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Reduction of Alpha-Bromopentanamides by Diborane with Simultaneous Hydrogenolysis of the Carbon-Bromine Bond

Antônio F.C. Alcântara and Dorila Piló-Veloso

Departamento de Química, ICEx, Universidade Federal de Minas Gerais,
31270-901 Belo Horizonte - MG, Brazil

David Lee Nelson*

Faculdade de Farmácia, Universidade Federal de Minas Gerais,
30180-112 Belo Horizonte - MG, Brazil

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Apresenta-se o estudo da hidrogenólise da ligação carbono-bromo nas α-bromoamidas quando a amida é reduzida com diborano sob diversas condições de reação. Redução e hidrogenólise completa ou parcial podem ocorrer para produzir tanto β-bromoaminas quanto aminas e amidas não-substituídas, dependendo da estrutura da α-bromoamida e das condições de reação. São apresentadas evidências das estruturas dos produtos por espectrometria de massas e análise espectral de ^{1}H-NMR e ^{13}C-NMR.

The study of the occurrence of the hydrogenolysis of the carbon-bromine bond in α-bromoamides when the amide is reduced with diborane under various reaction conditions is presented. Reduction and partial or complete hydrogenolysis may occur producing β-bromoamines, unsubstituted amides and unsubstituted amines, depending on the structure of the α-bromoamide and the reaction conditions. Evidence for the structures of the products is given by mass spectra, ^{1}H-NMR and ^{13}C-NMR spectral analyses.

Keywords: *hydrogenolysis, α-bromoamides, β-bromoamines, diborane*

Introduction

The reduction of aliphatic amides to amines constitutes an important step in the synthesis of many organic compounds. Such reductions have been efficiently carried out using nucleophilic reducing agents such as lithium aluminum hydride (LAH)[1] and sodium borohydride[2]; by electrophilic reducing agents such as aluminum hydride[3] and borane[4]; by catalytic hydrogenation[5]; by electroreduction[6], and by other reduction processes[7]. However, there are very few reducing agents which can be employed in the reduction of aliphatic haloamides to haloamines because of the facile hydrogenolysis of the carbon-halogen bond[3b,8].

The literature relates that diborane is one of the most appropriate reagents for the selective reduction of amides to amines[3b,9,10]. The mild reaction between amide and borane does not affect a large variety of other functional groups which are less susceptible to the reducing action of this reagent[9], including alkyl halides[10]. Even under rigorous conditions, alkyl bromides are generally stable in borane-THF[11]. It has also been observed that α-fluoro- and α-bromoamides do not suffer hydrogenolysis by boranes. Thus, diborane has been utilized in the reduction of haloamides to haloamines with excellent yields[12]. There are few cases in which hydrogenolysis of the carbon-halogen bond has occurred during reduction with diborane[13].

In the present work, during the synthesis of β-bromoamines from α-bromoamides utilizing diborane, partial or total hydrogenolysis of the carbon-bromine bond has been observed. Evidence for such hydrogenolysis is doubly important since it represents the first time that cleavage of

the carbon-halogen bond has been observed under these reaction conditions, as well as the fact that it limits the use of diboranes for the selective reduction of polyfunctional compounds. In order to better define the circumstances under which the hydrogenolysis occurs, the reduction of a series of N-alkyl-α-bromopentanamides (**1**) under diverse conditions was carried out, as were studies of the products formed.

Experimental

The infrared spectra were registered on a Perkin-Elmer model 283B spectrophotometer. The ^{1}H-RMN spectra were registered on a Varian EM 360-A spectrometer, the melting points were determined on a METTLER FP5 melting point apparatus, and ^{13}C-NMR spectra were registered on Brucker AC80 and Varian XL 100 spectrometers. Electron impact mass spectra were obtained on Varian Mat 311A and Finnigan 4000 instruments.

Materials

Hydrobromic acid and sodium borohydride were obtained from the Grupo Montedison Carlo Erba; adamantylamine, diglyme, calcium hydride, isobutylamine, n-butylamine, *sec*-butylamine and *t*-butylamine were purchased from Aldrich Chemical Company. Other reagents used were: cyclohexylamine (J.T. Baker); alumina, silica gel, tetrahydrofuran, dichloromethane (Merck); lithium aluminum hydride (Alfa Ventron); sodium (Riedel); and boron trifluoride (Eastman Organic Chemicals). N-alkyl-2-bromopentanamides were prepared from 1-pentanol by classical procedures involving oxidation to the pentanoic acid with potassium permanganate[14], reaction with thionyl chloride to form the acyl chloride, followed by conversion to the α-bromopentanoyl bromide by treatment with phosphorus and bromine[15]. Finally, the acyl bromide was converted to the amides through the reaction with primary amines in dichloromethane using the Schotten-Baumann technique[16]. All other reagents were reagent grade.

