the pyrazine went into solution. The solution was allowed to cool and concentrated in vacuo. The residue was triturated with hexane to give 1.7 g (99%) of a yellow powder, mp 124–125 °C. The analytical sample was prepared by recrystallization from cyclohexane with no change in melting point: NMR ($CDCl_3$) δ 3.20 (d, J = 2 Hz, 6), 3.43 (s, 6), 4.17 (s, 3), 5.35 (s, 1), 10.1 (s, 1); IR (KBr) 2225 (CN), 1743 (ester), 1608 (sh, pyrazine and C=N) cm^{-1}.

Anal. Calcd for $C_{13}H_{17}N_5O_5$: C, 48.29; H, 5.30; N, 21.66. Found: C, 48.39; H, 5.48; N, 21.41.

6-(Carbomethoxy)-3-cyano-2-[((dimethylamino)methylene)amino]-5-methylpyrazine 1-Oxide (9c). A solution of 0.20 g (0.96 mmol) of aminopyrazine **5c** in 5 mL of DMF dimethyl acetal was stirred at room temperature for 2 h and then worked up in the same manner as **9a** to give 0.24 g (96%) of a yellow powder, mp 114–115.5 °C. Two recrystallizations from cyclohexane provided the analytical sample: mp 115–117 °C; NMR ($CDCl_3$) δ 2.40 (s, 3), 3.19 (d, J < 1 Hz, 6), 4.05 (s, 3), 9.80 (s, 1); IR (KBr) 2215 (CN), 1738 (ester), 1605 (sh, pyrazine and C=N) cm^{-1}.

Anal. Calcd for $C_{11}H_{13}N_5O_3$: C, 50.18; H, 4.98; N, 26.61. Found: C, 50.39; H, 4.90; N, 26.59.

3-Cyano-5-(dimethoxymethyl)-2-[((dimethylamino)methylene)amino]pyrazine 1-Oxide (10a). A solution of 1.62 g (5 mmol) of methyl ester **9a**, 2.68 g (20 mmol) of lithium iodide, and 0.72 mL (40 mmol) of water in 100 mL of pyridine was heated to reflux under nitrogen for 1.5 h. The solution was allowed to cool, the solvent was removed in vacuo, the residue was dissolved in 50 mL of water, neutralized with 6 N HCl, and extracted with ethyl acetate (50 mL then 3 × 25 mL), the combined extracts were dried over Na_2SO_4, and the solvent was removed in vacuo to leave a brown oil which slowly crystallized. Recrystallization from toluene/cyclohexane with hot filtration from some insoluble gum gave 1.02 g (77%) of yellow needles: mp 106–107 °C; NMR ($CDCl_3$) δ 3.22 (s, 6), 3.44 (s, 6), 5.30 (s, 1), 8.33 (s, 1), 9.95 (s, 1); IR (KBr) 2225 (CN), 1608 (sh, pyrazine and C=N) cm^{-1}.

Anal. Calcd for $C_{11}H_{15}N_5O_3$: C, 49.80; H, 5.70; N, 26.40. Found: C, 49.95; H, 5.71; N, 26.59.

3-Cyano-2-[((dimethylamino)methylene)amino]-5-methylpyrazine 1-Oxide (10c). A solution of 0.10 g (0.38 mmol) of methyl ester **9c**, 0.20 g (1.5 mmol) of lithium iodide, and 0.054 mL (3.0 mmol) of water in 10 mL of DMF was heated to reflux for 1 h. The solution was allowed to cool, the solvent was removed in vacuo, the residue was dissolved in 10 mL of water, extracted with ethyl acetate (5 × 10 mL), and dried over Na_2SO_4, the solvent was removed in vacuo, and the yellow solid product was recrystallized from toluene/cyclohexane to give 0.064 g (82%) of yellow microcrystals, mp 172–174 °C. This material was spectrally identical with material prepared by the reaction of authentic **6c**[31] with DMF dimethyl acetal;[27] NMR (Me_2SO-d_6) δ 2.32 (s, 3), 3.10 (d, J = 4.5 Hz, 6), 8.35 (s, 1), 9.49 (s, 1); IR (KBr) 2225 (CN), 1600 (sh, pyrazine and C=N) cm^{-1}.

Anal. Calcd for $C_9H_{11}N_5O$: C, 52.67; H, 5.40; N, 34.13. Found: C, 52.59; H, 5.51; N, 34.10.

Registry No. 2a, 60705-25-1; **2b**, 73198-22-8; **4a**, 73198-23-9; **4b**, 73198-24-0; **4c**, 6743-49-3; **5a**, 73198-25-1; **5b**, 73198-26-2; **5c**, 73198-27-3; **5d**, 73198-28-4; **6a**, 73198-29-5; **6c**, 19994-56-0; **7a**, 73198-30-8; **7c**, 73198-31-9; **7d**, 73198-32-0; **8a**, 64440-77-3; **8c**, 17890-82-3; **9a**, 73198-33-1; **9c**, 73198-34-2; **10a**, 73198-35-3; **10c**, 73198-36-4; *tert*-butyl acetate, 540-88-5; methyl dimethoxyacetate, 89-91-8; aminomalononitrile tosylate, 5098-14-6.

Azetidines. 5. Reaction of 1,1,3,3-Tetramethyl- and 1-Benzyl-1,3,3-trimethylazetidinium Ions with Butyllithium and Phenyllithium. Deuterium Labeling as a Mechanistic Probe[1-3]

Max T. Wills,* Irene E. Wills,[4] Lawrence Von Dollen,[4] Barry L. Butler,[4] and John Porter[5]

Chemistry Department, California Polytechnic State University, San Luis Obispo, California 93407

Arthur G. Anderson, Jr.*

Department of Chemistry, University of Washington, Seattle, Washington 98195

Received January 21, 1980

The reactions of 1,1,3,3-tetramethylazetidinium iodide (**1**) and 1-benzyl-1,3,3-trimethylazetidinium bromide (**7**) with butyllithium and with phenyllithium were studied in ether. The products from the reaction of **1** with butyllithium were 1,3,3-trimethylpyrrolidine (**2**), 3,3-dimethyl-4-(methylamino)-1-butene (**3**), 1-(dimethylamino)-2,2-dimethylheptane (**4**), neopentylpyrrolidine (**5**), and 1-(dimethylamino)-2,2-dimethylcyclopropane (**6**). With phenyllithium, **1** gave **2** and 1-(dimethylamino)-2,2-dimethyl-3-phenylpropane (**11**). With butyllithium, **7** gave 2-phenyl-1,4,4-trimethylpyrrolidine (**8**), 1-benzyl-3,3-dimethylpyrrolidine (**9**), and 1-neopentyl-2-phenylpyrrolidine (**10**). The reaction of phenyllithium with **7** gave only **8** and **9**. Mechanistic information was obtained by labeling **1** with deuterium in three different ways: *N*-methyl-d_3, 2,2-d_2, and *N*-methyl-d_3-2,2-d_2. A primary kinetic isotope effect of 9.4 was found for the formation of **2** from 1-*N*-methyl-d_3. When **2** was formed from 1-2,2-d_2, a secondary kinetic isotope effect of 1.17 was measured. The formation of **4** from 1-2,2-d_2 was accompanied by a primary kinetic isotope effect of 4.7, suggesting a carbene intermediate. Ylide carbanions involving decomposition to a carbene carbanion in the formation of **3** and an azomethine ylide in the formation of **5** and **9** are probable intermediates. It is postulated that the azomethine ylides react with ethylene formed from the reaction of butyllithium with the solvent ether by means of a concerted (4 + 2) cycloaddition reaction. A primary kinetic isotope effect of 20 was found for the formation of pentylbenzene from dibenzyldimethylammonium bromide and butyllithium.

Previous papers in this series have reported the results of reactions of certain azetidinium salts with phenyllithium and alkali metal amides.[6] The findings provided evidence for the nature (e.g., carbene or ion pair) of the interme-

(1) Part 4: Anderson, A. G., Jr.; Wills, M. T. *J. Org. Chem.* **1968**, *33*, 3046.

(2) Support from the National Science Foundation (GY-7100) is gratefully acknowledged.

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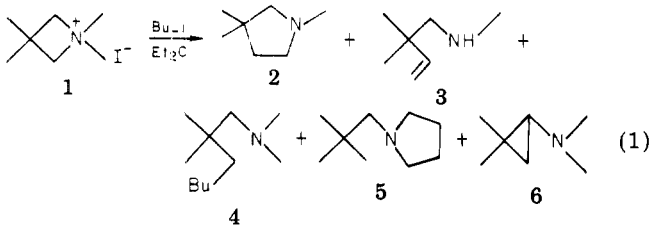
diates involved. In continuation of these studies, we have examined the behavior of two such salts, 1,1,3,3-tetramethylazetidinium iodide (1) and 1-benzyl-1,3,3-trimethylazetidinium bromide (7), and of selectively deuterium-labeled isomers (e.g., 1-d_2, 1-d_3 and 1-d_5) with both butyl- and phenyllithium.

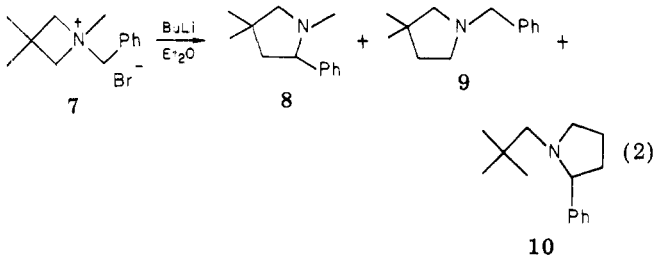
In the earlier studies[6] it was found that 1 gave 70% 1,3,3-trimethylpyrrolidine (2) and 7 gave 79% 2-phenyl-1,4,4-trimethylpyrrolidine (8) when treated with alkali metal amides in liquid ammonia. In the present study, the reaction of 1 with butyllithium in ether gave an approximately 80% total yield of six amines. Five of these have been identified as 2 (40%), 3,3-dimethyl-4-(methylamino)-1-butene (3) (33%), 1-(dimethylamino)-2,2-dimethylheptane (4) (23%), neopentylpyrrolidine (5) (3%), and 1-(dimethylamino)-2,2-dimethylcyclopropane (6) (ca. 1%) (eq 1). The structure of the sixth amine, obtained



(1)

in ca. 1% yield, has tentatively been determined to be 1-(dimethylamino)-2,2-dimethylnonane on the basis of its mass spectrum.[7]

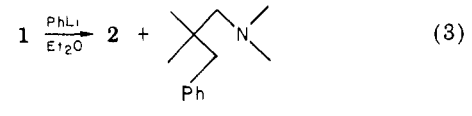
Reaction of the related azetidinium salt 7 with butyllithium in ether gave a 61% total yield of three amines. Gas chromatographic analysis and subsequent separation and characterization of the components of the mixture showed it to contain 8 (83%), 1-benzyl-3,3-dimethylpyrrolidine (9) (10%), and 1-neopentyl-2-phenylpyrrolidine (10) (7%) (eq 2). The Stevens rearrangements leading



