortho*-metalation of I or through intermediate formation of methylene intermediate I″ (equation 3).



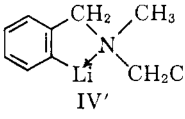
I″ I‴ (3)

It appears unlikely that the lithio intermediate that reacted with deuterium oxide to form IIa was I″ because I″ would be expected to give IIb on deuteration; it is known that deuteration of benzylmagnesium chloride gives toluene-*αd*.[6] Nor is it likely that the reactive intermediate was I‴, which would be expected to give a mixture of IIa and IIb on deuteration.

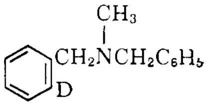
Similarly, dibenzylmethylamine (IV) gave the ring-deuterated derivative V, presumably through lithio intermediate IV′.

$(C_6H_5CH_2)_2NCH_3$

IV



IV′



V

That at least most of the deuterium of V was in one of the benzene rings was indicated by its n.m.r. spectrum, which had unsplit peaks at $\delta = 2.16$ and $\delta = 3.39$ p.p.m. and a multiplet centering at $\delta = 7.28$

---

[1] Supported by the U. S. Army Research Office, Durham.

[2] H. Gilman and J. W. Morton, *Org. Reactions*, **VIII**, 258 (1954).

[3] G. V. D. Tiers and J. H. Tiers, *J. Chem. Phys.*, **20**, 761 (1952).

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

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

[6] R. A. Choppin and C. H. Smith, *J. Am. Chem. Soc.*, **70**, 577 (1948); D. Bryce-Smith, V. Gold, and D. P. N. Satchell, *J. Chem. Soc.*, **1954**, 2743.

TABLE I

METALATION CONDITIONS, PRODUCTS OF DEUTERATION, AND EXTENTS OF DEUTERATION

Starting amine	Metalation: Time, hr.	Metalation: Temp., °C.	Deuterated product	D analysis, D atom/ molecule[a]	Boiling point of deuterated amine[b]
I	24	25[c]	Benzyldimethylamine-2*d* (IIa)	0.94	65–67° at 16 mm.
I	18	25	Benzyldimethylamine-2*d* (IIa)	0.92	64.5–65.5° at 15 mm.
IV	48	25	Dibenzylmethylamine-2*d*(V)	1.02	94–95° at 0.4 mm.
VIa	16	25	2-Methyl-d_1-benzyldimethylamine (VIIa)	1.01	81° at 16 mm.
VIb	3	25	2-Methyl-d_1-3-methylbenzyl dimethylamine (VIIb)	1.00	98.5–99.5° at 14 mm.
VIII	24	35[d]	N,N-Dimethyl-3-phenylpropylamine-αd_1 (IX)	0.66	94–95° at 13 mm.
X	24	35[d]	Destroyed by *n*-butyllithium		

[a] Combustion analysis by Josef Nemeth, Urbana, Ill. [b] Distillation through a 15-cm. Vigreux column. [c] Room temperature, approximately 25°. [d] Refluxing ether solution.

TABLE II

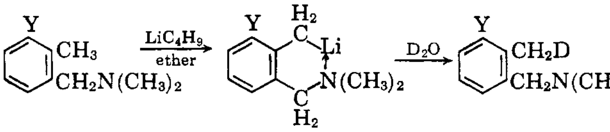
INFRARED SPECTRA OF DEUTERATED AND UNDEUTERATED COMPOUNDS IN THE 850–690-CM.$^{-1}$ REGION

Compound	Frequencies of strong peaks, ±3 cm.$^{-1}$: 850–837	800–710	near 700
Toluene[a]		729	694
Toluene-2*d*[a,b]		775,721	
I[c,d]	849	737	698
IIa[c,d]	847	777,734	696 (weak)
III[e]		803,780	700
IV[c,f]		749,739	701
V[c,f]		779,749,738	701
VIa[c,d]	843	763,745	
VIIa[c,d]	846	765,738	
VIb	846	773,725 (w)	
VIIb[c,d]	847	771,723 (w)	
VIII[c,f]		748	699
IX[c,f]		746	700

