

Samples were collected by using glass U-shaped tubes inserted into the exit port of the gas chromatograph and cooled in liquid nitrogen.

Materials. Amines 3 and 7 were prepared as described elsewhere.¹² Compound 5, a commercial sample, was distilled before use. Commercial (Alfa Inorganics) solutions of organolithium compounds were used. Hexane was stored over molecular sieves (4A).

Procedure for Reactions with Organolithium Compounds. Except where otherwise noted, the following procedure was used. A solution of the substrate was added slowly (15 min or more) to an ice-cooled, stirred solution of organolithium compound maintained under a positive pressure of nitrogen. The reaction mixture was heated as specified in each experiment and then cooled again before being quenched by slow addition of methanol (5–10 mL). The resulting mixture was filtered (some additional solvent sometimes was added to aid in this). The filtrate was washed with three portions of a saturated sodium bicarbonate solution and then dried (MgSO₄). Solvent was removed by distillation through a small column packed with glass helices (or sometimes by using a rotary evaporator), following which the column was removed and the residue distilled at reduced pressure.

Reactions of *N,N*-Dimethyl-3-phenyl-2-propen-1-amine (3). (a) **With *n*-Butyllithium; Isolation of 2-Benzyl-*N,N*-dimethyl-1-hexanamine (4a).** A solution of 3 (4.00 g, 24.8 mmol) in hexane (50 mL) was added to a hexane solution of *n*-butyllithium (27 mL, 2.35 M, 63 mmol). The resulting solution was heated at reflux temperature for 6 h, during which a suspension developed. Distillation gave 4a: 2.85 g (13.0 mmol, 52%); bp 90–95 °C (0.7 torr); ¹H NMR (CCl₄) δ 0.90 (m, 3, CH₂CH₃), 1.28 (m, 6, (CH₂)₃), 1.78 (m, 1, CH), ~2.0 (partially obscured m, 2, CH₂Ph or CH₂N), 2.15 (s, 6, N(CH₃)₂), 2.49 (d of d, *J* = 13, 7 Hz, 1, CHHPh or CHHN), 2.70 (d of d, *J* = 13, 5 Hz, 1, CHHPh or CHHN), 7.15 (m, 5, Ph); ¹H NMR (CF₃CO₂H) δ 0.92 (m, 3, CH₂CH₃), 1.40 (m, 6, (CH₂)₃), 2.16 (m, 1, CH), 2.74 (d, *J* = 5 Hz, 3, CH₃NCH₃), 2.84 (d, *J* = 5 Hz, 3, CH₃NCH₃), ~2.9 (partially obscured m, 2, CH₂Ph or CH₂N), 3.05 (m, 2, CH₂Ph or CH₂N), 7.28 (m, 5, Ph); mass spectrum, *m/z* 219.1992 (M⁺, calcd for C₁₅H₂₅N 219.1987). Anal. Calcd for C₁₅H₂₅N: C, 82.13; H, 11.49; N, 6.38. Found: C, 81.86; H, 11.34; N, 6.62. GC analysis (column A) showed only one significant peak.

(b) **With *tert*-Butyllithium; Isolation of 2-Benzyl-3,3-dimethyl-*N,N*-dimethyl-1-butanamine (4b).** A solution of 3 (3.00 g, 18.6 mmol) in pentane (40 mL) was added to a solution of *tert*-butyllithium (26 mL, 1.82 M, 47 mmol). The resulting suspension was heated at reflux temperature for 6 h. Distillation gave 4b: 2.30 g (10.5 mmol, 56%); bp 67–70 °C (0.4 torr); ¹H NMR (CCl₄) δ 0.92 (s, 9, C(CH₃)₃), 1.56 (m, at 100 MHz this absorption roughly resembled a quintet with *J* = 6 Hz, 1, CH), 1.98 (s, 6, N(CH₃)₂), 2.00 (partially obscured, probably d of d, *J* = 12.5, 7 Hz, 1, CHHPh or CHHN), 2.24 (d of d, *J* = 12.5, 5 Hz, 1, CHHPh or CHHN), 2.45 (d of d, *J* = 14, 7 Hz, 1, CHHPh or CHHN), 2.68 (d of d, *J* = 14, 5 Hz, 1, CHHPh or CHHN), 7.14 (m, 5, Ph); ¹H NMR (CF₃CO₂H) 1.06 (s, 9, C(CH₃)₃), 1.85 (m, 1, CH), 2.35 (d, *J* = 5 Hz, 3, CH₃NCH₃), 2.69 (d, *J* = 5 Hz, 3, CH₃NCH₃), 3.16 (m, 4, CH₂Ph and CH₂N), 7.38 (br s, 5, Ph); mass spectrum, *m/z* 219.1971 (M⁺, calcd for C₁₅H₂₅N 219.1987). Anal. Calcd for C₁₅H₂₅N: C, 82.13; H, 11.49; N, 6.38. Found: C, 82.31; H, 11.42; N, 6.49. GC analysis (column A) showed only one significant peak.