(2)

to 2, 8, and 9 were not surprising since ring strain is relieved in the course of these reactions.[1,6]

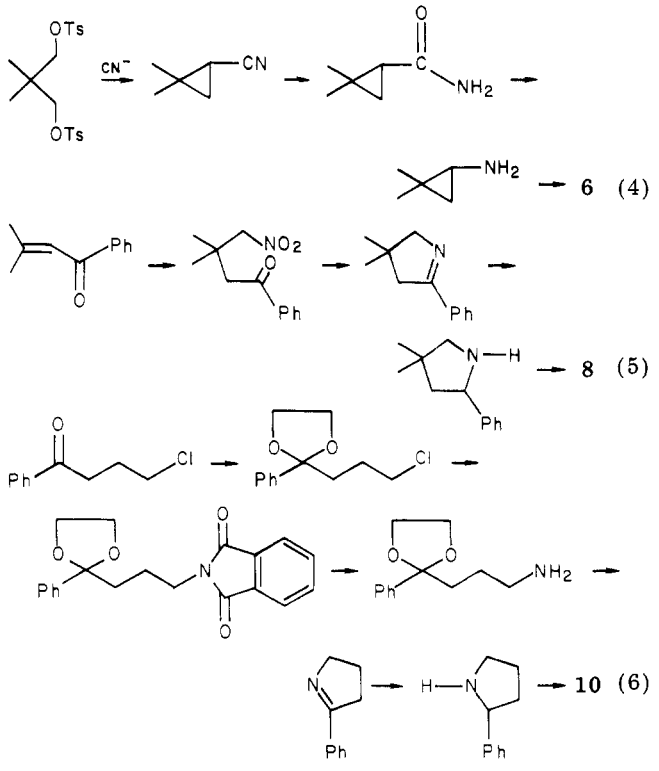
When the less basic but more nucleophilic reagent phenyllithium was used, the reaction with 1 gave only 28% 2 along with 48% of the substitution product 1-(dimethylamino)-2,2-dimethyl-3-phenylpropane (11) (eq 3),



(3)

and the reaction with 7 gave 8 (72%) and 9 (4%). It is interesting that 7 gave no substitution products with either butyl- or phenyllithium.

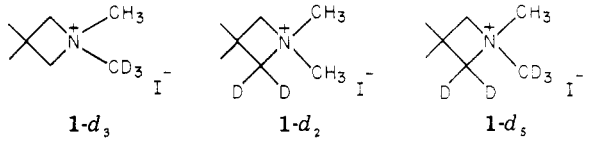
2, 3, 4, 5, and 9 were readily identified by their respective nuclear magnetic resonance and mass spectral characteristics (see Experimental Section). 6, 8, and 10 exhibited more complex spectral characteristics which did not provide conclusive structural evidence. Independent syntheses of these were therefore carried out (eq 4–6). The synthetic



samples were found to be identical (GLC and mass and NMR spectra) with the base–quaternary salt reaction products.

Mechanistic Studies

In order to gain a better understanding of the reaction of the quaternary salt 1 with butyllithium, the deuterium-labeled substrates 1-d_3, 1-d_2, and 1-d_5 were prepared.



Introduction of the methyl-d_3 group was accomplished by alkylation of the tertiary amine with methyl-d_3 iodide. The ring deuterium atoms were introduced by reduction of *N*-methylchloropivalamide[8] with lithium aluminum deuteride.

Formation of 2. The isotopic distribution in 2 when formed from an excess of butyllithium and 1-d_3 in ether was 90.4% 1-methyl-d_3-3,3-dimethylpyrrolidine and 9.6% 1,3,3-trimethylpyrrolidine-5,5-d_2 (eq 7). When formed under the same conditions from 1-d_2, the composition was 58% 1,3,3-trimethylpyrrolidine-2,2-d_2 and 42% 1,3,3-trimethylpyrrolidine-4,4-d_2 (eq 8). From 1-d_5, which had deuterium atoms at two positions, and butyllithium were

(3) Support from the California State University and Colleges in the form of a leave for creative activity is gratefully acknowledged.

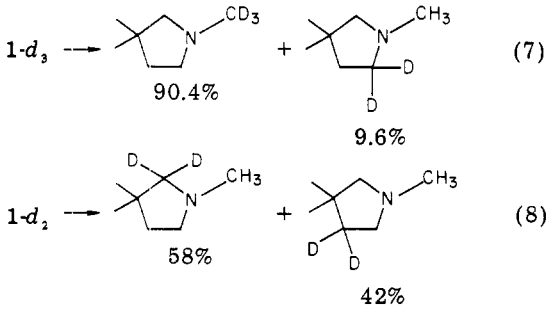
(4) Undergraduate research participants, California Polytechnic State University.

(5) Porter, John M.S. Dissertation, California Polytechnic State University, San Luis Obispo, CA, in preparation.

(6) Anderson, A. G., Jr.; Wills, M. T. *J. Org. Chem.* **1968**, *33*, 536.

(7) Mass spectrum, m/z 199 (M^+), fragment ions corresponding to a C_7H_{15} normal alkyl chain, 100 ($M^+ - C_7H_{15}$), and 58 ($CH_2{=}N^+(CH_3)_2$). This compound may result from the reaction of butyllithium with ethylene followed by reaction of the resulting n-$C_6H_{13}Li$ with 1 in the same manner as n-C_4H_9Li (eq 23).

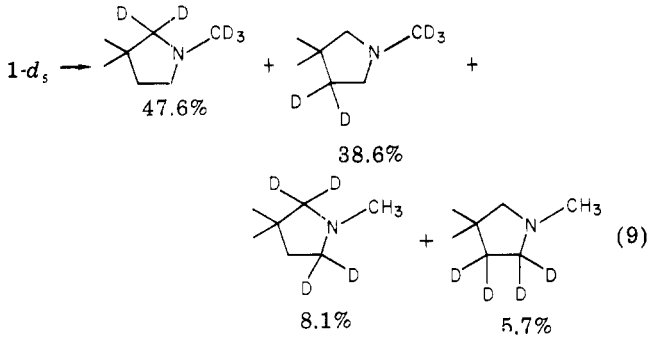
(8) Horrom, B. W.; Biermacher, U.; Hwang, K. "Abstracts of Papers", 155th National Meeting of the American Chemical Society, San Francisco, CA, March 1968, No. N10.



(7)

(8)

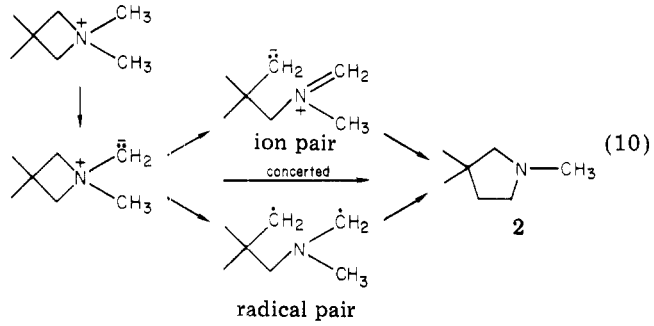
obtained four different isomers of **2**: *N*-methyl-d_3-2,2-d_2 (47.6%), *N*-methyl-d_3-4,4-d_2 (38.6%), *N*-methyl-d_0-2,2,5,5-d_4 (8.1%), and *N*-methyl-d_0-4,4,5,5-d_4 (5.7%) (eq 9).



(9)

The primary kinetic isotope effect, as calculated from the deuterium distribution in **2**, was 9.4 when the starting material was 1-d_3 and 6.2 when the starting material was 1-d_5. The deuterium distribution in **2** was measured by both nuclear magnetic resonance and mass spectrometry. While both methods gave comparable results, the mass spectrometric method was based on measurement of the abundance of the fragment $CH_2{=}N^+(CH_3)\dot{C}H_2$ which, in the case of **2**, was also the base peak. Measurement of the primary isotope effect (k_H/k_D = 6.2) in the reaction of 1-d_5 with butyllithium probably contained the largest uncertainty in that the sum of two fragments was compared with the sum of two other fragments. Additionally, deuterium was introduced into the starting material in two separate steps. The magnitude of the numerical value in this case probably represents a minimum.

The observation of a substantial primary kinetic isotope effect indicated that the rate-determining step in this Stevens rearrangement was ylide formation. Conjecture regarding the path by which such an ylide rearranges has existed for some time.[9] Arguments have centered around so-called concerted, ion-pair, and radical-pair mechanisms[10-24] (eq 10).



(10)

The unequal distribution of deuterium atoms in **2** formed from the reaction of 1-d_2 with excess butyllithium (eq 8) is a measure of a secondary deuterium isotope effect and gave a value of 1.17 per deuterium atom. For the reaction of 1-d_5, the value of the secondary deuterium isotope effect was obtained by comparing **2** (*N*-methyl-d_3-2,2-d_2) with **2** (*N*-methyl-d_3-4,4-d_2) and **2** (*N*-methyl-d_0-2,2,5,5-d_4) with **2** (*N*-methyl-d_0-4,4,5,5-d_4) and gave an average value of 1.15 per deuterium atom. The occurrence of a secondary deuterium isotope effect in the present study appears to be direct experimental evidence against a concerted mechanism for the Stevens rearrangement. It was suggested previously[6] that steric considerations of the Stevens rearrangement leading to **2** also provide an argument against a concerted mechanism.