Experimental procedure

The reductions of the N-alkyl-2-bromopentanamides (**1**) were performed using the following general procedure. The quantities of reagents used, the duration of the reactions and the respective yields of the amine and β-bromoamine products are presented in Table 1.

Diborane was generated externally by the normal procedure[17] and bubbled slowly under dry nitrogen over a period of "t" hours through a stirred mixture of "m" moles of N-alkyl-2-bromoalkanamide (**I**) in "n" mL THF in a three-necked round bottom flask equipped with a gas dry-

Table 1. Reaction data for the reduction reaction of N-alkyl-2-bromopentanamides with diborane in refluxing THF.

Amide	Quant Amide (x10^{-3} moles)	Vol. THF (ml)	Quant. Diborane (moles)	t^1 (h)	T^2 (h)	Workup Procedure	Yield of Amine^3 g(%)	Yield of β-Bromo Amine^3 g(%)
1a	30.5	100	0.132	7	30	a	4.30(69)	2.55(29)
1a	76.3	200	0.795	3	30	c	9.66(62)	5.73(26)
1a	38.2	200	0.265	7	30	d	3.35(43)	1.99(18)
1a	1.2	20	0.080	3	30	f	0.044(15)	0.025(6)
1a	22.9	150	0.132	4	30	g	2.47(52)	1.47(23)
1a	38.2	110	0.199	2	31	h	2.41(25)	1.36(11)
1b	33.9	100	0.132	6	32	b	4.50(74)	0
1b	43.2	150	0.585	3	20	g	4.73(61)	0
1b	12.7	40	1.060	5	27	h	0.43(15)	0
1c	53.0	150	0.132	3	48	a	9.23(97)	0
1c	45.3	150	0.132	8	26	g	3.15(39)	5.54(47)
1d	30.5	100	0.132	3	35	a	5.37(98)	0
1d	42.4	100	0.265	6	35	e	0.99(13)	0
1e	38.1	120	0.132	8	33	d	2.05(30)	4.43(45)
1f	25.5	100	0.132	7	28	a	6.50(99)	0
1f	28.7	120	0.132	2	28	c	6.80(92)	0

[1]Time required for the addition of diborane. [2]Reaction time under reflux after the addition of the diborane. [3]The percentage of the brominated amine relative to the dehalogenated amine was calculated from the relative intensities of the ^{1}H-NMR signals in the products. [4]Contaminated with amide and inorganic salts.

ing system at the inlet, a reflux condenser, and a system for destruction of effluent diborane at the outlet[17]. The temperature was maintained at 70-75 °C with a water bath. During this time, the solution changed from light yellow to transparent, followed by the formation of a white precipitate (amine-borane complex) which hindered stirring and bubbling of the gases through the mixture. After the addition of diborane, the mixture was stirred for an additional "T" hours when TLC and IR analyses (disappearance of the band near 1650 cm^{-1} attributed to the amide carbonyl absorption) showed that complete reduction was accomplished.

In order to eliminate traces of amides and boric acid derivatives from the crude product which are normally formed in these reactions, various methods were attempted for a work-up of the reaction mixture, depending on the α-bromoalkanamide used. In each case, 100 mL of 5% hydrochloric acid was first added slowly to the reaction mixture:

a) After acidification, the THF was distilled at atmospheric pressure. The resulting aqueous residue was concentrated at reduced pressure with frequent addition of NaOH pellets to maintain the pH close to 2. The volume was reduced until the solution became turbid and a slight white precipitate formed. The mixture was extracted first with ether to remove the unreduced amide and then with dichloromethane to separate the amine hydrochloride from the inorganic salts. The dichloromethane fractions were combined and dried over sodium sulfate, and the solvent was distilled under reduced pressure.

b) Upon acidification, the formation of two phases was observed. The organic phase was separated and the aqueous phase was extracted with dichloromethane. The combined organic fractions were dried over sodium sulfate, and the solvents were distilled at reduced pressure to yield a solid residue. This product was difficult to purify.

