CHEMICAL EVIDENCE FOR A DIDEHYDROAZEPINE IN REACTIONS OF HALOGENOAZEPINES WITH A STRONG BASE[1,2]

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Abstract - The reaction of 5-X-2-(diethylamino)-3H-azepine (X=F, Cl) with t-butyllithium leads in high yield to a mixture of 4- and 5-t-butyl-2-(diethylamino)-3H-azepine. The ratio between both compounds is about 2.5:1, which ratio is independent of the substituent X. As intermediate in these conversions 2-(diethylamino)-3H-4,5-didehydroazepine is proposed.

INTRODUCTION

There is overwhelming evidence for the intermediary existence of six-membered didehydroheteroarenes in reactions of halogenoheteroarenes with a strong base[3]. The transitory existence of seven-membered thio- and oxaheterocycles with a triple carbon-carbon bond has been found in the reaction of 5-bromo-2,3, 6,7-dibenzothiepin-S-dioxide[4] and 4-bromodibenzooxepine[5] with potassium t-butanolate. Didehydroazepine and didehydrobenzazepine have been postulated as credible intermediates in the N_2 or Ar matrix photolysis of phenylazide or naphthaleneazide[6,7] at around 10K. Till now no proof for the intermediary existence of a didehydroazepine in reactions of halogenoazepines with a strong base was found. In this paper we wish to report the first indications that didehydroazepines can act as intermediates in reactions of halogenoazepines with t-butyllithium.

RESULTS

When reacting 2-(diethylamino)-5-fluoro-3H-azepine (**1a**), prepared from p-fluoronitrosobenzene, triphenylphosphine and diethylamine[8], with potassium amide/liquid ammonia at -35°C or with lithium diisopropylamide/ether-1,2-dimethoxyethane at room temperature no reaction occurs. However, reaction of **1a** with t-butyllithium[9] in diethyl ether at -70°C occurs very smoothly. After quenching of the reaction mixture by methanol and work-up in an 80-90% yield a mixture of two isomeric compounds i.e. 4-t-butyl-2-(diethylamino)-3H-azepine (**5a**) and 5-t-butyl-2-(diethylamino)-3H-azepine (**6a**), ratio **5a** : **6a** = (2.5-3.0) : 1 was obtained. The structure of both compounds could easily be assigned by comparison of the ^{1}H-NMR spectra of both compounds. Although the formation of this mixture of isomers could indicate the intermediacy of the 4,5-didehydroazepine 2, a combination of the $S_N(AE)$ipso process and the $S_N(AE)$cine process could also explain the formation of

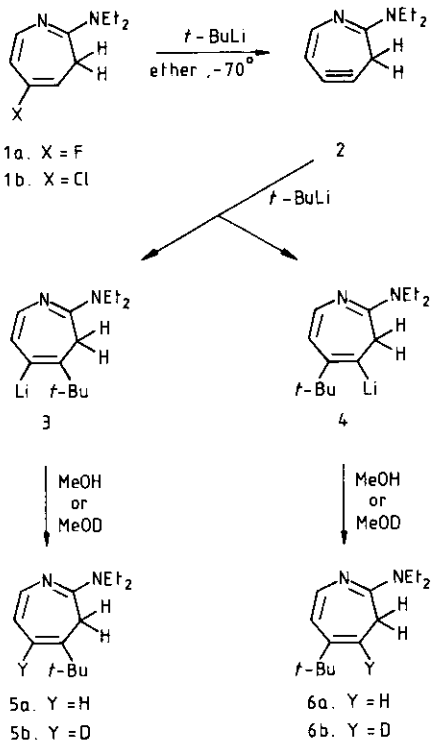

Table 1 Mass spectromectrically determined deuterium content of the reaction products **5b** and **6b**

starting material	reaction products					
	5b			**6b**		
	% 0D	% 1D	% 2D	% 0D	% 1D	% 2D
	1.2	98.8	-	1.9	97.8	0.3
1a						
	1.3	98.7	-	2.2	97.5	0.3
	1.2	98.8	-	2.2	97.5	0.3
1b						
	1.2	98.8	-	1.9	97.8	0.3

both products[10]. When 5-chloro-2-(diethylamino)-3H-azepine (**1b**) reacted with t-butyllithium, a mixture of the same compounds **5a** and **6a** was obtained; the ratio **5a** : **6a** is nearly the same as obtained from the fluoro compound **1a** i.e. (2.5-3.0) : 1. The fact that from both **1a** and **1b** in nearly the same ratio **5a** : **6a** is obtained strongly advocates the intermediacy of **2** and excludes the occurrence of competitive addition-elimination processes, since in that case the ratio **5a** : **6a** should have been changed.