[a] Spectra in dilute solution; see ref. 3. [b] Another report [J. Turkwitch, H. A. McKenzie, L. Friedman, and R. Spurr, *J. Am. Chem. Soc.*, **71**, 4045 (1949)] states thatt oluene-2*d* has strong peaks at 785, 765, 725, 716, and 695 cm.$^{-1}$. However, it appears likely that the latter peak has a molar absorbance index of less than 20 (see ref. 3). [c] Spectra of neat liquid film between sodium chloride plates. [d] Recorded using a Perkin-Elmer Model 21 spectrophotometer. [e] Dilute carbon tetrachloride solution. Reported spectrum for this acid has strong peaks at 800, 779, and 700 cm.$^{-1}$ (ref. 3). [f] Recorded using a Perkin-Elmer Model 237 Infracord.

p.p.m. (deuteriochloroform solution, internal tetramethylsilane standard) in the approximate area ratios 3.0:3.8:8.7. The location of most of the deuterium in the *ortho*-position of one of the rings was indicated by the infrared spectrum of V (see Table II.)

In contrast to amines I and IV, 2-methyl- and 2,3-dimethylbenzyldimethylamines, VIa and VIb, afforded the side-chain deuterated amines VIIa and VIIb, respectively. This indicates that the lithio intermediates were VIa′ and VIb′ (equation 4).



(4)

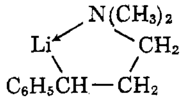
VIa. Y = H VIa′ VIIa. Y = H
VIb. Y = CH_3 VIb′ VIIb. Y = CH_3

That the deuterium of amine VIIa was mainly on the 2-methyl side chain was indicated by the fact that the *ortho*-CH_3 singlet in the n.m.r. spectrum of undeuterated VIa was split to a triplet and reduced in area in the n.m.r. spectrum of VIIa; the spectra were otherwise identical. Similarly, one of the ring-CH_3 singlets in the n.m.r. spectrum of VIb was split and reduced in area in the otherwise identical spectrum of VIIb. The location of the deuterium in a side chain was confirmed by the infrared spectra of amines VIIa and VIIb in the 850–690-cm.$^{-1}$ region; these spectra were nearly identical with those of the undeuterated precursors VIa and VIb (Table II). The unchanged frequencies of the dimethylaminomethyl group vibrations on deuteration of VIa and VIb support the above conclusion.

Even N,N-dimethyl-3-phenylpropylamine (VIII) appeared to give the side-chain deuterated amine IX, presumably through lithio intermediate VIII′. However, metalation of VIII was not complete under more severe conditions than those which gave essentially complete metalation of the above amines.

$C_6H_5CH_2CH_2CH_2N(CH_3)_2$
VIII

$C_6H_5CHDCH_2CH_2N(CH_3)_2$
IX



VIII′

The infrared spectrum of amine IX was practically identical with that of VIII in the 850–690-cm.$^{-1}$ region; this indicates side-chain deuteration but gives no information about the location of the deuterium on the side chain. The n.m.r. spectrum was uninformative. Presumably the most likely position for side-chain metalation is alpha to the benzene ring, as shown by VIII′.

Incidentally, treatment of N,N-dimethyl-2-phenylethylamine (X) with refluxing, ethereal butyllithium followed by deuteration afforded no amine product boiling above room temperature. Possibly β-elimination occurred to give dimethylamide ion and styrene. Polymeric material, possibly polystyrene, was formed.

$C_6H_5CH_2CH_2N(CH_3)_2$
X

Discussion

Since benzene is ring-metalated and toluene side-chain metalated to only very small extents on prolonged refluxing with etheral *n*-butyllithium,[7] the metalations described are evidently greatly facilitated by the γ-

---

(7) R. V. Young, *Iowa State Coll. J. Sci.*, **12**, 177 (1937) [*Chem. Abstr.*, **32**, 4979 (1938)]. H. Gilman, H. A. Pocevitz, and O. Baine, *J. Am. Chen. Soc.*, **62**, 1514 (1940).

and δ-substituent effects of the tertiary amine group. Although the mechanism of these metalations has not yet been established, the transition state presumably involves coördination of the free pair of electrons of the amine with lithium.