c) The process was similar to that used in procedure a, except that the aqueous solution was completely evaporated, followed by successive solid-liquid extractions of the residue with ether and dichloromethane.

d) After acidification to pH = 1, the THF was distilled and the residue was extracted with ether. After careful addition of NaOH pellets, the resulting solutions at pH = 2, 3 and 4, respectively, were each extracted with ether. The volume of the final (pH = 4.0) aqueous solution was reduced until a white precipitate formed, and was followed by extraction with dichloromethane. This organic fraction was dried over sodium sulfate, and the solvent was distilled under reduced pressure.

e) Two phases formed upon acidification and these were separated. The pH of the aqueous phase was adjusted to 13 by the addition of NaOH pellets, and the amine was separated. The aqueous phase was extracted with ether and the organic phases were combined with the amine. The combined organic fractions were dried over sodium sulfate and the ether was distilled. The residue was redissolved in dry ether, and dry HCl was passed through the solution to form the amine hydrochloride.

f) After acidification, the THF was distilled at atmospheric pressure. The pH was adjusted to 13 with NaOH pellets and the amine was separated. The aqueous phase was extracted with ether and the organic fractions were combined and dried over sodium sulfate. After distilling the ether, the residue was dissolved in dry ether and converted to hydrobromide salt by bubbling dry HBr through the solution.

g) After adjusting the pH to 2, the THF was distilled and the aqueous residue was extracted with ether. The pH of the aqueous phase was adjusted to 13, the amine was separated, and the aqueous phase was extracted with ether. The combined organic fractions were dried over sodium sulfate and distilled. The residue was dissolved in dry ether and converted to its hydrochloride salt by passing dry HCl through the solution.

h) Worked-up as in procedure f. The combined organic fractions obtained from extraction at pH = 13 were dried over NaOH pellets. After bubbling dry HBr through the dried ether solution obtained from the reduction of **1b,** transparent crystals, (mp 181-185 °C) formed. In the case of **1a**, a mixture of products was obtained. These were shown to correspond to the amine without the β-bromine atom.

The amine hydrochloride obtained from the reduction of **1f** was purified by column chromatography on neutral alumina, eluting with dichloromethane. The remaining amine hydrochlorides were recrystallized from dichloromethane. In the reactions where a mixture of products was obtained, it was not possible to separate the amine hydrochloride products in which hydrogenolysis had occurred from the bromoalkanamine hydrochlorides by normal methods of recrystallization or chromatography. The compositions of the mixtures containing the amine and β-bromoamine hydrochlorides were determined by proton nuclear magnetic resonance using the ratio of the integration of the signal due to the hydrogen alpha to the halogen in the bromoamines (3.70-3.98 δ) to that of the signals due to the hydrogens with lower δ values. This method was acceptable for the determination of the proportion of bromoamine to dehalogenated amine since the percentage of error was approximately 7%.

1. Reduction of ***1a.*** MS [m/z(%)]: 249(1), 247(1), 206(10), 204(10), 169(2), 168(4), 160(2), 154(2), 126(12), 124(1), 113(8), 112(100), 98(2), 96(2), 86(3), 83(5), 82(2), 70(3), 69(5), 68(2), 56(16), 55(11). ^{13}C-NMR ($CDCl_3$, δ): 66.85, 58.08, 56.95, 50.70, 48.72, 44.32, 38.37, 28.88, 28.53, 25.51, 24.64, 24.44, 22.00, 20.18, 13.75, 13.09. ^{1}H-NMR ($CDCl_3$, δ): 9.17 (m, 2H), 4.62 (m, 0.3H), 2.68-3.60 (m, 3H), 1.17-2.60 (m, 14H), 0.70-1.17 (m, 3H). IR

(KBr, cm^{-1}): 3400, 2940, 2840, 2620, 2550, 1575, 1450, 1260, 1090, 1035, 800.

2. Reduction of ***1b***. MS [m/z(%)]: 180(0.1), 178(0.2), 144(3), 143(2), 129(10), 128(100), 86(21), 84(3), 82(3), 81(1), 80(3), 79(1), 72(4), 71(8), 70(6), 69(1), 59(3), 58(76), 57(26), 56(7), 55(7). ^{13}C-NMR ($CDCl_3$, δ): 56.71, 41.70, 28.94, 25.98, 25.66, 21.87, 13.67. ^{1}H-NMR ($CDCl_3$, δ): 9.20 (m, 2H), 2.47-3.30 (m, 2H), 1.75-2.40 (m, 2H), 1.10-1.70 (m, 4H), 1.50 (s, 9H), 0.90 (t, 3H, J = 6 Hz). IR (KBr, cm^{-1}): 3400, 2940, 2850, 2780, 2470, 1590, 1475, 1460, 1380, 1325, 1265, 1240, 1210, 1130, 1055, 1005, 745.

