Tetrahedron Vol. 47, No. 1, pp. 47-52, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00

STUDY OF THE REACTION OF SODIUM AMIDE IN LIQUID AMMONIA WITH HEXAHYDRO-(1H)-2-BENZAZONINIUM SALTS : ACCESS TO 2-AZA-(7)-METACYCLOPHANES[1]

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(*Received in Belgium* 11 *September* 1990)

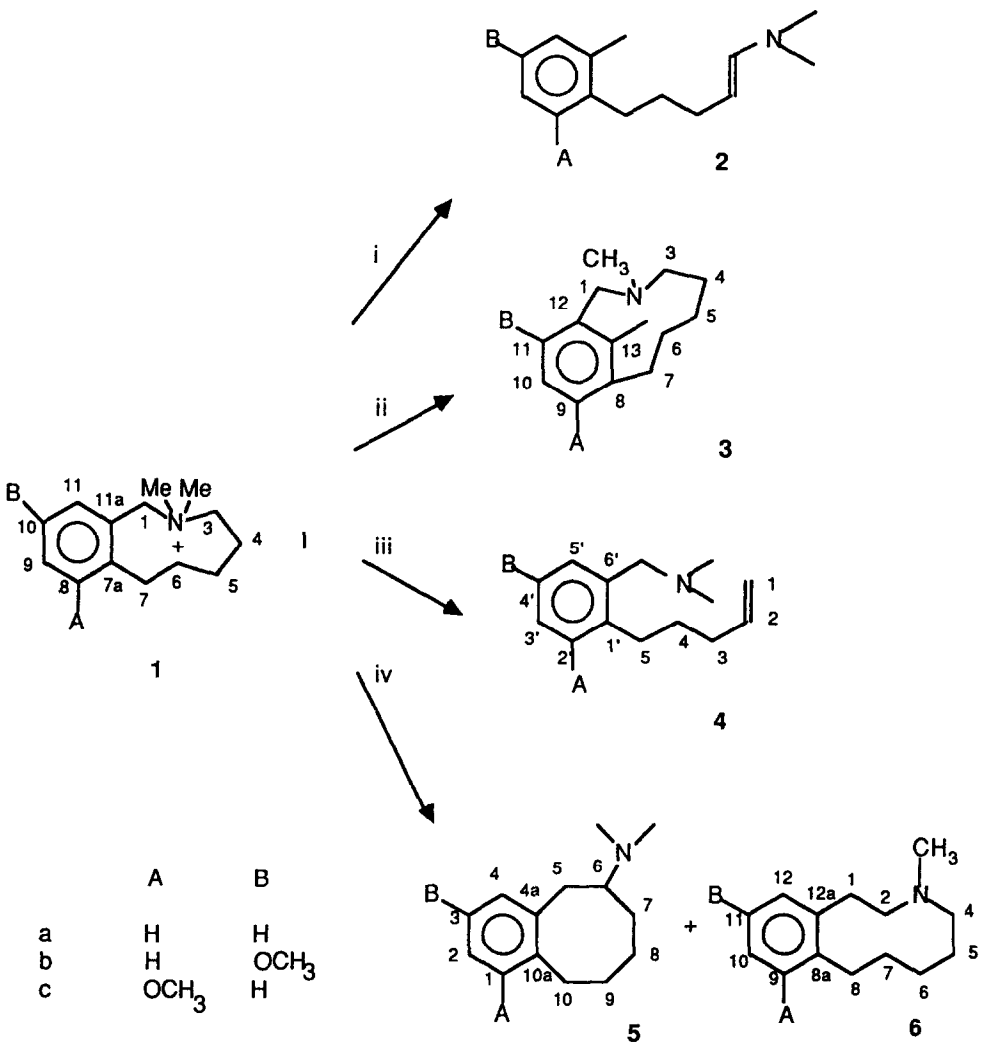
Abstract : The rearrangement of hexahydro-(1H)-2-benzazoninium ylides in liquid ammonia yields a mixture of amines : metacyclophanes arise from Sommelet-Hauser transposition, alkenes from an Hofmann elimination, enamines from a process which is discussed here , and two other minor compounds from a Stevens shift . Dynamic NMR of azametacyclophanes will be discussed .