In accordance with the S_N(EA)-mechanism, involving the didehydroazepine **2**, it was found that when the reaction mixture obtained from **1a** or **1b** and t-butyllithium is quenched with deuteromethanol **5b** and **6b** are obtained, containing 100% of deuterium incorporated in position 5 of **5b** and position 4 of **6b** (see table). From all these results it seems justified to assume the occurrence of the S_N(EA)-mechanism in these reactions.

EXPERIMENTAL

Melting points are uncorrected. ^{1}H-NMR spectra were recorded on a Varian EM 390 spectrometer or a Hitachi-Perkin Elmer R-24B spectrometer. Mass spectra were recorded on a AEi-902 instrument.

2-(Diethylamino)-5-fluoro-3H-azepine (**1a**)[8]

To a boiling, mechanically stirred mixture of triphenylphosphine (71 g = 270 mmol) and dry diethylamine (350 ml) in a 1 l three-neck flask, under a continuous stream of nitrogen a solution of p-fluoronitrosobenzene (12.4 g = 100 mmol) in 80 ml dry THF was added in 30 min; then the combined mixture was boiled during 7 h. The diethylamine was distilled off and the residue was stirred with petroleum ether (bp 40-60°C, 500 ml). The solid mass was filtered off, stirred with a new portion of petroleum ether (bp 40-60°C) and filtered off again. The combined filtrates were evaporated giving a residue which was dissolved in ether (50 ml) and shaken with a solution of oxalic acid dihydrate (12.6 g, 100 mmol) in water (50 ml). The aqueous layer was basified and extracted with ether. After drying with sodium sulfate and removing the ether an oil (6.21 g) was left which was subjected to destillation in vacuo to give **1a** (4.87 g, 27%, bp 78-79°C/0.3 mm, n_d^{20} = 1.5294). ^{1}H-NMR: ($CDCL_3$): δ 7.13 (dd, $J_{6,7}$ = 8.4 Hz, J_{FH} = 5.4 Hz, 1H, H-7); 5.60 (m, $J_{6,7}$ = 8.4 Hz, $J_{4,6}$ = 1.8 Hz, J_{FH} = 9.6 Hz, 1H, H-6); 4.47 (m, $J_{3,4}$ = 7.8 Hz, $J_{4,6}$ = 1.8 Hz, J_{FH} = 9.6 Hz, 1H, H-4); 3.37 (q, 4H, NCH_2); 2.50 (d, $J_{3,4}$ = 7.8 Hz, J_{FH} = 1.5 Hz, 2H, H-3); 1.13 (t, 6H, CH_3); MS accurate mass: calcd. 182.1219 for $C_{10}H_{15}FN_2$; obs. 182.1218. Anal. Calcd. for $C_{10}H_{15}FN_2$: C, 65.90; H, 8.30. Found: C, 65.61; H, 8.45.

5-Chloro-2-(diethylamino)-3H-azepine (**1b**)

Although a prescription for the preparation of **1b** is given[11], we describe here a more detailed and

precise procedure. In each of 10 Carius tubes was brought p-chloronitrobenzene (3.15 g = 20 mmol), tris-diethylaminophosphine (9.88 g = 40 mmol) and diethylamine (25 ml). After sealing, the tubes were heated and shaken during 18 h at 120°C. The contents of the tubes were combined, the diethylamine was removed by using a rotation evaporator and the residue obtained was subjected to destillation in vacuo. The fraction with bp 126.0 - 127.5°C/0.7 mm) was dissolved in isopropanol (140 ml) and mixed with a solution of oxalic acid dihydrate (25.2 g, 200 mmol) in isopropanol (200 ml). Some directly formed precipitate was filtered off using a glass filter and the filtrate was kept overnight. The next day a precipitate of the oxalate of **1b**, fraction I, 19.83 g, mp = 100-105°C) was obtained and removed by filtration. Dry ether (900 ml) was added to the filtrate causing the precipitation of an additional amount of the oxalate (fraction II, 7.48 g, mp 109.5-110.5°C). Fraction I was recrystallized from isopropanol-cyclohexane (3:1), giving 18.84 g, mp 107.0-109.0°C. Total yield 26.32 g (45%, based on the amount of the used p-chloronitrobenzene. A solution of the oxalate in water (150 ml) was basified with a concentrated potassium hydroxide solution and extracted with ether. After drying and removing the ether, the residue was subjected to destillation in vacuo to give pure **1b** (16.4 g, 42%; bp 96.5-97°C/0.2 mm; N_D^{20} = 1.5718; mp = 39-40°C after storing in a refrigerator. ^{1}H NMR ($CDCl_3$): δ 7.07 (d, $J_{6,7}$ = 7.8 Hz, 1H, H-7); 5.67 (d, $J_{6,7}$ = 7.8 Hz, $J_{4,6}$ = 1.1 Hz, 1H, H-6); 5.10 (t, $J_{3,4}$ = 8.4 Hz, $J_{4,6}$ = 1.1 Hz, 1H, H-4); 3.37 (q, 4H, NCH_2); 2.62 (br d, $J_{3,4}$ = 8.4 Hz, 2H, H-3); 1.17 (t, 6H, CH_3).