Experimental[8]

Starting Amines.—Benzyldimethylamine (I, b.p. 178–179°) was obtained commercially.

Dibenzylmethylamine (IV) was prepared from 130 g. (1.03 moles) of benzyl chloride and 78 g. (2.6 moles) of methylamine in 600 ml. of methanol (refluxed overnight). The methanol was removed, and the residue was dissolved in 2 *N* hydrochloric acid. This solution was washed twice with ether and made basic with solid sodium hydroxide. The liberated amine mixture was extracted with ether. The extract was dried over magnesium sulfate and fractionated to give 44 g. (35%) of benzylmethylamine, b.p. 68–69° at 12 mm., reported b.p. 180–181° at 765 mm.,[9] and 47 g. (43%) of IV, b.p. 96–97° at 0.45 mm., reported b.p. 178–180° at 32 mm.[10]

2-Methylbenzyldimethylamine (IVa, b.p. 78–79° at 13 mm.) and 2,3-dimethylbenzyldimethylamine (VIb, b.p. 98–99° at 13 mm.) were synthesized by the ortho substitution–rearrangements of benzyltrimethylammonium iodide and 2-methylbenzyltrimethylammonium iodide, respectively.[11] The reported boiling points are 80–80.2° at 14 mm. and 99–101° at 14 mm., respectively.[11]

N,N-Dimethyl-3-phenylpropylamine (VIII) was prepared from 153 g. (0.77 mole) of 3-phenyl-1-propyl bromide (b.p. 107–108° at 9 mm.) and 140 g. (3.1 moles) of dimethylamine in 500 ml. of absolute ethanol (warmed at 55° for 2 hr. and left to stand overnight). The reaction mixture was worked up essentially as described above for isolation of amine IV to give 72 g. (58%) of amine X, b.p. 95–96° at 7.3 mm. The picrate melted at 98.5–99.5°, reported m.p. 99°.[12]

N,N-Dimethyl-2-phenylethylamine (X) was prepared from 120 g. (2.7 moles) of dimethylamine and 172 g. (0.94 mole) of 2-phenylethyl bromide essentially as described above for preparation of amine X. Fractionation gave 93 g. (66%) of amine XII in two fractions, b.p. 82–84° at 8 mm. (21 g.) and b.p. 84–85° at 8 mm. (72 g.), reported b.p. 205°.[13]

Metalations and Deuterations (Table I).—In a 50- or 125-ml. erlenmeyer flask were combined 0.03–0.08 mole of starting amine and 0.06–0.16 mole of ethereal *n*-butyllithium, prepared and analyzed as described.[2] The flask was filled with anhydrous ether, tightly stoppered, and allowed to stand for 3–48 hr. at room temperature. The resulting solution was poured in a stream of nitrogen into a 500-ml. erlenmeyer flask containing a stirred mixture of 5–8 ml. of deuterium oxide (99.8% deuterium) and 50–75 ml. of anhydrous benzene. The benzene was used to absorb some of the heat of reaction. The resulting mixture was stirred for 1 hr. The organic layer was filtered free of the damp solid which had separated, dried over magnesium sulfate, and the solvent was distilled. In all cases except that of amine X, the recovery of undistilled deuterated amines was nearly quantitative. The crude amines were fractionated through a 15-cm. Vigreux column, a mid-cut being collected for deuterium analysis (see Table I).

Metalation of amine VIII and the attempted metalation of amine X were effected by refluxing the amine with 2 molecular equivalents of *n*-butyllithium in ether under nitrogen for 24 hr. in a 300-ml. three-neck flask. Deuterium oxide was slowly added to the resulting mixture, and the reaction mixture was worked up as described for the other deuterations.