The secondary isotope effect in this system is the result of unimolecular cleavage of the ylide derived from 1-d_2 (or 1-d_5). Whether the cleavage results in formation of a radical or carbanion is uncertain. Studies of the α secondary deuterium isotope effect have shown a universal pattern of $k_H/k_D \simeq 1.15$ per deuterium atom for reactions involving hybridization changes from sp^3 to sp^2. Most examples involve the formation of carbonium ions and radicals and the effect is thought to be controlled largely by changes in the vibrational frequencies from ground to transition state.[25] The few examples found involving a carbanion intermediate, unlike the present case, possess structures in which electron delocalization may occur and would, therefore, also involve a hybridization change from sp^3 to sp^2.[26] The secondary isotope effect found in the formation of **2** from 1-d_2 (and 1-d_5) is therefore most simply attributable to the radical-pair mechanism which provides for a hybridization change from a strain-distorted sp^3 geometry to an sp^2 geometry for the carbon concerned. Since no example was found which was structurally comparable to the present case, perhaps the ion-pair mechanism with a hybridization change from the distorted sp^3 to a normal lithium carbanion structure with either retention or inversion (which would presumably involve an S_E2-like transition state) cannot be excluded. Indeed, the analogous generation of a carbanion intermediate in the formation

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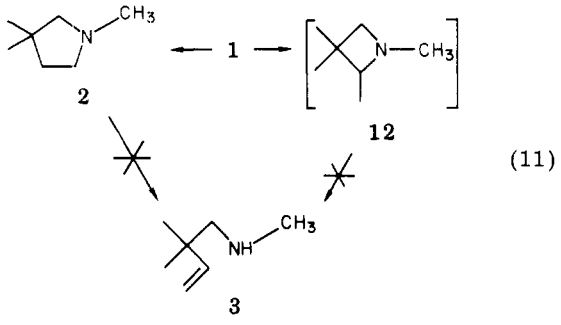
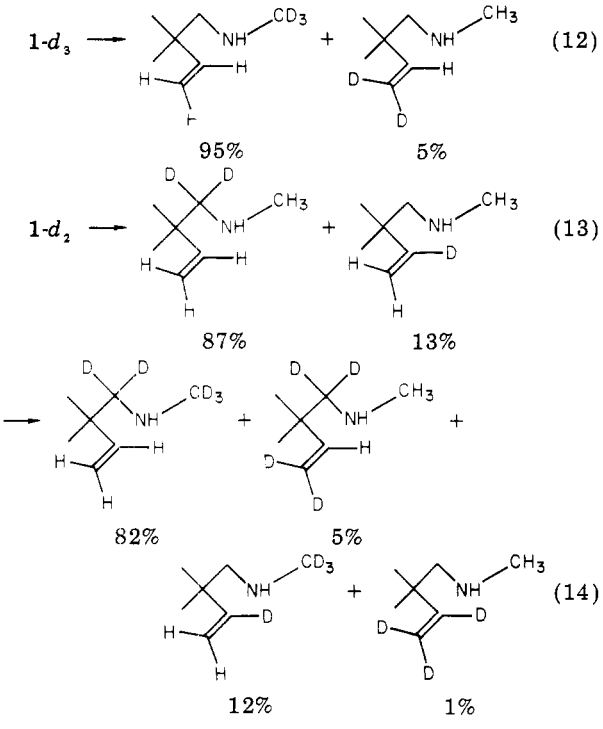
of **5** (eq 27) seems most probable and here, also, a secondary isotope effect of 1.18 per deuterium was observed.

Formation of 3. This product could have been formed from the reaction of either **2** or **12** with the base by a β elimination process (eq 11). Since **12** was not found as


(11)

a product in the reaction of **1** with butyllithium, it was synthesized independently. Both **2** and **12** were found to be unreactive to butyllithium.

Examination of the deuterium distribution in **3** when formed from labeled **1** gave the results shown in eq 12–14.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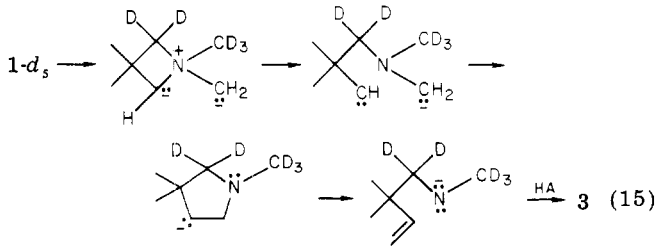
A mechanism consistent with these results involves formation of an ylide carbanion, ring opening to a carbene carbanion, ring closure, elimination, and subsequent protonation. This scheme is illustrated for the formation of **3** from **1**-d_5 involving the path of lowest energy (eq 15). It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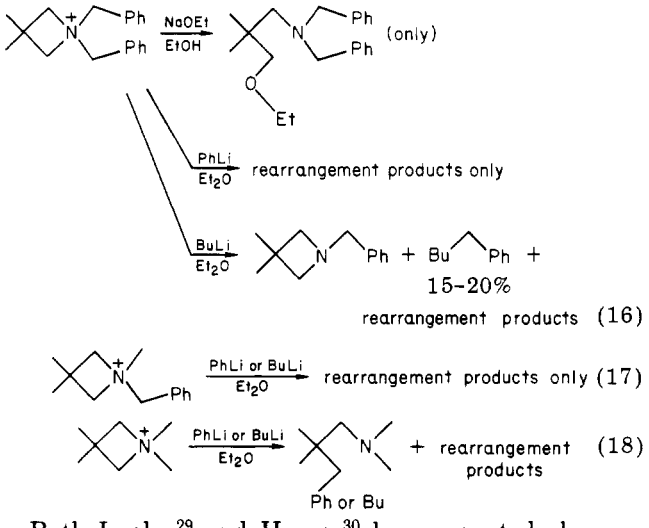
should be noted that generation of an ylide carbanion would involve a "double" primary kinetic isotope effect. Thus removal of two hydrogens would be the lowest energy pathway while removal of two deuteriums would be the highest energy pathway.

The difference in the kinetic acidities of the methyl and ring methylene hydrogens (the bonds to the latter have more s character because of the angle strain in the ring[27]) may account for the difference in the "double" isotope effects evidenced by the different labeled product ratios of **3** from **1**-d_3 and **1**-d_2 (eq 12 and 13).

Formation of 4 and 11. The 1,1-dibenzyl-3,3-dimethylazetidinium ion reacts with sodium ethoxide in ethanol to give exclusively nucleophilic ring opening,[1] with phenyllithium in ether to give only rearrangement products[28] (no nucleophilic displacement), and with butyllithium in ether to give ca. 15–20% of pentylbenzene plus 1-benzyl-3,3-dimethylazetidine (in addition to rearrangement products).[28] The 1-benzyl-1,3,3-trimethylazetidinium ion, **7**, gave no displacement products with either phenyllithium in ether or butyllithium in ether. The 1,1,3,3-tetramethylazetidinium ion, **1**, however, gave 23% of the "apparent" displacement product **4** with butyllithium in ether (eq 1) and 48% of the "apparent" displacement product **11** with phenyllithium in ether (eq 3). These differences in behavior of the quaternary ions (eqs 16–18) seemed anomalous and forced reconsideration of the initial assumption that S_N2 product structures necessarily were formed by S_N2 reactions.[6]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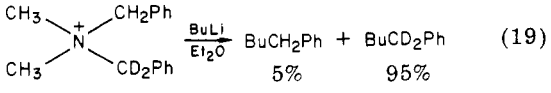
(18)

Both Lepley[29] and Hauser[30] have reported cleavage products in the reaction of butyllithium with the dibenzyldimethylammonium ion. Lepley stated that the production of pentylbenzene and benzyldimethylamine was "evidently predominantly an S_N2 displacement ..." simply because the displacement product ratio, pentylbenzene/benzyldimethylamine, remained constant as the initial butyllithium concentration was varied. We have repeated this reaction with dibenzyl-α,α-d_2-dimethylammonium bromide and have found that the pentylbenzene produced is a mixture of 95% pentylbenzene-α,α-d_2 and 5% pentylbenzene-α,α-d_0 (eq 19). Benzyldimethylamine was formed in larger yields than pentylbenzene and contained no deuterium in 84% of the molecules, one deuterium atom at the benzylic methylene in 12% of the molecules, and two deuterium atoms at the


(19)

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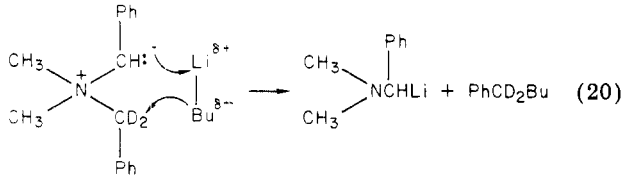
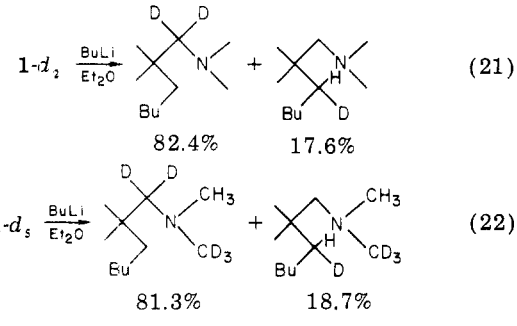
benzylic methylene in 5% of the molecules. The higher yield of benzyldimethylamine (than pentylbenzene)[29] and the deuterium distribution, which did not correspond with that of the deuterium distribution in the pentylbenzene, suggested that benzyldimethylamine was formed by two or more pathways. A mechanism to explain the observation of the unusual deuterium distribution in the pentylbenzene would appear to require abstraction of a proton (deuteron) prior to any displacement reaction. The approximate calculated primary kinetic isotope effect for this reaction is 20. A possible mechanism for the displacement involving the reaction of a second molecule of butyllithium with the intermediate ylide is shown (eq 20).



(20)

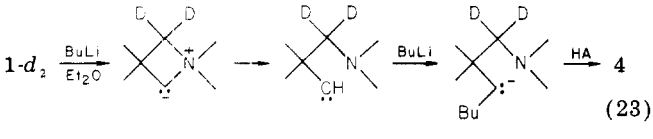
When **4** was generated from **1**-d_2, the label distribution was 82.4% 1-(dimethylamino)-2,2-dimethylheptane-*1,1*-d_2 and 17.6% 1-(dimethylamino)-2,2-dimethylheptane-*3*-d_1 (eq 21). When the starting material was **1**-d_5, 81.3% of



(21) (22)

the product contained two deuteriums at C-1 and 18.7% contained one deuterium at C-3 (eq 22).

Mechanistically, therefore, the generation of **4** must involve formation of an ylide with the negative charge on the ring, decomposition of the ylide to a carbene, reaction of the carbene with a second butyllithium, and subsequent protonation of the intermediate carbanion (eq 23).

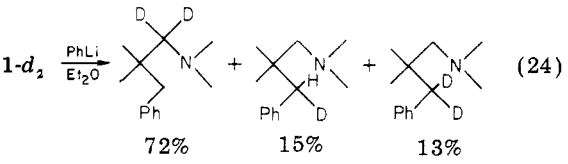


(23)

It was suggested previously that the ylide-to-carbene-to-carbanion mechanism could be the reaction path in the ring-opening reaction of 1,1,3,3-tetramethyl-2-phenylazetidinium iodide with phenyllithium.[6] In that instance, quenching the reaction mixture with heavy water led to 80% incorporation of deuterium in the ring-opened product at the carbon bearing the phenyl groups.

The formation of ylides from **1**-d_2 and **1**-d_5 is accompanied by primary kinetic isotope effects of 4.7 and 4.3, respectively. It is interesting that these values of the primary kinetic isotope effect for methylene ylide formation leading to **4** are considerably less than those for methyl ylid formation leading to the Stevens product **2** (k_H/k_D of 9.4 and 6.2 from **1**-d_3 and **1**-d_5, respectively). This finding is consistent with that observed in the formation of **3** (above) and may, again, be due to the kinetic-acidity difference between the methyl and ring methylene carbon–hydrogen bonds.