3. Reduction of ***1c***. MS [m/z(%)]: 223(3), 221(3), 180(41), 178(44), 142(10), 137(1), 136(10), 135(2), 134(28), 128(11), 100(11), 98(5), 87(6), 86(100), 78(3), 72(6), 70(7), 69(29), 59(3), 58(3), 57(15), 56(7), 55(6). ^{13}C-NMR ($CDCl_3$, δ): 66.17, 56.94, 55.64, 54.99, 54.16, 48.68, 37.96, 28.88, 25.77, 25.65, 25.19, 22.09, 20.71, 19.06, 18.58, 13.82, 13.32. ^{1}H-NMR ($CDCl_3$, δ): 8.66-9.90 (m, 2H), 4.70 (m, 0.45H), 2.80-3.70 (m, 3.5H), 1.35-2.65 (m, 7H), 1.15 (d, 6H, J = 7 Hz), 1.03 (t,3H, J = 6 Hz). IR (KBr, cm^{-1}): 3380, 2960, 2770, 2570, 2400, 1575, 1445, 1425, 1380, 1355, 1295, 1280, 1265, 1190, 1125, 1110, 1020, 995, 970, 885, 740.

4. Reduction of **1d**. MS [m/z(%)]: 194(0.2), 192(0.2), 180(1), 178(2), 150(1), 148(4), 144(3), 142(1), 129(1), 128(12), 115(8), 114(100), 98(1), 94(2), 87(2), 86(36), 84(2), 82(2), 80(2), 72(5), 71(4), 70(8), 69(4), 68(1), 58(27), 57(18), 56(15), 55(10). ^{13}C-NMR ($CDCl_3$, δ): 55.67, 44.86, 28.99, 25.68, 22.14, 15.28, 13.85, 10.13. ^{1}H-NMR ($CDCl_3$, δ): 8.95 (m, 2H), 2.75-3.40 (m, 3H), 1.67-2.40 (m, 4H), 1.10-1.60 (m, 4H), 1.47 (d, 3H, J = 7 Hz), 1.0 (t, 6H, J = 6 Hz). IR (KBr, cm^{-1}): 3500, 2960, 2760, 2450, 2380, 1575, 1445, 1380, 1305, 1245, 1210, 1130, 1100, 1085, 1045, 990, 960, 890, 755, 720.

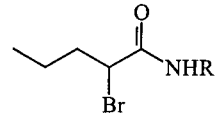
5. Reduction of ***1e***. MS [m/z(%)]: 223(1), 221(1), 180(6), 178(6), 143(3), 142(6), 134(2), 128(4), 113(1), 100(17), 98(3), 87(7), 86(100), 84(3), 72(3), 70(9), 69(17), 57(13), 56(12), 55(7). ^{13}C-NMR ($CDCl_3$, δ): 53.49, 48.31, 47.95, 47.36, 47.14, 38.02, 28.46, 27.36, 27.13, 25.03, 21.60, 19.78, 19.62, 13.35, 13.06, 12.77. ^{1}H-NMR ($CDCl_3$, δ): 8.90-10.0 (m, 2H), 4.65 (m, 0.40H), 2.60-3.80 (m, 3.6H), 1.10-2.40 (m, 10H), 1.04 (t, 6H, J = 6 Hz). IR (KBr, cm^{-1}): 3420, 2920, 2770, 2570, 2440, 2400, 1850, 1580, 1450, 1410, 1380, 1340, 1305, 1255, 1205, 1135, 1100, 1055, 1025, 950, 915, 875, 830, 780, 725.