General procedure for the t-butylation

All used glassware was dried in a stove at 100-140°C. The experiments were performed under nitrogen. TMEDA was distilled from sodium and stored on sodium. In a three-neck flask of 250 ml a solution of **1a** (0.455 g = 2.5 mmol) or **1b** (0,504 g = 2.5 mmol) in ether (20 ml) was stirred for 20 min at -70°C. A solution of t-butyllithium (6.8 ml, 1.5 M in pentane, 10 mmol, Aldrich) was added using a syringe, causing a pale yellow colour. After 1 min TMEDA (1 ml) was added using a syringe. The colour changed into brownish yellow. The mixture was stirred during 15 min and then quenched with ethanol (1 ml) or deuteromethanol (2 ml) using a syringe. The reaction mixture was allowed to come to room temperature. The solvents were removed by evaporation, the residue was taken up in ether, dried with sodium sulfate and again evaporated to dryness. An oil was left which was subjected to preparative TLC (SiO_2/ethyl acetate + 1% triethylamine, R_F **1a** = 0.89; R_F **1b** = 0.88; R_F **5a** = 0.73; R_F **6a**; = 0.51. Total yield of **5a**, **5b** and **6a**, **6b** is 80-88%, the ratio of the amount of **5a** (**5b**) to that of **6a** (**6b**) being 2.3-3.0 : 1.

4-t-Butyl-2(diethylamino)-3H-azepine (**5a**)

Oil. ^{1}H NMR ($CDCl_3$): δ 7.00 (d, $J_{6,7}$ = 7.8 Hz, $J_{5,7}$ = 0.9 Hz, 1H, H-7); 6.13 (d, $J_{5,6}$ = 6.0 Hz,

$J_{5,7}$ = 0.9 Hz, 1H, H-5); 5.72 (dd, $J_{5,6}$ = 6.0 Hz, $J_{6,7}$ = 7.8 Hz, 1H, H-6); 3.45 (q, 4H, NCH_2); 2.70 (br s, 2H, H-3); 1.12 (t+s, 15H, CH_3); MS: m/e = 220.

Picrate of **5a**, mp 121-122°C; mixed mp with picric acid 74-119°C. Anal. Calcd. for $C_{20}H_{27}N_5O_7$: C, 53.44; H, 6.06. Found: C, 53.14; H, 6.33. **5b**. ^1H NMR ($CDCl_3$): δ 6.13 no absorption; 5.72 (d, $J_{6,7}$ = 7.8 Hz, H-6).

5-t-Butyl-2-(diethylamino)-3H-azepine (**6a**)

Oil. ^1H NMR ($CDCl_3$): δ 7.08 (d, $J_{6,7}$ = 8.4 Hz, 1H, H-7); δ 5.87 (d, $J_{6,7}$ = 8.4 Hz, $J_{4,6}$ = 1.2 Hz, 1H, H-6); δ 4.97 (t, $J_{3,4}$ = 7.2 Hz, $J_{4,6}$ = 1.2 Hz, 1H, H-4); δ 3.38 (q, 4H, NCH_2); δ 2.60 (br, 2H, H-3); δ 1.10 (t+s, 15H, CH_3); MS accurate mass: calcd. 220.1939 for $C_{14}H_{24}N_2$; obs. 220.1941.

Picrate of **6a**, mp 112.0-113.0°C (ethanol, -30°C). Anal. Calcd. for $C_{20}H_{27}N_5O_7$: C, 53.44; H, 6.06. Found: C, 53.75; H, 6.14. **6b**. ^1H NMR ($CDCl_3$): δ 4.97 no absorption.

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as formed it is converted into **2**.

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