When **1**-d_2 was allowed to react with phenyllithium in ether, the measured secondary deuterium isotope effect for the formation of **2** was 1.17 per deuterium atom. In addition to **2**, the ring-opened product **11** was formed and was found to have a deuterium distribution of 72% d_2 at C-1, 15% d_1 at C-3, and 13% d_2 at C-3 (eq 24). In this

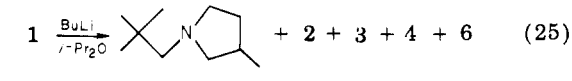


(24)

case, therefore, 26% of the product was formed by direct nucleophilic displacement by phenyllithium on **1**-d_2 while 74% of the product was formed via a carbene mechanism as suggested for the formation of **4**. The measured primary kinetic isotope effect for the formation of **11** from **1**-d_2 was approximately 3.8. Compound **3** was not formed in this reaction.

Formation of 5, 10, and 15. Even though these products were formed in relatively small amounts, the fact that **5** and **10** each contained two more carbon atoms than the corresponding starting material seemed novel. The yields of **5** relative to the combined yield of **2**, **3**, **4**, and **6** were 3% when formed from **1**, 1% from **1**-d_3, 5% from **1**-d_2, and 2% from **1**-d_5, respectively. These yields correspond qualitatively to the relative ease of formation of the respective ylide carbanions by removal of a proton from both of the *N*-methyl groups by butyllithium.

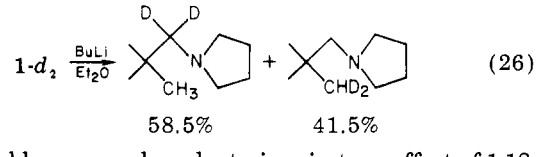
When **1** was allowed to react with butyllithium in dimethyl ether, **5** was not formed. This suggested that the source of the additional carbon atoms could be the solvent. The reaction was carried out in diisopropyl ether to test this possibility, and 1-neopentyl-3-methylpyrrolidine (**13**) was obtained in ca. 5% yield along with the other products obtained in diethyl ether (eq 25).



(25)

13

When **5** was formed from **1**-d_2, the product contained all of the deuterium atoms on the neopentyl group with 58.5% of the molecules containing two deuterium atoms on the neopentyl methylene and 41.5% of the molecules containing two deuterium atoms on one of the neopentyl methyl groups (eq 26). The formation of **5** is thus ac-



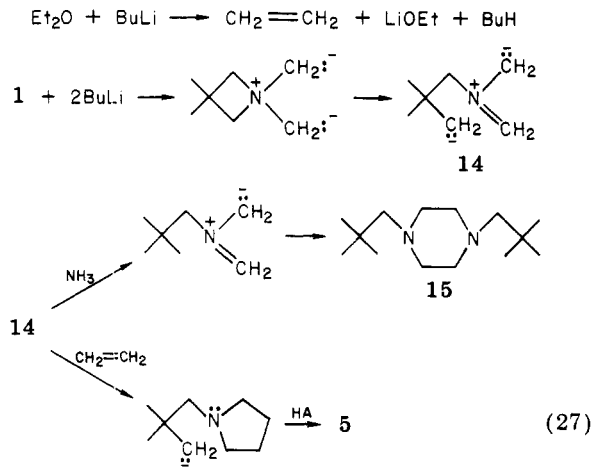
(26)

companied by a secondary deuterium isotope effect of 1.18. A mechanism consistent with these observations is given in eq 27. That butyllithium can react with ethers to give elimination products (in this case ethylene from diethyl ether) has been established by other investigators.[31]

The formation of **5** therefore appears to involve a symmetry-allowed (4 + 2) cycloaddition reaction between an azomethine ylide and ethylene. Huisgen, Scheer, and Huber[32] have reported that thermolysis of dimethyl 1-(4-methoxyphenyl)aziridine-2,3-dicarboxylate results in conrotatory ring opening to give an azomethine ylide which subsequently undergoes a (4 + 2) cycloaddition reaction

(31) Letsinger, R. L.; Pollart, D. F. *J. Am. Chem. Soc.* **1956**, *78*, 6079, and references cited therein. Maercker, A.; Demuth, W. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 75. Maercker, A.; Theyson, W. *Justus Liebigs Ann. Chem.* **1971**, *747*, 70.

(32) Huisgen, R.; Scheer, W.; Huber, H. *J. Am. Chem. Soc.* **1967**, *89*, 1753.



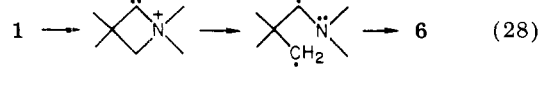
with dimethyl acetylenedicarboxylate. In the present study, the proposed azomethine ylide (14) formed from 1 did not undergo an electrocyclic transformation to 1-neopentylaziridine. The absence of this product was established by gas chromatographic comparison of the retention time of authentic neopentylaziridine with the reaction products from 1.

It is probable that the last (protonation) step in the formation of 5 occurs when the reaction is quenched with water. It is also probable that the neopentyl carbanion which is formed in this reaction possesses a tetrahedral geometry. Formation of this carbanion occurs at a slower rate when the neopentyl carbon is substituted by deuterium, and accordingly a secondary deuterium isotope effect (k_H/k_D = 1.18) was measured. This would seem to imply a significant change in the hybridization of the carbon orbitals in going to the transition state as discussed for the formation of 2 from 1-d_2 (or 1-d_5) above.

Formation of the proposed ylide carbanion intermediate (eq 27) also by sodium amide in liquid ammonia provides an explanation for the formation of ca. 1% *N,N*-dineopentylpiperazine (15) in this solvent.[33] In this case, rapid reprotonation on the neopentyl carbanion would take place prior to further reaction. Concerted dimerization of 14 is forbidden by orbital symmetry rules, but a stepwise process in the polar solvent ammonia is not precluded. At the time that this experiment was carried out, the possibility of electrocyclic ring closure of 14 to form 1-neopentylaziridine had not been considered, and it is possible that this reaction path may exist in ammonia or in other solvents where dienophiles are absent.

It is possible that the same ylide carbanion proposed as a precursor leading to 3 in this study (eq 15) was also formed with $NaNH_2/NH_3$.[33] In that instance, however, the charged pyrrolidine ring, if formed at all, could be easily protonated by the solvent.

Formation of 6. The low yield and difficulty of separation of this substance from other products prevented the isolation of a sufficient amount pure enough for direct characterization. A small quantity, obtained by preparative gas chromatography, was converted to the picrate salt. Its identity was established by comparison with synthetic 6. A reasonable mechanism by which 6 could be formed involves a radical path (eq 28).



(33) This product was formed in ca. 1% yield and was reported as an unidentified dimer in earlier studies: Anderson, A. G., Jr.; Wills, M. T. *J. Org. Chem.* **1968**, *33*, 3046.

(34) Kharasch, M. S.; Brown, H. C. *J. Org. Chem.* **1940**, *62*, 925.

Experimental Section

General. Melting points are uncorrected. Nuclear magnetic resonance spectra were obtained on Varian Model A-60, Varian HA-100, or Jeolco Model C60HL spectrometers and are reported in δ values (parts per million downfield from a tetramethylsilane internal standard). Mass spectra were recorded on a Hitachi Perkin-Elmer Model RM54 or RM50 instrument. Analyses were performed by Galbraith Laboratories, Knoxville, TN, or Midwest Microlab, Inc., Indianapolis, IN. Gas–liquid chromatography (GLC) was carried out both quantitatively and preparatively with 0.25 in. × 6 ft columns of 10% Apiezon, 10% diisooctyl phthalate, or 10% silicon gum rubber on a Hewlett-Packard F and M Model 700 instrument equipped with both flame-ionization and thermal-conductivity detectors. Thermal response characteristics of the latter were checked by injection of mixtures of known composition. The products were stable to the GLC conditions. Butyllithium (22% solution in hexane) and phenyllithium (20% solution in benzene–ether) were purchased from Aldrich. Methyl-d_3 iodide (99.5 atom %) and $LiAlD_4$ (99.5 atom %) were purchased from International Chemical and Nuclear Corporation, Irvine, CA. Diethyl ether was distilled from $LiAlH_4$ prior to use. Other solvents were reagent grade.

Reaction of 1,1,3,3-Tetramethylazetidinium Iodide (1) with Butyllithium in Ether. To a suspension of 15.0 g (62.5 mmol) of pulverized 1 in 300 mL of ether under dry N_2 was added 50 mL (172 mmol) of 22% butyllithium solution. The mixture was stirred at room temperature for 24 h. After the dropwise addition of 5 mL of water, the mixture was poured into excess 5% H_2SO_4. The acidic solution was extracted with three 50-mL portions of ether, cooled, and made strongly basic with 50% NaOH solution. The amine mixture was extracted into ether and dried (Na_2SO_4). Removal of the ether by distillation (12-in. column packed with steel wool) left 6.0 g (80% total yield) of oily products. GLC analysis of this mixture using a silicone gum rubber column, helium flow rate of 70 mL/min, and initial oven temperature of 65 °C showed the presence of 1-(dimethylamino)-2,2-dimethylcyclopropane (6, 1%), retention time 1.6 min, 1,3,3-trimethylpyrrolidine (2, 40%), retention time 2.4 min, and 1-(methylamino)-2,2-dimethyl-3-butene (3, 33%), retention time 2.9 min. After 3.6 min, the oven temperature was raised (30 °C/min) to 150 °C and 1-neopentylpyrrolidine (5, 3%), retention time 7.0 min, and 1-(dimethylamino)-2,2-dimethylheptane (4, 23%), retention time 9.1 min, were obtained.

Samples of the pure amines were obtained by trapping the effluent from the gas chromatograph in small tubes cooled in a dry ice–acetone mixture. Compound 2 was identical (NMR spectrum, GLC retention time, and picrate melting point) with an authentic sample obtained previously.

1-(Methylamino)-2,2-dimethyl-3-butene (3): mass spectrum, m/z 113 (M^+), 44 (base peak, $CH_3NH^+{=}CH_2$); NMR (CCl_4) δ 0.60 (s, 1 H, NH), 1.0 (s, 6 H, $C(CH_3)_2$), 2.33 (s, 2 H, NCH_2), 2.36 (s, 3 H, NCH_3), ABC pattern for 3 H centered at 4.90 (2 d of d, $=CH_2$) and 5.85 (2 d, =CH). Anal. Calcd for $C_{12}H_{23}NO$ [pivalyl amide derivative (oil)]: C, 73.04; H, 11.75. Found: C, 73.29; H, 11.84.