6. Reduction of ***1f***. MS [m/z(%)]: 222(1), 221(4), 178(3), 165(14), 164(100), 136(7), 135(54), 112(2), 108(2), 107(4), 106(3), 94(8), 93(8), 91(5), 82(2), 81(4), 80(3), 79(10), 78(1), 77(6), 71(3), 70(2), 69(2), 68(1), 67(6), 65(2), 58(1), 57(3), 56(2), 55(7). ^{13}C-NMR ($CDCl_3$, δ): 57.45, 40.00, 38.35, 35.58, 29.25, 29.05, 26.28, 22.20, 13.92. ^{1}H-NMR ($CDCl_3$, δ): 9.12 (m, 2H), 2.67-3.14 (m, 2H), 2.15 (m, 8H), 1.73 (m, 9H), 1.17-1.50 (m, 4H), 0.93 (t, 3H, J = 6 Hz). IR (KBr, cm^{-1}): 3350, 2930, 2880, 2800, 2740, 2690, 2550, 2440, 2360, 1960, 1860, 1630, 1570, 1450, 1370, 1340, 1305, 1295, 1270, 1245, 1100, 1075, 1020, 1005, 975, 940, 910, 930, 730.

Results

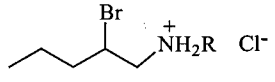
Table 1 shows the crude yields of the amine and β-bromoalkanamine hydrochlorides obtained from the reduction of the α-bromoamides. It can be seen that work-up procedure a was the most efficient. Since the N-alkyl-2-bromopentanamides are soluble in ether and dichloromethane and the amine and β-bromoamine hydrochlorides are soluble only in dichloromethane, extraction with ether removed the unreacted α-bromoamides from the products. Subsequent extraction of the products with dichloromethane eliminated the inorganic salts.

The occurrence of hydrogenolysis was confirmed by ^{1}H-NMR, ^{13}C-RNM and mass spectra analyses. In the proton magnetic resonance spectra of the products, signals corresponding to the proton alpha of the bromine atom were observed only in the spectra of the products obtained from the reduction of **1a** (δ 4.62), **1c** (δ 4.70) and **1e** (δ 4.65). The mass spectral data for the products of the reduction of amides **1a - 1f** show that the percentage of fragments which can only arise from the halogenated amine hydrochloride (**2**) are relatively low. In the spectra of the reduction products obtained from amides **1b**, **1d** and **1f**, there is no real evidence of the existence of the brominated amine. However, in the case of **2a**, **2c** and **2e**, significant peaks for the molecular ions (1.48 / 1.39%, 3.15 / 3.00% and 0.95 / 0.95%, respectively) and for the loss of a propyl radical (Eq. 1: 10.39 / 10.20%, 43.66 / 40.85%, and 5.90 / 5.62%, respectively) can be observed. The low intensity of the molecular ion peak corresponding to Structure **2** may be attributed to the lability of the carbon-bromine bond under the conditions of analysis. These conditions inhibit its detection because of the facile decomposition to bromine-



1

1a. R = cyclohexyl
1b. R = *t*-butyl
1c. R = isobutyl
1d. R = *sec*-butyl
1e. R = n-butyl
1f. R = adamantyl

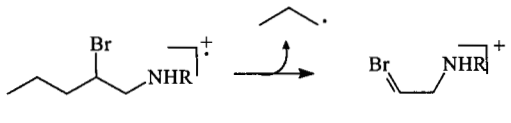


2

2a. R = cyclohexyl
2b. R = *t*-butyl
2c. R = isobutyl
2d. R = *sec*-butyl
2e. R = n-butyl
2f. R = adamantyl

Structures 1 and 2.

free fragments[18]. In the case of **2c** and **2d**, the M-43 peak may also result from the fragmentation shown in Eq. 2. The greater intensity of this peak for **2c** is no doubt due to the greater ease of the loss of an isopropyl as opposed to a propyl radical.



(1)

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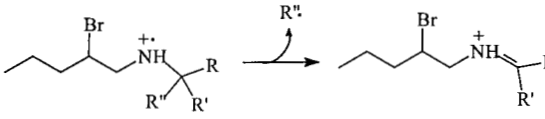

(2)

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The ^{13}C-NMR spectrophotometric data for each of the reaction products resulting from the reduction of amides **1b**, **1d** and **1f** indicate that these have Structures **5** to **7**, thus confirming the mass spectra in which no significant peaks corresponding to brominated amines were observed. Table 2 shows the observed and calculated values for the chemical shifts of the carbon atoms indicated in Structures **5** to **7.** The calculated values for the chemical shifts in this and the following tables were empirically based on the increments caused by the -NHR, -NH_3+ and -NR_3+ substituents[21]. Using the SFORD and DEPT techniques, the beta carbon was shown to be methylene, thus indicating that hydrogenolysis of the carbon-bromine bond occurred.