Oxidation of Amine IIa.—A sample of amine IIa containing 0.92 D atom/molecule was oxidized with alkaline potassium permanganate by the procedure described[14] for a related oxidation to give benzoic acid-2*d* (III), m.p. 121.5–122°, containing 0.93 D atom/molecule.

---

[8] Melting points and boiling points are uncorrected. N.m.r. spectra were determined by Mr. John Baxter and Mr. James Randall using a Varian HR-60 device and by the Varian A-60 Applications Laboratory, Palo Alto, Calif. Deuterium analysis (combustion–falling drop) was performed by Josef Nemeth, Urbana, Ill.

[9] H. Emde, *Arch. Pharm.*, **247**, 251 (1909).

[10] G. M. Coppinger, *J. Am. Chem. Soc.*, **76**, 1372 (1954).

[11] S. W. Kantor and C. R. Hauser, *ibid.*, **73**, 4122 (1951).

[12] L. Senfter and J. Tafel, *Ber.*, **27**, 2309 (1894).

[13] J. v. Braun, *ibid.*, **43**, 2309 (1910).

[14] F. N. Jones and C. R. Hauser, *J. Org. Chem.*, **26**, 2979 (1961).

Bicyclic Bases. V. Epoxidation of 7-Diphenylmethylenenorbornenes[1]

GEORGE I. POOS AND JANET D. ROSENAU

McNeil Laboratories, Inc., Fort Washington, Pennsylvania

Received May 23, 1962

The *endo*-diphenylfulvene-*N*-methylmaleimide adduct I is shown to epoxidize preferentially at the diphenylmethylene double bond with perbenzoic acid. The structure and stereochemistry of the resulting monoepoxide II is proved. Epoxidation of the *exo*-imide IX is shown to give only the ring monoepoxide X. However, the *endo*-benzamide XIV epoxidizes to give a mixture of monoepoxides. These differences are attributed to the operation of a field effect in the case of the imides.

In part IV of this series,[2] we described the preparation of a series of aryl-substituted bridged hydroisoindolines by lithium aluminum hydride reduction of the corresponding diarylfulvene-maleimide adducts. In the course of this work, it became of interest to investigate the epoxidation of the *endo* doubly unsaturated imide I. Alder and co-workers had reported[3] on the oxidation of the *endo*-maleic anhydride–diphenylfulvene adduct with excess peracetic acid at 80–90°. Their product, obtained after mild saponification, was an oxido lactone hydroxy carboxylic acid resulting from oxidation of both double bonds and interaction of the ring epoxide with a carboxy function. In the case of the *exo*-maleic anhydride–diphenylfulvene adduct, the German workers[3] obtained a rearranged hydroxy lactone carboxylic acid resulting from oxidation of only the ring double bond. It was also reported[3] that the dihydronorbornane-*exo*-adduct failed to react with peracetic acid under the same conditions.

With our *endo*-imide I, we hoped to epoxidize preferentially the ring double bond in order to obtain ring substituted analogs of pharmacologically interesting hydroisoindolines.[2] The known reactivity of the norbornene double bond[4] and possible steric hindrance of the tetrasubstituted exocyclic double bond of I led us to predict the desired selective oxidation.

When imide I was treated with an equivalent amount of perbenzoic acid in chloroform solution at room temperature, a single monoepoxide was obtained in 84%

---

[1] Presented in part at the Fourth Delaware Valley Regional American Chemical Society Meeting, Philadelphia, Pa., January 26, 1962.

[2] G. I. Poos, M. M. Lehman, E. B. Landis, and J. D. Rosenau, *J. Med. Pharm. Chem.*, **5**, 883 (1962).

[3] K. Alder, F. W. Chambers, and W. Trimborn, *Ann.*, **566**, 27 (1950).

[4] H. Kwart and L. J. Miller, *J. Am. Chem. Soc.*, **83**, 4552 (1961).