1-(Dimethylamino)-2,2-dimethylheptane (4): mass spectrum, m/z 171 (M^+), 58 (base peak, $(CH_3)_2N^+{=}CH_2$); NMR (CCl_4) δ 0.85 (s, 6 H, $C(CH_3)_2$), 0.90 (t, 3 H, term CH_3), 1.27 (m, 8 H), 2.04 (s, 2 H, NCH_2), 2.25 (s, 6 H, $N(CH_3)_2$); $n^{22}{}_D$ 1.4279; methiodide derivative, mp 241–242 °C after recrystallization from ethanol. Anal. Calcd for $C_{11}H_{25}N$: C, 77.12; H, 14.71. Found: C, 77.18; H, 14.88.

1-Neopentylpyrrolidine (5): mass spectrum, m/z 141 (M^+), 84 (base peak, $(CH_2)_4N^+{=}CH_2$); NMR (100 MHz, CCl_4), δ 1.17 (s, 9 H, $C(CH_3)_3$), 1.80 (p, 4 H), 2.40 (s, 2 H, *t*-BuCH_2N), 2.75 (t, 4 H, ring NCH_2); identical (GLC retention time, NMR spectrum) with authentic sample.

1-(Dimethylamino)-2,2-dimethylcyclopropane (6): mass spectrum, m/z 113 (M^+), 98 (base peak, $M^+ - CH_3$); identical (GLC retention time, picrate mp and mixture mp 178–179 °C after recrystallization from ethanol) with an authentic sample.

1-(Dimethylamino)-2,2-dimethylcyclopropane (6): 2,2-Dimethyl-1,3-propanediol (52 g, 0.5 mol) in 100 mL of pyridine was added to a cooled (−5 °C) solution of 286 g (1.5 mol) of *p*-toluenesulfonyl chloride in 500 mL of pyridine. The mixture

was stirred for 3 h (<0 °C) and then let stand overnight. The mixture was poured onto ice (1000 g) and the precipitate, after washing with water, 5% H_2SO_4, 5% Na_2CO_3, and again with water, was collected. Two recrystallizations from aqueous acetone gave 200 g (96%) of the ditosylate derivative, mp 118–119 °C (lit.[35] mp 116–120 °C).

A mixture of 206 g (0.5 mol) of the ditosylate and 74 g (1.5 mol) of NaCN in 1 L of ethylene glycol was heated with vigorous stirring. The product was distilled from this mixture during 2 h. The fraction distilling from 100 to 198 °C was collected. Water (300 mL) was added to the distillate which was then extracted with pentane (3 × 100 mL). The pentane extract was dried (Na_2SO_4) and then evaporated. Distillation of the residue gave 34 g (71%) of 1-cyano-2,2-dimethylcyclopropane: bp 149–151 °C; n^{22}_D 1.4258 (lit.[36] bp 154 °C; n^{23}_D 1.4262).

The nitrile (70 g, 0.74 mol) was added in one portion to 180 g (4.5 mol) of NaOH in 650 mL of water. The mixture was refluxed for 48 h, cooled, and extracted with pentane (3 × 100 mL). The aqueous solution was acidified with H_2SO_4 and extracted with ether (4 × 100 mL). Drying ($MgSO_4$), evaporation of the solvent, and distillation of the residue gave 71 g (85%) of 2,2-dimethylcyclopropane-1-carboxylic acid: bp 113–114 °C (35 mm); n^{20}_D 1.4400 [lit.[36] bp 100 °C (10 mm); n^{20}_D 1.4385].

The acid (54 g, 0.63 mol) was converted to the acid chloride with thionyl chloride (50 g, 0.71 mol) according to a literature procedure. Distillation gave 60 g (89%) of 2,2-dimethylcyclopropane-1-carbonyl chloride: bp 119–120 °C; n^{22}_D 1.4522 (lit.[36] bp 118 °C; n^{22}_D 1.4518).

The acid chloride (70 g, 0.53 mol) was added dropwise with cooling and stirring to 600 mL of an ether solution saturated with anhydrous NH_3 over a period of 2 h. Filtration, evaporation of the ether, and recrystallization of the product from ethyl acetate gave 60 g (98%) of 2,2-dimethylcyclopropane-1-carboxamide, mp 174–175 °C (lit.[36] mp 176–178 °C).

Bromine (14 mL) was added dropwise to a stirred solution of 42 g (1.05 mol) of NaOH in 350 mL of H_2O at 0–5 °C. The amide (10.5 g, 0.17 mol) was added to this solution in one portion. The mixture was stirred near 0 °C for 1.5 h and was then allowed to warm to room temperature. The mixture was distilled onto solid KOH. Separation of the organic product and distillation gave 7.8 g (55%) of 2.2-dimethylcyclopropylamine, bp 85–86 °C; n^{25}_D 1.4305.

The primary amine (10.3 g, 0.12 mol) was added dropwise with cooling to 31 g of 90% formic acid solution. Formaldehyde (27 mL, 37% solution, 0.4 mol) was then added and the mixture heated to 90 °C for 8 h. After the mixture was allowed to cool, 60 mL of 4 M HCl was added and the whole evaporated until only a yellow syrup remained. Water (15 mL) was added. The aqueous solution was extracted with ether (3 × 25 mL) and then made basic with 50% NaOH. The liberated amine after drying (KOH) was distilled and gave 8.1 g (62%) of 1-(dimethylamino)-2,2-dimethylcyclopropane (**6**), bp 93–94 °C; picrate, after one recrystallization from ethanol, mp 178–179 °C. Anal. Calcd for $C_{13}H_{18}N_4O_7$: C, 45.62; H, 5.30; N, 16.37. Found: C, 45.57; H, 5.25; N, 16.31.

Reaction of 1-Benzyl-1,3,3-trimethylazetidinium Bromide (7) with Butyllithium in Ether. To a suspension of 8.0 g (25.2 mmol) of **7** in 200 mL of ether under dry N_2 was added 30 mL (100 mmol) of 22% butyllithium solution. The mixture was stirred for 24 h at room temperature and then worked up as described for the reaction of **1**. The crude amine mixture after vacuum distillation amounted to 2.9 g (61% total yield based on a product molecular weight of 189). GLC on silicone gum rubber at 150 °C separated 2-phenyl-1,4,4-trimethylpyrrolidine (**8**, 83%), retention time 9.7 min, 1-benzyl-3,3-dimethylpyrrolidine (**9**, 10%), retention time 10.6 min, and 1-neopentyl-2-phenylpyrrolidine (**10**, 7%), retention time 14.0 min. A small amount (ca. 2% of total) of very low-boiling amine (retention time 1.4 min) was not characterized. Preparative GLC was used to obtain pure samples of the products.

2-Phenyl-1,4,4-trimethylpyrrolidine (**8**) was identical (GLC retention time, picrate melting point, NMR spectrum) with an authentic sample.[1]

1-Benzyl-3,3-dimethylpyrrolidine (**9**): mass spectrum, m/z 189 (M^+), 188 ($M^+ - H$), 133 ($M^+ - (CH_3)_2C{=}CH_2$), 132, 112 ($M^+ - C_6H_5$), 98 ($M^+ - CH_2C_6H_5$), 91 ($M^+ - (CH_3)_2C(CH_2)_3N$), 65, 55, 42; NMR (100 MHz, CCl_4) δ 1.06 (s, 6 H), 1.54 (t, 2 H), 2.22 (s, 2 H), 2.55 (t, 2 H), 3.48 (s, 2 H), 7.18 (m, 5 H).

1-Neopentyl-2-phenylpyrrolidine (**10**) was identical (mass spectrum, NMR spectrum, GLC retention time) with an authentic sample.

1-Neopentyl-2-phenylpyrrolidine (10). A mixture of 10.0 g (55 mmol) of 4-chlorobutyrophenone in 100 mL of benzene, 4.0 g (65 mmol) of ethylene glycol, and 0.5 g of *p*-toluenesulfonic acid was refluxed for 5 h with water removal by means of a Dean–Stark trap. After being cooled, the solution was washed with 10% Na_2CO_3 solution (3 × 100 mL) and dried (Na_2SO_4). The solvent was evaporated (reduced pressure) and a solution of the residual dioxolane derivative in 100 mL of dimethylformamide plus 10.0 g (54 mmol) of potassium phthalimide was stirred overnight. The mixture was then heated to 150 °C for 10 min. The cooled mixture was diluted with 300 mL of water and extracted with 200 mL of methylene chloride. The organic layer was washed with water (2 × 100 mL) and then dried (Na_2SO_4). The solvent was evaporated and the residue was recrystallized from ethanol to give 10.5 g (57%) of the dioxolane derivative of 4-phthalimidobutyrophenone as short colorless needles, mp 134–136 °C.

Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15. Found: C, 71.15; H, 5.76; N, 3.99.

To the above dioxolane derivative (10.0 g, 29 mmol) dissolved in 200 mL of ethanol was added a solution of 12.0 g of KOH in 15 mL of water. The mixture was refluxed for 6 h, cooled, and acidified with 200 mL of 3 M HCl. Most of the ethanol was removed by distillation, and the remaining solution was made strongly basic with KOH. The mixture was extracted with ether (2 × 50 mL). The combined extracts were washed with water (2 × 50 mL) and saturated salt solution (100 mL) and then dried (Na_2SO_4). Evaporation of the ether left 2.7 g of an oil residue, IR (neat) 3333 cm^{-1}. A solution of this material, assumed to be crude 2-hydroxy-2-phenylpyrrolidine, in 100 mL of benzene containing 0.5 g of *p*-toluenesulfonic acid was distilled until the volume reached ca. 10 mL. Water (50 mL) was added and the mixture was extracted with 50 mL of ether. A small portion of this ether extract was evaporated to dryness. The IR spectrum (neat) of the residue had a strong band at 1645 cm^{-1} (C=N stretch) but no OH band. The remaining ether solution, presumed to contain 2-phenyl-1-pyrroline, was added dropwsie to a slurry of 2.0 g (50 mmol) of $LiAlH_4$ in 50 mL of dry ether with stirring. The mixture was stirred overnight at room temperature. Saturated Na_2CO_3 solution (8.0 mL) was added dropwise and the precipitated salts were removed by filtration and washed with small portions of ether. Evaporation of the ether gave 1.2 g of crude 2-phenylpyrrolidine as a colorless oil, IR (neat) 3280 cm^{-1} (NH stretch). To a solution of this material in 20 mL of CH_2Cl_2 containing 5 mL of triethylamine was added 2.0 mL of pivalyl chloride, and the mixture was stirred for 1 h. It was then washed with water (2 × 50 mL), 5% HCl (2 × 50 mL), 5% NaOH (2 × 50 mL), and again with water (50 mL). After being dried (Na_2SO_4), this solution was added to a slurry of 1.0 g of $LiAlH_4$ in 40 mL of ether. The mixture was stirred overnight and then treated with 4.0 mL of saturated Na_2CO_3 solution. Filtration and evaporation of the ether gave an undetermined amount of crude 1-neopentyl-2-phenylpyrrolidine (**10**). This substance was purified by preparative GLC: mass spectrum, m/z 217 (M^+), 160 (base peak, $M^+ - C(CH_3)_3$), 131, 91. The NMR spectrum (100 MHz) and GLC retention time were recorded. The IR spectrum showed only CH stretching.