Table 3 presents the chemical shift values for the products of the reduction of amide **1a**. These values are assigned as indicated in Structures **8** and **9**.

Table 4 shows the chemical shift values observed in the ^{13}C-NMR spectra of the products obtained from the reaction of amide **1c** with diborane in THF. The assignments correspond to the calculated values for Structures **10** and

Table 2. Observed and calculated values of the chemical shifts of the carbons of the pentyl chain corresponding to Structures **5**, **6** and **7**, respectively, obtained from the reduction of amides **1b**, **1d** and **1f**. Values in δ.

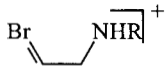
Carbon	Observed values			Calculated values*
	5	**6**	**7**	
C_1	41.70	44.86	40.00	(50.5) [44.5] {40.0}
C_2	28.94	28.99	29.25	(30.8) [28.3] {30.3}
C_3	25.98	25.68	26.28	(30.2) [27.7] {30.2}
C_4	21.87	22.14	22.20	(22.3) [22.3] {22.8}
C_5	13.67	13.85	13.92	(13.5) [13.5] {14.0}

*Empirically determined chemical shifts caused by the -NHR (cited between parentheses), NH_3^+ (cited between brackets) and the NR_3^+ (cited between braces) substituents.

Table 3. Observed and calculated values of the chemical shifts of the carbons of the pentyl chain corresponding to Structures **8** and **9**, respectively, obtained from the reduction of amide **1a**. Values in δ.

Carbon	Observed Values		Calculated Values for Structure **9***
	8	**9**	
C_2	28.53	58.08	(56.6) [54.1] {56.1}
C_3	25.51	48.72	(40.1) [37.6] {40.1}
C_4	22.00	20.18	(18.1) [18.1] {18.6}
C_5	13.75	13.09	(12.7) [12.7] {13.2}

*Empirically determined chemical shifts caused by the -NHR (cited between parentheses), -NH_3^+ (cited between brackets) and the -NR_3^+ (cited between braces) substituents. The calculated values for for the chemical shifts for Structure **8** are cited in Table 2.



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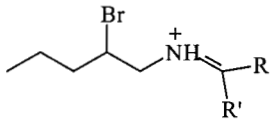

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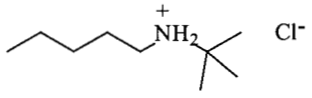

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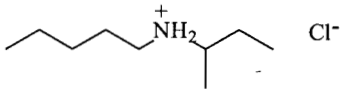

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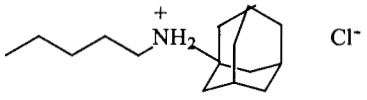

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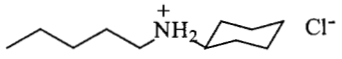

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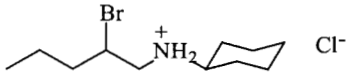
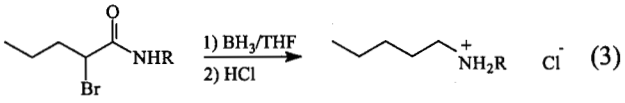


9

Structures 3 to 9.

11. Finally, Table 4 also presents the chemical shift values observed in the ^{13}C-NMR spectra of products **12** and **13** obtained from the reduction of **1e**. Thus, the NMR and MS spectrometric data for the products of the reaction of amides **1b**, **1d** and **1f** suggest the absence of a carbon-bromine bond in these products, since only fragments arising from the respective debrominated secondary amine hydrochlorides were detected. Hence, the reduction reaction of these amides can be represented by Eq. 3.



(3)

On the other hand, the mass spectra of the products obtained from the reduction of **1a**, **1c**, and **1e** show fragment peaks corresponding to the debrominated amines, as well as peaks which confirm the presence of the carbon-bromine bond in the fragment. The reduction of these amides can be represented by Eq. 4.

The degree of hydrogenolysis of the carbon-bromine bond during reduction was determined by analysis of the ^{1}H-NMR spectra. The ratio of the integration curve of the hydrogen alpha to the bromine to those of the remaining signals of the hydrocarbon portion of the molecules was calculated. The ratios of bromo-amine to debrominated amine obtained in the reduction of **1a-1f** were **1a**, 3:7; **1b**, 0:1; **1c**, 55:45; **1d**, 0:1; **1e**, 3:2; and **1f**, 0:1.