Reaction of 1-Phenyl-1-propene (5) with *n*-Butyllithium. Isolation of 2-Benzylhexane (6). A solution of 5 (4.0 g, 33.8 mmol) in hexane (40 mL) was added to a hexane solution of *n*-butyllithium (36.6 mL, 2.35 M, 86 mmol), and the resulting solution was heated at reflux temperature for 36 h. Distillation gave 6: 1.7 g (9.6 mmol, 29%); bp 44–47 °C (0.25 torr); ¹H NMR (CCl₄) δ 0.80 (d, *J* = 6 Hz, 3, CHCH₃), 0.88 (m, 3, CH₂CH₃), 1.24 (m, 6, (CH₂)₃), ~1.70 (m, 1, CH), 2.33 (d of d, *J* = 13, 6 Hz, 1, CHHPh), 2.59 (d of d, *J* = 13, 6 Hz, 1, CHHPh), 7.14 (m, 5, Ph). A second fraction (1.0 g) was obtained [bp 122–130 °C (0.15 torr)], but the material responsible for it was not identified.

A distillate of 2.2 g was obtained from a similar reaction that was heated at reflux for only 6 h. The distillate was mainly 5, containing less than 10% of 6.

Competition of 3 and 5 for a Limited Amount of *n*-Butyllithium. A solution of 3 (2.20 g, 13.6 mmol), 5 (1.61 g, 13.6 mmol), and decane (1.94 g, 13.6 mmol) in hexane (30 mL) was added to a hexane solution of *n*-butyllithium (5.0 mL, 2.35 M, 11.8 mmol) which had been diluted with additional hexane (10 mL). The resulting solution was heated at reflux temperature for 24 h. Distillation gave a liquid: 4.4 g; bp 25–150 °C (0.5 torr). The ¹H NMR spectrum showed principally absorptions due to 4, 5, and decane. GLC analysis (column B, the decane served as an internal standard) showed substantial peaks due to 4 and 5 and a small peak due to 3. No other significant peaks were observed.

Reaction of *N,N*-Dimethyl-3-phenyl-2-propyn-1-amine (7) with *n*-Butyllithium. Isolation of 2-Butyl-*N,N*-dimethyl-3-phenyl-2-propen-1-amine (8). A solution of 7 (2.00 g, 12.6 mmol) in hexane (25 mL) was added to a hexane solution of *n*-butyllithium (16 mL, 2.37 M, 38 mmol). The resulting solution was heated at reflux for 2 h. A precipitate appeared soon after refluxing began. Methanol (5 mL) and water (5 mL) were added carefully followed by diethyl ether and more water. The layers were separated, and the aqueous layer was extracted with two additional portions of diethyl ether. The combined organic layers were dried (MgSO₄), and most of the solvent was removed at reduced pressure. Distillation gave 8: 0.43 g (2.0 mmol, 16%); bp 84–95 °C (1.0 torr); ¹H NMR (CDCl₃) δ 0.93 (m, 3, CH₂CH₃), 1.35 (m, 4, (CH₂)₂CH₃), 2.24 (m, 8, N(CH₃)₂ and =CCH₂CH₂), 2.93 (br s, 2, CH₂N), 6.57 (br s, 1, =CH), 7.28 (m, 5, Ph); IR (CCl₄) 1650 cm⁻¹ (C=C). A sample of the distillate was purified by GC (column C, 175 °C) to free it from a trace of 7. Anal. Calcd for C₁₅H₂₃N: C, 82.89; H, 10.67; N, 6.44. Found: C, 82.82; H, 10.52; N, 6.74. A considerable amount of tar remained in the distillation flask.