Anal. Calcd for $C_{15}H_{23}N$: C, 82.89; H, 10.67; N, 6.44. Found: C, 82.87; H, 10.62; N, 6.60.

Reaction of 1,1,3,3-Tetramethylazetidinium Iodide (1) with Phenyllithium in Ether. To a stirred suspension of 2.4 g (10 mmol) of **1** in 100 mL of ether under dry N_2 was added 10 mL (24 mmol) of 20% phenyllithium solution. The mixture was stirred at room temperature for 24 h. After the addition of 0.2 mL of water, the mixture was poured into 100 mL of 5% H_2SO_4 and extracted with ether (2 × 50 mL). The acidic solution was cooled and made alkaline with 50% NaOH solution. Most of the ether was removed by distillation and the residue analyzed by GLC. The two amine products were **2** (0.3 g, 28%) and 1-(di-

(35) Brown, R. F.; Van Gulick, N. M. *J. Am. Chem. Soc.* **1955**, *77*, 1089.

(36) Nelson, E. R.; Lane, L. A. *J. Am. Chem. Soc.* **1957**, *79*, 3467.

methylamino)-2,2-dimethyl-3-phenylpropane (11, 0.91 g, 48%). Distillation under reduced pressure gave 0.8 g of 11 as a colorless oil: bp 118–122 °C (30 mm); n^{25}_D 1.5124; NMR (CCl_4) δ 0.80 (s, 6 H, $C(CH_3)_2$), 2.06 (s, 2 H, CH_2Ph), 2.25 (s, 6 H, $N(CH_3)_2$), 2.48 (s, 2 H, NCH_2), 7.07 (m, 5 H, C_6H_5). The picrate, after one recrystallization from ethanol, had mp 153–156 °C. Anal. Calcd for $C_{19}H_{24}N_4O_7$: C, 54.28; H, 5.75; N, 13.33. Found: C, 54.32; H, 5.85; N, 13.27.

Reaction of 1-Benzyl-1,3,3-trimethylazetidinium Bromide (7) with Phenyllithium in Ether. The same procedure given for the reaction of 1 was followed. A suspension of 7 (1.6 g, 5 mmol) in 50 mL of ether was treated with 5 mL (12 mmol) of phenyllithium solution and stirred for 8 h. Workup gave 0.82 g of crude product. Distillation and subsequent GLC showed the presence of 8 (78%) and 9 (4%).

1,3,3-Trimethylazetidine-*2,2-d*$_2$. β-Chloropivalyl chloride was prepared by the method of Kharasch and Brown.[34] The acid chloride, 73 g (0.47 mol), was added dropwise with stirring and cooling to 150 mL of 40% methylamine solution. The aqueous solution was extracted with ether (2 × 150 mL) which was then washed with water, dried (Na_2SO_4), and evaporated to give 62 g (88%) of *N*-methyl-3-chloropivalamide as a colorless oil which formed colorless crystals on standing, mp 42–45 °C.

An ether solution of 4.5 g (25 mmol) of the amide was added to 1.0 g (25 mmol) of $LiAlD_4$ in 100 mL of dry ether.[8] The mixture was stirred for 24 h at room temperature and then treated dropwise with 4.0 mL of saturated Na_2CO_3 solution. The salts were removed by filtration and the ether solution was dried (Na_2SO_4). The azetidine was stored as an ether solution. A sample of the pure amine was obtained by preparative GLC for analysis: NMR (CCl_4) δ 1.16 (s, 6 H, $C(CH_3)_2$), 2.17 (s, 3 H, NCH_3), 2.83 (s, 2 H, CH_2), with resolution showing isotopic purity to ±5%; mass spectrum, *m/z* 101 (M^+), 100 ($M^+ - H$), 99 ($M^+ - D$), with the last two corresponding to β cleavage. Additional data indicating that the isotopic purity was >99% were provided by mass spectral analysis of the benzyl-α,α-d_2 bromide prepared with the same $LiAlD_4$ (see below) and of the relative amounts of the fragment ions obtained in the reaction of the methiodide derivative (1-d_2) leading to 2 and 5 (see below).

1-Methyl-*d*$_3$-1,3,3-trimethylazetidinium Iodide (1-*d*$_3$), 1,1,3,3-Tetramethylazetidinium-*2,2-d*$_2$ Iodide (1-*d*$_2$), and 1-Methyl-*d*$_3$-1,3,3-trimethylazetidinium-*2,2-d*$_2$ Iodide (1-*d*$_5$). To a stirred ether solution of the appropriate amine was added an equivalent quantity of either methyl iodide or methyl-d_3 iodide. The quaternary salt in each instance began to precipitate immediately. After 24 h, the salt was collected and recrystallized from a minimum of ethanol to give 1-d_3, 1-d_2, and 1-d_5, mp 188–189 °C, 188–189 °C, and 187–189 °C, respectively. The non-deuterium-containing salt 1 had mp 188–189 °C [lit.[37] mp 188–189 °C]. NMR, 1-d_3: NMR (D_2O) δ 1.50 (s, 6 H, $C(CH_3)_2$), 3.34 (s, 3.02 H, NCH_3), 4.27 (s, 4 H, NCH_2). 1-d_2: NMR (D_2O) δ 1.50 (s, 6 H, $C(CH_3)_2$), 3.34 (s, 6.0 H, NCH_3), 4.27 (s, 2 H, NCH_2). 1-d_5: NMR (D_2O) δ 1.50 (s, 6 H, $C(CH_3)_2$), 3.34 (s, 3.0 H, NCH_3), 4.27 (s, 2.0 H, NCH_2).

Reaction of 1-Methyl-*d*$_3$-1,3,3-trimethylazetidinium Iodide (1-*d*$_3$) with Butyllithium in Ether. To a suspension of 1.0 g (4.1 mmol) of 1-d_3 in 100 mL of dry ether under dry N_2 was added 8 mL (28 mmol) of a 22% butyllithium solution. The mixture was stirred at room temperature for 24 h, 0.5 mL of water was added, and, after filtration, the ether solution was extracted with 10% H_2SO_4 (2 × 25 mL). The acid extracts were combined and washed with fresh ether. The acid extract was made strongly basic with 50% NaOH solution with stirring and cooling. The amine mixture was extracted into a minimum of ether and analyzed by GLC as described for the reaction of 1 with butyllithium. The amines obtained (the first three were isolated by preparative GLC; yields from peak areas) were 2 (31%), 3 (24%), 4 (43%), 5 (1%), and 6 (1%). 2: NMR (CCl_4) δ 1.03 (s, 6 H, $C(CH_3)_2$), 1.49 (t, 2 H, CCH_2C), 2.14 (s, slightly >2 H, NCH_2 plus NCH_3), 2.44 (t, slightly <2 H, NCH_2); mass spectrum (18 eV), *m/z* (relative intensity) 57 (0.4), 58 (0.5), 59 (10.7), 60 (100, for $CH_2{=}N^+(CD_3)\dot{C}H_2$), 61 (7.0). 3: NMR ($CCl_4$) δ 2.35 (s, slightly >2 H, NCH_2 and NCH_3), plus other peaks, except for absence of most of NCH_3, as described for unlabeled 3 above; mass spectrum (13 eV), *m/z* (relative intensity) 44 (5.3), 45 (0.6), 46 (1.1), 47 (100, for $CH_2{=}NH^+CD_3$), 48 (2.8), with the peak at 46 indicative of incomplete labeling of CD_3I used to prepared 1-d_3. 4: NMR (CCl_4) δ 2.04 (s, 2 H, NCH_2), 2.25 (s, 3 H, NCH_3), plus other peaks as described for unlabeled 4 above; mass spectrum (13 eV), *m/z* (relative intensity) 60 (0.3), 61 (100, $CH_2{=}N^+(CH_3)CD_3$), 62 (4.2).

Reaction of 1,1,3,3-Tetramethylazetidinium-*2,2-d*$_2$ Iodide (1-*d*$_2$) with Butyllithium in Ether. The same procedure was used as for the reaction of 1-d_3 and butyllithium to give (yields from GLC peak areas) 2 (63%), 3 (19%), 4 (12%), 5 (5%), and 6 (<1%). The first four were isolated by preparative GLC and isotopic analyses performed as follows. 2: NMR (CCl_4) δ 1.49 (5) and 2.44 (t) with relative areas of 44 and 56%, respectively, corresponding to 61% C-2-d_2 and 39% C-4-d_2 assuming no loss of deuterium. The triplet at δ 2.44 showed relative intensities of 1:4:1 (predicted 1:6:1 for no loss of deuterium and no secondary isotope effect), corresponding to <50% C-4-d_2 molecules and consistent with the analysis of CCH_3 vs. NCH_3 plus C-2-CH_2 absorptions; mass spectrum (18 eV), *m/z* (relative intensity) 57 (70, $CH_2{=}N^+(CH_3)_2$), 58 (7.0), 59 (100, $CD_2{=}N^+(CH_3)_2$), 60 (6.0), corresponding to a $CD_2{=}N^+(CH_3)_2$ to $CH_2{=}N^+(CH_3)_2$ ratio of 1.38:1 and a secondary isotope effect, k_H/k_D, of 1.17 per deuterium atom. 3: NMR (CCl_4) δ 0.60 (s, 1 H, NH), 1.0 (s, 6 H, $C(CH_3)_2$), 2.35 (s, slightly >2 H, NCH_2 plus NCH_3), ABC pattern for slightly <3 H centered at 4.90 and 5.85; mass spectrum (13 eV), *m/z* (relative intensity) 44 (14.4, $CH_2{=}N^+CH_3$), 45 (2.7), 46 (100, $CD_2{=}NH^+CD_3$), 47 (3.1), corresponding to the composition of 3 as 87% $CH_2{=}CHC(CH_3)_2CD_2NHCH_3$ and 13% $CH_2{=}CDC(CH_3)_2CH_2NHCH_3$. Part of the peak at *m/z* 45 may be due to $CHD{=}NH^+CH_3$. 4: NMR (CCl_4) showed absorption for NCH_2 (δ 2.04) very small relative to NCH_3 (δ 2.25) signal (sensitivity not sufficient for reliable quantiative comparison); mass spectrum (18 eV), *m/z* (relative intensity) 56 (0.0), 57 (0.1), 58 (21.3, $CH_2{=}N^+(CH_3)_2$), 59 (2.0), 60 (100, $CD_2{=}N^+(CH_3)_2$), 61 (5.9), for a calculated primary isotope effect, k_H/k_D, of 4.7. 5: mass spectrum (13 eV), *m/z* 143 ($M^+ = C_9H_{17}D_2N^+$), 86 ($CD_2{=}N^+(CH_3)_4$), 84 ($CH_2{=}N^+(CH_2)_4$), with *m/z* 86 to 84 intensity ratio of 1:1.42 (calculated for no secondary deuterium isotope effect, 1:1), and (70 eV) 128 ($M^+ - CH_3$), 126 ($M^+ - CD_2H$), with *m/z* 128 to 126 intensity ratio of 6.2:1 (calculated for no secondary deuterium isotope effect, 5:1), corresponding to the composition of 5 as 41.5% $(CH_3)_2(CD_2H)CCH_2N(CH_2)_4$ and 58.5% $(CH_3)_3CCD_2N(CH_2)_4$ and a secondary isotope effect, k_H/k_D, of 1.18 per deuterium atom.