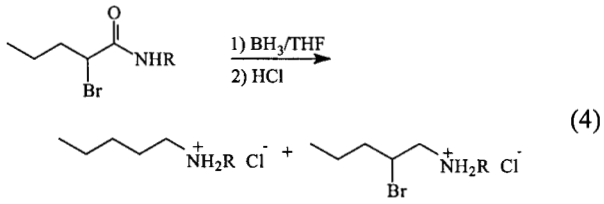
Discussion

The literature[10] cites intermediates that can serve as models for explaining the hydrogenolysis of amides **1a-1f** observed in this study. The reduction of an alkyl halide by hydride has been observed to be affected in different ways by the presence of a neighboring heteroatom[22]: by nucleophilic participation to form an intermediate "onium" ion; by the formation of a monodentate complex with the reagent, liberating hydride by intramolecular reaction; by the formation of a bidentate complex with the halide between the neighboring group and the reagent, this complex attacking and reducing a second molecule; by steric effects; by alteration of the reduction potential of the neighboring group; by favoring a free radical mechanism; or by promoting cyclization with displacement of the halide ion.

Table 4. Observed values for the chemical shifts of the pentyl chain carbons corresponding to Structures **10** and **11**, obtained from the reduction of **1c**, and of Structures **12** and **13**, obtained from the reduction of **1e**, respectively.* Values in δ.

Carbon	Structures*			
	10	**11**	**12**	**13**
C_1	48.68	66.17	47.14	53.49
C_2	28.88	56.94	28.46	48.31
C_3	25.19	54.16	25.03	38.02
C_4	22.09	25.65	21.60	19.78
C_5	13.82	13.32	13.34	12.77

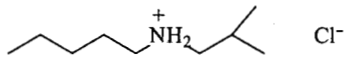
*The calculated values for the chemical shifts of the carbons of Structures **10**, **11**, **12** and **13** are given in Tables 6 and 7.



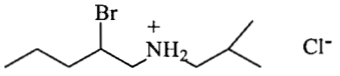
(4)

It is possible that the reduction of amides occurs though the formation of amino-borane adducts. These adducts are known to present a reactivity very different from diborane[9c]. However, according to the literature amino-boranes reduce acyl halides, aldehydes and ketones, but are inert in reactions with carboxylic acids and amides[9a]. On the other hand, few studies of the reaction of amino-boranes with alkyl halides which establish their power to carry out hydrogenolysis of carbon-halogen bonds have been encountered[13b].

The literature also indicates that, contrary to the saturated alkyl halides which are inert, allyl or vinyl halides react rapidly with diborane. The first step of the reaction involves hydroboration to form a haloalkylborane. Depending on the distance between the halogen and boron in



10



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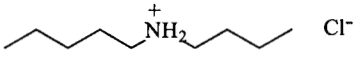

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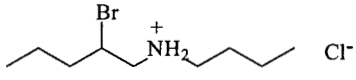
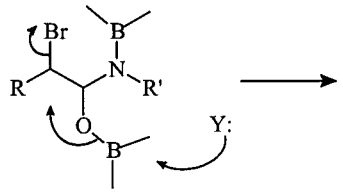


13

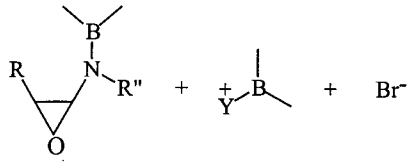
Structures 10 to 13.

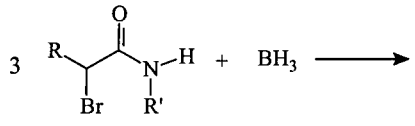
the intermediate, different types of products may be formed upon reaction with a base or nucleophile[10].

In order to classify the hydrogenolysis of the carbon-bromine bond at the alpha position of amides among the possibilities presented in the previous paragraph, a viable alternative would involve a mechanism via a cyclic transition state, similar to that which occurs in Eq. 5. However, if the literature data for the reduction of primary and secondary amides are taken into account, it is possible that an initial reaction occurs with the active hydrogen of the amide group, liberating molecular hydrogen according to Eq. 6[9h]. Hydrogenolysis of the carbon-bromine bond should occur only after partial reduction of the amide carbon.