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Registry No. 3, 33962-90-2; 4a, 33083-85-1; 4b, 33083-84-0; 5, 637-50-3; 6, 3200-11-1; 7, 2568-65-2; 8, 86969-86-0.

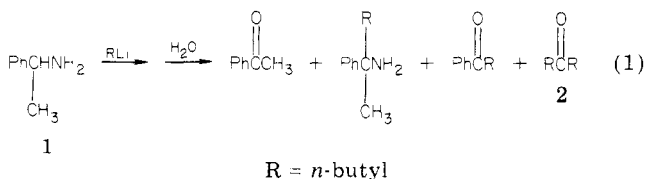
Fragmentation of Metalated Primary Amines Having Tertiary Organic Groups¹

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We have previously reported^{2,3} reactions, such as the example in eq 1, of primary amines and organolithium



compounds that lead to formation of (1) primary amines in which the organic group of the organolithium compound is incorporated at the α-carbon and (2) imines or compounds such as ketones that result from transformations of the imines following quenching of the reactions. The

(1) Most of this work is taken from: Cabré, S. M.S. Dissertation, The Pennsylvania State University, University Park, PA, 1975.

(2) Richey, H. G., Jr.; Erickson, W. F.; Heyn, A. S. *Tetrahedron Lett.* 1971, 2187. Erickson, W. F.; Richey, H. G., Jr. *Ibid.* 1972, 2811.

(3) Richey, H. G., Jr.; Erickson, W. F. *J. Org. Chem.*, in press.

(12) Richey, H. G., Jr.; Moses, L. M.; Domalski, M. S.; Erickson, W. F.; Heyn, A. S. *J. Org. Chem.* 1981, 46, 3773.

Several arylamines were refluxed with *n*-butyllithium to see if any elimination process would occur. Aniline, *p*-toluidine, and *p*-methoxyaniline were recovered in good yields after 20 h⁷ and *o*-methoxyaniline, 2,6-diisopropylaniline, and *o*-(*p*-tolylthio)aniline after 72 h.⁸

Discussion

The reactions described in this paper confirm the prior assumption that lithiated primary amines having tertiary organic groups undergo ready carbon-carbon bond cleavage.^{2,3} Failure to observe cleavage when a 1:1 ratio of organolithium compound to amine was used suggests that dimetalation facilitates elimination of lithium hydride.

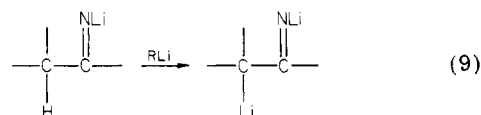
The ease with which different organic groups are cleaved potentially provides significant information about the mechanism of the fragmentation step. The observation that amine 14 reacts completely with cleavage of the phenyl group under conditions that lead to significant recovery of starting amines 6, 8, and 12 suggests that loss of phenyl in the fragmentation step is particularly favorable. Ready cleavage of phenyl also is suggested by the earlier work;^{2,3} reactions of benzylamine and of 1 with *n*-butyllithium for example, led to more rapid formation of 2 than did reactions of 1-hexanamine. At least six features of these complex reaction systems are enumerated below, however, that make it risky to equate the rate of product formation with the ease of cleavage.

(1) The second metalation (to form $RNLi_2$) is much slower than the rapid first metalation (to form $RNHLi$), and whether it is sometimes the rate-limiting step for elimination is not known.³ If dimetalation is rate limiting, then an electron-withdrawing group such as phenyl should promote metalation, leading to more rapid cleavage, an effect separate from its influence on the actual cleavage step.

(2) Aggregation of lithium-containing species may vary somewhat for reactions of the different reactant amines described here, and hence may affect reaction rates. In fact, even a single intermediate generated in different ways (e.g., 4 generated directly from 5 or in several steps from $R'R''CHNH_2$ and RLi) will be in solutions having different compositions and may exhibit different reactivities.