Reaction of 1-Methyl-*d*$_3$-1,3,3-trimethylazetidinium-*2,2-d*$_2$ Iodide (1-*d*$_5$) with Butyllithium in Ether. The same procedure was used as for the reaction of 1-d_3 and butyllithium. The amines obtained (first three isolated by preparative GLC; yields from peak areas) were 2 (55%), 3 (24%), 4 (18%), 5 (2%), and 6 (<1%). 2: NMR (CCl_4) exhibited all signals found for unlabeled compound (above) with qualitatively more H atoms at C-5 than at C-4 and more D than H at N-CH_3; mass spectrum, *m/z* (relative intensity) 57 (1.2), 58 (0.6), 59 (12, $CH_2{=}N^+(CH_3)\dot{C}D_2$), 60 (81, $CH_2{=}N^+(CD_3)\dot{C}H_2$), 61 (17, $CD_2{=}N^+(CH_3)CD_2$), 62 (100, $CD_2{=}N^+(CD_3)\dot{C}H_2$), 63 (8.4), in agreement with the existence of both primary and secondary kinetic isotope effects, with intensity ratios of 62 + 60 to 61 + 59 of 6.2:1 (primary isotope effect), 62 to 60 of 1.23:1, and 61 to 59 of 1.4:1 (average secondary isotope effect of 1.15 per deuterium atom). 3: NMR (CCl_4) showed absorptions for the vinylic, CCH_3, and NH hydrogens as described above for unlabeled material but with a very small peak for NCH_2 hydrogens; mass spectrum (13 eV), *m/z* (relative intensity) 44 (0.9, $CH_2{=}NH^+CH_3$), 45 (0.4), 46 (6.2, $CD_2{=}NH^+CH_3$), 47 (14, $CH_2{=}NH^+CD_3$), 48 (4), 49 (100, $CD_2{=}NH^+CD_3$), 50 (2.8), corresponding to the composition of 3 as 82% $CD_3NHCD_2C(CH_3)_2CH{=}CH_2$, 12% $CD_3NHCH_2C(CH_3)CD{=}CH_2$, 5% $CH_3NHCD_2C(CH_3)_2CH{=}CD_2$, and 1% $CH_3NHCH_2C(CH_3)_2CD{=}CD_2$. 4: NMR ($CCl_4$) showed a ratio of NCH_3 to NCH_2 of 8:1, corresponding to 84% NCD_2; mass spectrum (13 eV), *m/z* (relative intensity) 60 (1.3), 61 (23.1, $CH_2{=}N^+(CH_3(CD_3)$, 62 (4.8), 63 (100, $CD_2{=}N^+(CH_3)CD_3$), 64 (5.1), with the ratio of *m/z* 63 to 61 of 4.3:1 (primary kinetic isotope effect).

Reaction of 1,1,3,3-Tetramethylazetidinium-*2,2-d*$_2$ Iodide (1-*d*$_2$) with Phenyllithium in Ether. The reaction was run as described for 1 and phenyllithium with 0.6 g (2.5 mmol) of 1-d_2

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and 3.0 mL (7.2 mmol) of phenyllithium solution. After workup, preparative GLC afforded **2** (ca. 50%) and **11** (ca. 50%). **2**: mass spectrum, m/z 58 and 60, intensity ratio of 1.43:1 at 15 eV and 1.41:1 at 13 eV, corresponding to a secondary isotope effect of 1.19 per deuterium atom and 59% C-2-d_2 and 41% C-4-d_2 in **2**. **11**: mass spectrum (12 eV), m/z (relative intensity) 58 (37, $CH_2{=}N^+(CH_3)_2$), 59 (3.2), 60 (100, $CD_2{=}N^+(CH_3)_2$), 61 (4.6), corresponding to 27% ion 58 and 73% ion 60. After correction for ^{13}C natural abundance the mass spectrum (relative intensity) for the tropylium ion fragment had m/z 91 (100), 92 (21), 93 (17). The calculated composition of **11** was 72% $PhCH_2C(CH_3)_2CD_2N(CH_3)_2$, 15% $PhCHDC(CH_3)_2CH_2N(CH_3)_2$, and 13% $PhCD_2C(CH_3)_2CH_2N(CH_3)_2$.

Reaction of 1,1,3,3-Tetramethylazetidinium Iodide (1) with Butyllithium in Dimethyl Ether and in Diisopropyl Ether. To a stirred suspension of 5.0 g (21 mmol) of **1** in 75 mL of dimethyl ether or diisopropyl ether was added 18 mL (60 mmol) of butyllithium solution. The reaction in dimethyl ether was stirred at the boiling point (dry ice–acetone condenser) for 48 h. The reaction in diisopropyl ether was stirred at room temperature for 24 h. Workup of both reactions as described for diethyl ether gave the amine products as ether solutions. GLC analysis of the reaction for dimethyl ether showed the presence of **2**, **3**, **4**, and **6** but not **5**, and that of the reaction for diisopropyl ether showed **2**, **3**, **4**, **6**, and 1-neopentyl-3-methylpyrrolidine (**13**, ca. 5%), retention time 7.7 min [retention time of **5** is 7.0 min under the same conditions]. Preparative GLC gave a sample of pure **13**: mass spectrum, m/z (relative intensity) 155 (9.6, M^+), 140 (20, $M^+ - CH_3$), 98 (100, $M^+ - C_4H_9$), 84 (8, $M^+ - C_5H_{11}$).

Benzyl-α,α-d_2 Bromide. To a slurry of 1.02 g (24 mmol) of $LiAlD_4$ in 75 mL of dry ether was added a solution of 5.8 g (39 mmol) of freshly distilled ethyl benzoate in 20 mL of ether over a period of 20 min. The mixture was stirred for 2 h and then treated dropwise with 4 mL of saturated Na_2CO_3 solution. Filtration and evaporation of the ether gave 4.65 g of benzyl-α,α-d_2 alcohol. The alcohol was dissolved in 75 mL of cyclohexane and a slow stream of anhydrous HBr was passed through the solution for 2 h. The conversion to the bromide was followed by GLC (silicon gum rubber, 140 °C). The aqueous layer was separated and the cyclohexane solution dried ($CaCl_2$). Evaporation of the solvent and distillation of the residue under reduced pressure gave 5.0 g (74%) of benzyl-α,α-d_2 bromide as a colorless oil: bp 93–94 °C (25 mm); mass spectrum, m/z (relative intensity) 170 (0.5), 171 (0.1), 172 (100), 173 (9.6), 174 (95), 175 (7), corresponding to an isotopic purity of greater than 99.5 atom %; tropylium ion fragments intensities at m/z 91 and 92 were 0 and <1, respectively.

Reaction of Dibenzyl-α,α-d_2-dimethylammonium Bromide with Butyllithium in Ether. The quaternary salt was prepared as colorless needles (ca. 95% yield) by treating an ether solution of benzyldimethylamine with an equivalent of benzyl-α,α-d_2 bromide, letting the mixture stand overnight, and recrystallizing the precipitated salt from ethanol.

To a suspension of 0.8 g (2.6 mmol) of the quaternary salt in 20 mL of dry ether was added 6.0 mL (12 mmol) of a 15% butyllithium solution. The mixture was stirred under dry N_2 for 24 h. After the addition of water (0.2 mL), the mixture was extracted with 10% H_2SO_4 (3 × 15 mL). The remaining ether solution was washed with water (2 × 25 mL), dried (Na_2SO_4), and evaporated to give 0.15 g of a neutral residue. GLC analysis of this residue showed it to be pentylbenzene (32% total yield) and *trans*-stilbene (6% total yield). The acid extract was made strongly basic with 50% NaOH and the amine products were extracted into ether and dried (Na_2SO_4). Evaporation of the ether gave an undetermined quantity of an amine mixture.[29] Preparative GLC was used to isolate pure pentylbenzene from the neutral fraction and pure benzyldimethylamine from the amine fraction.

Pentylbenzene: mass spectrum, m/z (relative intensity) 148 (5.05 ± 0.08), 149 (1.50 ± 0.07), 150 (100), 151 (12.0 ± 0.15), 152 (0.69 ± 0.02), corresponding to a ratio of α,α-d_2 to unlabeled of 19.8 ± 0.3:1 and k_H/k_D = 19.8 ± 0.3 (primary isotope effect).

Benzyldimethylamine: mass spectrum (13 eV), m/z (relative intensity) 134 (8.1 ± 0.3), 135 (100), 136 (25.1 ± 0.2), 137 (6.4 ± 0.1), 138 (0.9 ± 0.02). Comparison with an authentic unlabeled sample, mass spectrum (13 eV), m/z (relative intensity) 135 (100), 136 (11.3 ± 0.5), 137 (0.57 ± 0.02), gave, after correction for ^{13}C natural abundance, a product composition of 84% unlabeled, 12% α-d_1, and 4% α,α-d_2 benzyldimethylamine.

1,2,3,3-Tetramethylazetidine (12). Methylmagnesium iodide was prepared from 7.5 g (0.25 g atom) of magnesium and 45 g (0.25 mol) of methyl iodide in dry ether. The Grignard reagent was transferred to a dropping funnel and added to a solution of 44 g (0.2 mol) of 2,2-dimethyl-3-(*N*-methylbenzamido)propanal[6] in 800 mL of ether over a period of 1 h. The mixture was stirred for 3 h and then poured onto a mixture of ice (300 g) and 5% H_2SO_4 (200 mL). Evaporation of the solvent from the separated, washed (water and saturated NaCl solution), and dried (Na_2SO_4) ether layer gave 37 g of colorless oil which solidified on standing. Recrystallization from benzene–cyclohexane gave 32 g (54%) of 3,3-dimethyl-4-(*N*-methylbenzamido)-2-butanol: mp 65–67 °C; IR (KBr) 3333 (OH stretch) and 1626 cm^{-1} (amide C=O). Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.43; H, 9.10; N, 5.90.