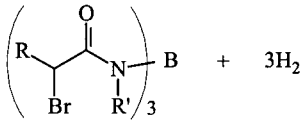


14 (5)





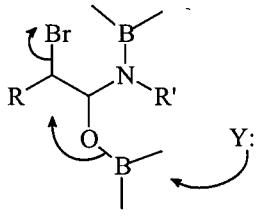
(6)



Taking these observations into consideration, an intermediate (Structure **14**) may be proposed which, in the presence of a base, may react in the two different modes indicated in Eqs. 5 and 7 to form an epoxide or an aziridine intermediate, respectively.

In general, epoxides are slowly reduced by diborane to form alcohols and complex mixtures as products[23]. In the literature consulted, no consensus as to the probable products of the reduction of aziridines by diborane was encountered.

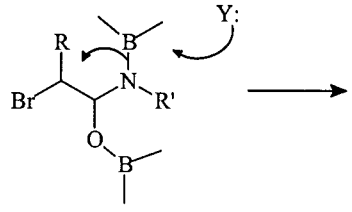
Among the products of the reduction of amides **1a-1f** with diborane, no presence of alcohols was detected. For amides **1b**, **1d** and **If**, only non-brominated amines were obtained and in high yields. For the other amides, the products formed by hydrogenolysis of the carbon-bromine bond were obtained, in addition to the halogenated amines. The hydrogenolysis of the carbon-bromine bond via an epoxide-type intermediate should not have occurred since



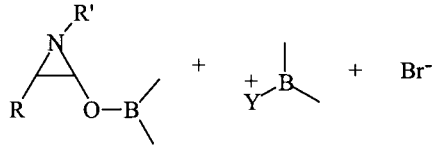
14

Structure 14.

this is labile, reacting easily in acid, alkaline or neutral medium. With respect to the possible formation of the aziridine intermediate (Eq. 7), no definite conclusion can be reached.



14 (7)



A pathway involving the formation of an epoxide intermediate appears to be improbable. Beta-haloamines have been observed to react by cyclization with the displacement of the halide to form aziridines[22]. Taking these facts into consideration, an alternative mechanism involving the formation of an aziridine before the reduction of the amide group may explain the formation of the amines cited above. The aziridine would then be reduced in a reaction analogous to the reduction of epoxides. Thus, the aziridine could be formed via the intermediate shown in Eq. 7, or from the β-bromoamine.

Thus far, it has been shown that although diborane does not reduce carbon-bromine bonds in alkyl halides or in β- and γ-haloamides, it can reduce this bond in α-haloamides. It may be concluded, therefore, that the relative proximity of the carbon-bromine bond to the nitrogen of the amide group and/or the steric and inductive effects of the N-alkyl substituents in halogenated amides are determining factors for the occurrence of the hydrogenolysis of these substances. Products **2b, 2d** and **2f** present no significant peaks attributable to the brominated fragments. Since in **2b** and **2f**, the N-alkyl substituents have tertiary carbons bound to the nitrogen, there exists the possibility that these bulky N-alkyl substituents facilitate the hydrogenolysis of the

carbon-bromine bond during the reduction of the α-bromoamide.

Conclusion

Mass spectral and NMR data confirme the hydrogenolysis of the carbon-bromine bond in N-substituted α-bromoamides. The hydrogenolysis of the carbon-bromine bond alpha to the amide group by diborane may be influenced by the steric effects of the N-alkyl substituent since total hydrogenolysis occurs when this group is adamantyl, *sec*-butyl or *t*-butyl. However, when the N-alkyl substituent is n-butyl, isobutyl, or cyclohexyl, only partial hydrogenolysis of the carbon-bromine bond occurs. The degree of hydrogenolysis which occurred during the reduction of the α-bromoamides could be determined by the analysis of the ^{1}H-NMR spectra.

Acknowledgments

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13. (a) The hydrogenolysis of the carbon-halogen bond in N-(2-iodoethyl)alcanamides has been observed upon reduction with borane/THF [S.K. Gupta and P.A. Whitehouse, *J. Med. Chem.* **10**, 692 (1967)]. (b) Alkyl bromides and chlorides are reduced by diborane or borane-triethylamine, both in nitromethane. In these cases, the degree of hydrogenolysis is directly related to the intermediate carbonium ion formed [S. Matsumura and N.Tokura, *Tetrahedron Lett.* 4703 (1968) and S. Matsumura and N. Tokura, *Tetrahedron Lett.* 363 (1969)]. (c) The reduction of the carbon-halogen bond has also been observed with N-(3-bromopropyl)amides [Y. Hourminer, *J. Org. Chem.* **40**, 1361 (1975)].
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