(3) Reaction rates may be affected by insolubility of intermediates. The nature of the solids observed in some of the reactions (particularly of 6, 8, 17, and the aromatic amines) reported in this paper was not investigated. In earlier work, however, hydrolysis of a solid isolated from a reaction of 1 and *n*-butyllithium furnished methane as well as hydrogen.³

(4) The reactions are affected by the disappearance of the organolithium compound in side reactions which may occur at different rates for different reactant amines. Even though an excess of *n*-butyllithium is used, its disappearance is demonstrated by the significant effect of adding additional amounts to the reaction of 8. The disappearance could be due to its thermal decomposition⁹ and to metalation¹⁰ of various species in the reaction mixture. Metalations of those *N*-lithioimine intermediates that have α -hydrogens¹¹ (eq 9) are particularly likely.



(5) If the eliminated organic groups end up as organolithium compounds, then any readdition of these organolithium compounds to the *N*-lithioimines will reduce apparent rates. In the reactions of 6, 8, and 12, it is unlikely that the organolithium compounds that could be formed by elimination would compete effectively with the *n*-butyllithium present initially in considerable excess. Since an internal organolithium function might compete more effectively with external *n*-butyllithium, however, it is conceivable that ring cleavage occurs in the reactions of 14 and 17 but is not observed because of readdition of the organolithium functions.

(6) The rate of cleavage of the $R''-C$ bond in 4 depends not only on the ability of the group that is lost (R'') to stabilize the transition state but also on the ability of the groups that remain (R and R'). Since the α -carbon of the amine advances from sp^3 toward sp^2 hybridization in the cleavage step, conjugative as well as inductive effects of R and R' could be important. Steric effects, significant on the rates of cleavage of alkoxides,⁴ may also be important.

The first four problems enumerated above are removed by considering only the relative rates of loss of different groups from the same substrate (e.g., the relative ease of cleavage of R , R' , and R'' from 4). The problem (6) of the stabilizing effects of the groups that remain should be minimized in those reactions (of 6, 8, and 12) in which R , R' , and R'' are alkyl groups. The abilities of primary, secondary, and tertiary alkyl groups to stabilize whatever character develops at the α -carbon of 4 during cleavage should vary much less than their abilities to stabilize the character (e.g., radical, carbanionic) that develops at the α -carbon of the group that is cleaved. Moreover, in the reactions of 6, 8, and 12, the problem (5) of reversibility is minimized; methyllithium and the primary organolithium compounds that form from cleavage of these substrates should not be more reactive toward addition than is the *n*-butyllithium present initially in large excess.

A large amount of benzyl cleavage took place in the reaction of 6. However, the composition of the product mixture does not rule out the possibility that cleavage from dilithiated 6 of methyl was more rapid than of benzyl, the loss of benzyl occurring only after subsequent addition-elimination steps. At least 37% of 12 reacted by cleavage of methyl rather than neopentyl. Because of the incomplete material balance, however, the possibility that the remainder of the reaction proceeded by loss of neopentyl cannot be rigorously excluded.

The results of the reaction of 8, however, are significant. At least a 52% yield of product (10 and 11) arose from loss of methyl, but only 15% (9) from cleavage at some stage of the pentadecyl group. In fact, cleavage of methyl from metalated 8 certainly exceeds 52% since the *N*-lithioimines that are precursors of 10 and 11 might be converted (by elimination-addition sequence) to the precursors of 2 and 9 or (by α -metalation followed by condensation) to higher molecular weight materials. Conversely, initial cleavage of the *n*-pentadecyl group from metalated 8 is probably less than the observed yield of 9 since 9 can arise

(8) Recovery of these amines is not surprising, since several arylamines have been treated with an excess of an organolithium compound in the course of synthetic procedures without unexpected products being observed. For a collection of references, see: Pozharskii, A. F.; Zvezdina, E. A. *Russ. Chem. Rev. (Engl. Transl.)* 1973, 42, 37; *Usp. Khim.* 1973, 42, 65.