A solution of 15 g (64 mmol) of the benzamide derivative in 125 mL of ethanol containing 35 g of KOH and 50 mL of water was refluxed for 4 h, diluted with water (1 L), and then distilled until most of the ethanol was removed. The resulting aqueous solution was continuously extracted (24 h) with ether. The ether extract was dried (Na_2SO_4) and evaporated, and the residue was distilled under reduced pressure to give 6.4 g (76%) of 4-(methylamino)-3,3-dimethyl-2-butanol: bp 84–85 °C (10 mm); IR (neat) 3333 cm^{-1} (OH and NH stretch). Anal. Calcd for $C_7H_{17}NO$: C, 64.07; H, 13.06; N, 10.67. Found: C, 64.15; H, 13.10; N, 10.52.

To a solution of 5.2 g (40 mmol) of the amino alcohol in 100 mL of CCl_4 cooled to 0 °C was added 5.0 g (43 mmol) of $ClSO_3H$ over a period of 20 min with vigorous stirring. The mixture was allowed to warm to room temperature and stirred for an additional 2 h. After evaporation of the solvent (reduced pressure), the residue was taken up in a minimum of 95% ethanol and diluted with excess ether which gave 7.0 g (83%) of 1-(methylamino)-2,2-dimethyl-3-sulfatobutane as a colorless, fine powder, mp 226–228 °C dec. Anal. Calcd for $C_7H_{17}NO_4S$: C, 39.79; H, 8.11; N, 6.63. Found: C, 39.70; H, 8.15; N, 6.51.

The sulfato derivative (3 g, 14 mmol) was refluxed in 400 mL of 10% NaOH for 2 h and the product was then steam distilled onto solid NaOH. Separation of the organic layer and distillation gave 1.2 g (76%) of 1,2,3,3-tetramethylazetidine (**12**): bp 105–108 °C; NMR (CCl_4, 100 MHz) δ 0.95 (d, 3 H, J = 5 Hz), 0.99 (s, 3 H), 1.11 (s, 3 H), 2.7 (s, 3 H), 2.37 (d, 1 H, J = 5 Hz), 3.01 (d, 1 H, J = 5 Hz). The methiodide, after one recrystallization from ethanol, had mp 210–211 °C dec. Anal. Calcd for $C_8H_{18}NI$: C, 37.66; H, 7.11; N, 5.49. Found: C, 37.58; H, 7.08; N, 5.61.

Reaction of 1,2,3,3-Tetramethylazetidine (12) and 1,3,3-Trimethylpyrrolidine (2) with Butyllithium in Ether. To 70 mL of dry ether containing 0.4 g (3.5 mmol) each of **2** and **12** was added 16 mL of 22% butyllithium solution. The mixture was stirred for 24 h at room temperature. During this time, aliquots were periodically removed, quenched with water, and analyzed by GLC. The starting materials remained unchanged.

Registry No. **1**, 19275-00-4; **1**-d_2, 73433-68-8; **1**-d_3, 73433-69-9; **1**-d_5, 73433-70-2; **2**, 16911-20-9; **2** picrate, 73433-71-3; **2** (*N*-CD_3), 29886-70-2; **2** (2,2-d_2), 73433-72-4; **2** (4,4-d_2), 73433-73-5; **2** (5,5-d_2), 73433-74-6; **2** (*N*-CD_3,2,2-d_2), 73433-75-7; **2** (*N*-CD_3,4,4-d_2), 73433-76-8; **2** (2,2,5,5-d_4), 73433-77-9; **2** (4,4,5,5-d_4), 73433-78-0; **3**, pivalylamide derivative, 73433-80-4; **3**, 73433-79-1; **3** (*N*-CD_3), 73433-81-5; **3** (4,4-d_2), 73433-82-6; **3** (1,1-d_2), 73433-83-7; **3** (3-*d*), 73433-84-8; **3** (1,1,4,4-d_4), 73433-85-9; **3** (*N*-CD_3,3-*d*), 73433-86-0; **3** (3,4,4-d_3), 73433-87-1; **4**, 73433-88-2; **4** methiodide, 73433-89-3; **4** (*N*-CD_3), 73433-90-6; **4** (1,1-d_2), 73433-91-7; **4** (3-*d*), 73433-92-8; **4** (*N*-CP_3,1,1-d_2), 73433-93-9; **4** (*N*-CD_3,3-*d*), 73433-94-0; **5**, 59427-40-6; **5** (α,α-d_2), 73433-95-1; **5** (γ,γ-d_2), 73433-96-2; **6**, 73433-97-3; **6** picrate, 73433-98-4; **7**, 73433-99-5; **8**, 16911-21-0; **8** picrate, 16911-22-1; **9**, 73434-00-1; **10**, 73434-01-2; **11**, 73434-02-3; **11** picrate, 73434-03-4; **11** (1,1-d_2), 73434-04-5; **11** (3-*d*), 73434-05-6; **11** (3,3-d_2), 73434-06-7; **12**, 73434-07-8; **12** methiodide, 73434-08-9; **13**, 73434-09-0; butyllithium, 109-72-8; 2,2-dimethyl-1,3-propanediol, 126-30-7; *p*-toluenesulfonyl chloride, 98-59-9; 2,2-dimethyl-1,3-propanediol ditosylate, 22308-12-9; 1-cyano-2,2-dimethylcyclopropane, 5722-11-2; 2,2-dimethylcyclopropane-1-carboxylic acid, 931-26-0; 2,2-dimethylcyclopropane-1-carbonyl chloride, 50675-57-5; 2,2-dimethylcyclopropane-1-carboxamide, 1759-55-3; 2,2-dimethylcyclopropylamine, 73434-10-3; 4-chlorobutyrophenone, 939-52-6; 2-(3-chloropropyl)-2-phenyldi-

oxolane, 3308-98-3; potassium phthalimide, 1074-82-4; 2-(3-phthalimidopropyl)-2-phenyldioxolane, 3308-99-4; 2-hydroxy-2-phenylpyrrolidine, 73434-11-4; 2-phenyl-1-pyrroline, 700-91-4; 2-phenylpyrrolidine, 1006-64-0; pivalyl chloride, 3282-30-2; phenyllithium, 591-51-5; 1,3,3-trimethylazetidine-2,2-d_2, 73453-13-1; β-chloropivalyl chloride, 4300-97-4; methylamine, 74-89-5; *N*-methyl-3-chloropivalamide, 73434-12-5; ethyl benzoate, 93-89-0; benzyl-α,α-d_2 alcohol, 21175-64-4; benzyl-α,α-d_2 bromide, 51271-29-5; dibenzyl-α,α-d_2-dimethylammonium bromide, 73434-13-6; benzyldimethylamine, 103-83-3; pentylbenzene, 538-68-1; *trans*-stilbene, 103-30-0; pentylbenzene-α,α-d_2, 68639-74-7; benzyldimethylamine-α-*d*, 3535-98-6; benzyldimethylamine-α,α-d_2, 38161-07-8; 2,2-dimethyl-3-(*N*-methylbenzamido)propanal, 15451-21-5; 3,3-dimethyl-4-(*N*-methylbenzamido)-2-butanol, 73434-14-7; 4-(methylamino)-3,3-dimethyl-2-butanol, 73434-15-8; 1-(methylamino)-2,2-dimethyl-3-sulfatobutane, 73434-16-9.

Catalytic Asymmetric Induction in Oxidation Reactions. Synthesis of Optically Active Epoxynaphthoquinones

Henk Pluim and Hans Wynberg*

Department of Organic Chemistry, The University of Groningen, Nijenborgh 16, 9747 AG Groningen, The Netherlands

Received December 27, 1979

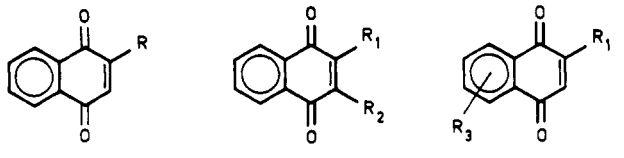
Optically active 2,3-epoxides of a variety of substituted 1,4-naphthoquinones have been prepared in an asymmetric synthesis. Enantiomeric excesses of up to 45% were realized. Some data could be obtained concerning the influence of substituents on the enantiomeric excess. Furthermore, the absolute configurations could be deduced from the CD spectra.

The roles of vitamin K[1,2] and its epoxide[3,4] are of considerable current interest. Since many quinones and a few quinone epoxides have been shown to possess antimicrobial and antitumor activity and since the quinone epoxides seem to play an important role in metabolic processes, the synthesis of *optically active*[5] quinone epoxides seemed to us to be an important goal.

The preparation of chiral epoxides in good optical yields is difficult and often tedious. Epoxides do not lend themselves to the classical method of diastereomeric resolution unless the compounds contain an additional functional group. Consequently, asymmetric synthesis using chiral peracids or metal catalyzed epoxidations using peroxides have been the subject of much activity.[6a-c] Recently electron-deficient olefins (e.g., chalcones, quinones) have been epoxidized with H_2O_2 or *t*-BuOOH in an asymmetric synthesis, using quinine salts as chiral catalysts, in optical yields of up to 55%.[7a-c]

The reactions have been carried out under phase-transfer conditions. The great versatility of phase-transfer catalysts has provided a stimulus for extensions into the area of catalytic asymmetric synthesis.

Chiral catalysts based on alkaloids or amino acid salts have produced modest but encouraging results.[8] That this reaction is a true counterion effect rather than a solvent effect is shown by the zero optical yields achieved under non-phase-transfer conditions in the presence of quinine. In the present study the above-described phase-transfer epoxidation method has been applied to a great variety of naphthoquinones. To obtain a better insight into the influence of substituents on the enantiomeric excess by the epoxidation reaction, we synthesized naphthoquinones with different substituents at carbon two (see Tables I and II).



Additionally, 2,3-disubstituted and 2,5-, 2,6-, and 2,7-disubstituted 1,4-naphthoquinones were prepared. In order to correlate the reaction mechanism, the structure of substrate, and the extent of asymmetric induction, i.e., enantiomeric excess, one must determine a number of parameters. In addition to the knowledge of the absolute configuration of the product, the influence of minor structural variations on the enantiomeric excess needs to be cleared up.

Synthesis of Starting Materials

For the synthesis of substituted 1,4-naphthoquinones several protocols are possible. The classical method is the oxidation of substituted naphthalenes by means of chromic anhydride in acetic acid.[9a] Other oxidants such as H_5IO_6[9b] and H_2O_2[9c] have also been used. A disadvantage of this method is the low yield (normally lower than 30%) as well

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0022-3263/80/1945-2498$01.00/0