(9) Wakefield, B. J. "The Chemistry of Organolithium Compounds"; Pergamon Press: Oxford, 1974; Chapter 15.

(10) For reviews of metalation by organolithium compounds, see ref 9, Chapter 3. Mallan, J. M.; Bebb, R. L. *Chem. Rev.* 1969, 69, 693.

(11) Metalation of *N*-alkylimines is well-known (ref 9, Chapter 8). For an example of metalation of an *N*-lithioimine, although in a solvent mixture more favorable than hexane for metalation, see: Cuvigny, N.; Normant, H. C. R. *Hebd. Seances Acad. Sci., Ser. C* 1967, 265, 245.

not only from cleavage of 8 but also from further reactions of the *N*-lithioimine that would result from initial loss of a methyl group. The precursor of 9 should not be prone to disappearance by conversion to intractable materials. In fact, the yield of 9 matches that of 2, a product of further reaction in which *all* alkyl groups of 9 have been lost.

Even making allowance for the statistical factor favoring loss of methyl, it is likely that the primary alkyl group is cleaved in preference to a methyl group in the initial cleavage of 8. Other results³ suggest, though less conclusively, that phenyl and 2-phenylethynyl (PhC≡C) groups also are cleaved particularly rapidly. The results are in accord with carbanionic but not radical character developing on the group being cleaved in the rate-determining step of the cleavage. A similar conclusion was drawn from a study of the loss of alkyl groups (generally primary > secondary > tertiary) from alkoxides.⁴

Experimental Section

¹H NMR spectra were taken at 60 MHz with Me₄Si as an internal reference. Absorptions are reported with the following notations: s, singlet; m, complex multiplet; c, complex overlapping absorptions. Analytical and preparative GC separations were performed by using a thermal-conductivity instrument with helium as the carrier gas and the following columns constructed out of aluminum tubing: A, XE-60 (15%) on Gas Chrom Q (80-100 mesh), 0.25 in. × 6 ft; B, SF-96 (10%) on Chromosorb W (45-60 mesh), 0.25 in. × 6 ft. The *n*-butyllithium was a commercial (Ventron Corp.) hexane solution (~2.4 M); hydrolysis of this solution produced some octane which was noted in all GC analyses of reaction products. The amines were commercial samples (Aldrich Chemical Co.). Hexane was stored over Na.

Reaction Procedure. The amine, dissolved in hexane (ca. 2 mL/mmol), was added slowly (ca. 15 min) to the *n*-butyllithium solution which was maintained under a positive pressure of nitrogen, cooled in an ice bath, and magnetically stirred. The reaction mixture then was heated at reflux temperature and stirred for the specified period of time. Ethanol or methanol (15 mL) was added, followed by addition of water (15 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (2 × 10 mL), and the combined organic layers were dried (MgSO₄). Most of the solvent was removed either in vacuo or by distillation using a small Vigreux column; this procedure would have removed any products with volatilities comparable to or greater than hexane.

Product mixtures generally were subjected to GC analysis. By use of glass U-shaped tubes inserted into the exit port of the gas chromatograph and cooled in liquid nitrogen, small samples of each significant component were collected for spectral analysis. The structures of products were determined from their NMR and IR spectra. Spectra are reported here only for compounds for which authentic samples are not readily available.

When GC analysis was used to determine yields, a known weight of a linear alkane generally was added to the crude product. Yields were determined by assuming that the detector responded equally to equal weights of different compounds.

Reaction of 1,1-Dimethyl-2-phenyl-1-ethanamine (6). GC analysis (column B, 135 °C) of the reaction that had a 1:4 ratio of amine to *n*-butyllithium gave three peaks. Peak 1 (relative retention time 1.0) was due to 7, peak 2 (1.1) to 2, and peak 3 (2.0) to 6. Yields were determined by using undecane (1.6) as the internal standard.

A reaction using a 1:1 ratio of reactants gave a crude product (85%) having NMR and IR spectra virtually identical with those of 6 and exhibiting principally the GC peak due to 6.

Reaction of 1,1-Dimethyl-1-hexadecanamine (8). GC analysis (column A) gave five peaks. Peak 1 (relative retention time 1.0) was due to 2, peak 2 (1.2) to 9, and peak 3 (2.3) to 8. Peak 4 (2.9) was due to 10: IR (CCl₄) 1720 cm⁻¹ (C=O); ¹H NMR (CCl₄) τ 7.61 (m, 2, CH₂C=O), 7.91 (s, 3, CH₃C=O), 8.71 (c, 26, CH₃(CH₂)₁₃), 9.11 (m, 3, CH₂CH₂). Peak 5 (7.7) was due to 11: IR (CCl₄) 1720 cm⁻¹ (C=O); ¹H NMR (CCl₄) τ 7.70 (c, 4, CH₂COCH₂), 8.72 (c, 30, other CH₂'s), 9.10 (m, 6, CH₃). Compounds 10 and

11 solidified in the collection tubes. Yields were determined using heptadecane as the internal standard.

Reaction of 2,2,4-Trimethyl-2-pentanamine (12). GC analysis (column B, 120 °C) gave four peaks. Peak 1 (relative retention time 1.0) was due to 13: IR (CCl₄) 1710 cm⁻¹ (C=O); ¹H NMR (CCl₄) τ 7.73 (s, 2, CH₂), 7.95 (s, 3, CH₃C=O), 8.98 (s, 9, (CH₃)₃C). Peak 2 (1.4) was due to 12, peak 3 (2.1) to an unidentified component, and peak 4 (4.0) to 2. Yields were determined by using undecane (relative retention time 5.0) as the internal standard.

Reaction of 1-Phenylcyclohexanamine (14). GC analysis (column A, 100 °C) gave two peaks. Peak 1 (relative retention time 1.0) was due to 15 and peak 2 (3.4) to 16.³ The yields were calculated by assuming that the crude product consisted only of the compounds (15 and 16) for which GC peaks were observed, since the spectra of the crude product were consistent with its being composed mainly of 15 and 16.

Reaction of 1-Adamantanamine (17). Because of the low solubility of 17 in hexane, the *n*-butyllithium was added to 17 suspended in hexane (5 mL/mmol). A considerable amount of precipitate was present throughout the reflux period. The crude product (92%) exhibited IR and NMR spectra essentially identical with those of 17.

Reactions of Arylamines. Because of the low solubility of *p*-methoxyaniline and of *o*-(*p*-tolylthio)aniline in hexane, in the reactions of these amines the *n*-butyllithium was added to the amine suspended in hexane. The crude product from each of the reactions exhibited spectra essentially identical with those of the reactant.

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Registry No. 2, 502-56-7; 6, 21404-88-6; 7, 108-88-3; 8, 35177-30-1; 9, 629-62-9; 10, 2922-51-2; 11, 87012-80-4; 12, 107-45-9; 13, 590-50-1; 14, 2201-24-3; 15, 108-94-1; 16, 2626-61-1; 17, 768-94-5.

Microbial Hydroxylation of Heteroyohimbine Alkaloids

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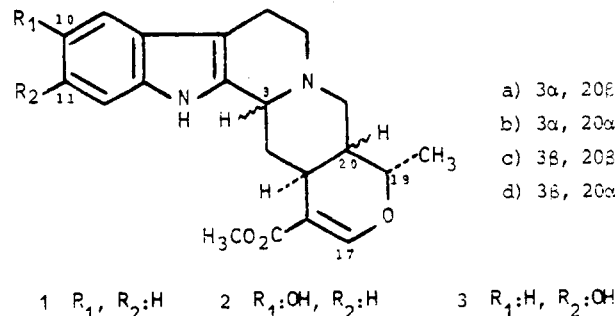
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Microbial transformations of therapeutically useful indole alkaloids have been studied extensively over the past several decades to obtain new active derivatives.¹ Surprisingly, less attention has been paid to the widespread naturally occurring heteroyohimbine alkaloids. As the sole example of a potentially reasonably useful process in this class is the regiospecific hydroxylation of ajmalicine (1a)



(1) For leading references see: Holland, H. L., In "The Alkaloids"; Rodrigo, R. G. A., Ed.; Academic Press: New York, 1981; Vol. 18, p 323.