Introduction

[n]-Metacyclophanes have been the subject of many investigations [2] although the compounds with a nitrogen atom in the polymethylene chain are unknown . We have recently reported the synthesis of derivatives of 2,3,4,5,6,7-hexahydro-(1H)-2-benzazonines [3] . We here report a study of the reaction of sodium amide with liquid ammonia of the methiodides of these compounds : 2-aza-(7)-metacyclophanes, 5(o-tolyl)-N,N-dimethyl-1-amino-1-pentenes and 5-(6'-N,N-dimethyl aminomethylphenyl)-1-pentenes are the three major products in the reaction.

Results and discussion

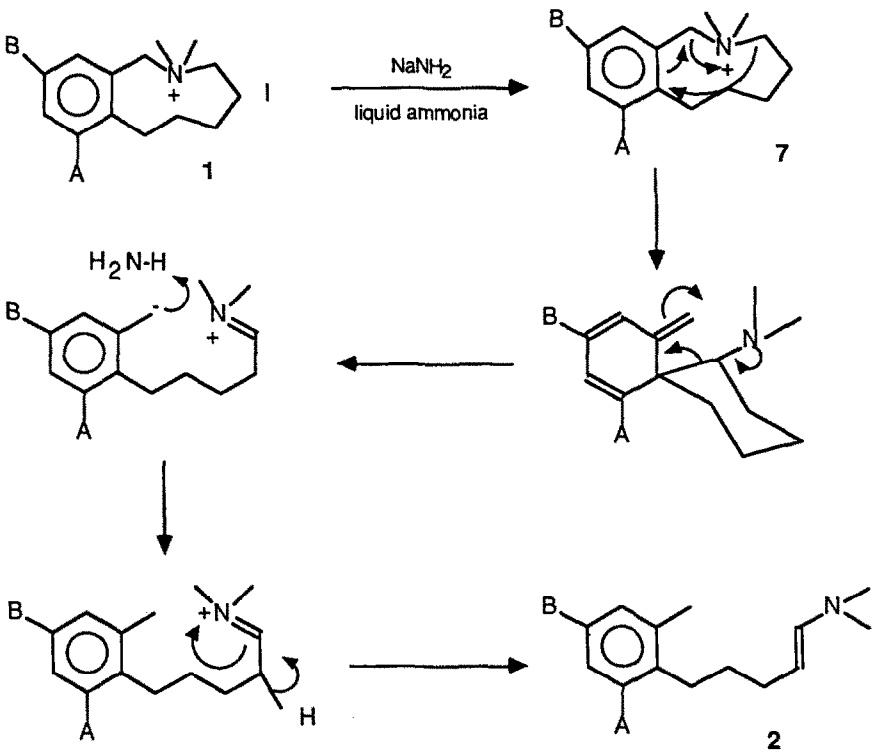
Treatment of **1** with sodium amide in liquid ammonia yields a mixture of amines (Scheme 1) : metacyclophanes **3** arise from a Sommelet - Hauser rearrangement[4], alkenes **4** from an Hofmann elimination[5], and compounds **5** and **6** from a Stevens 1,2 shift[4]. We have previously reported the formation of enamines during the rearrangement of ammonium ylides.



i : see scheme 2 ; ii : Sommelet-Hauser rearrangement ; iii : Hofmann elimination ; iv : Stevens transposition

Starting Compound	Na equivalent	Reaction Time (h)	Yield %	2 %	3 %	4 %	5 %	6 %	others %
1a	2	3	75	11	46	28	8	4	3
1b	3	1	87	32	46	15	5	3	
1c	3	1	82	32	20	15	18	12	

SCHEME 1



SCHEME 2

They are the sole rearrangement products of 2,2-dimethyl-1,2,3,4,5,6-hexahydro-2-benzazocinium salts [6] . On the other hand, rearrangement of N,N-dimethyl hexahydrothieno (2,3-c) and (3,2-c) azocinium (or azoninium) salts leads to spirannic amines[7], which gives enamines upon thermolysis [8] .To explain these results, we postulate the formation (Scheme 2) of ylide **7** which undergoes a (2,3) sigmatropic rearrangement to give a spirannic amine ; contrary to the thienyl compounds, the spirannic derivative of the phenyl series cannot be isolated and spontaneously gives an imminium ion through a six membered cyclic transition state (an homolytic process can also be proposed) followed by an anionic rearrangement to **2** The difference of stability of the spirannic compounds in the phenyl and thienyl series could result of the difference of resonance energies of the thiophene and the benzene ring . Increasing reaction time lowers the yield of the enamine which is degradated by the basic

medium . The Sommelet-Hauser and the Stevens rearrangements compete as is shown by the distribution of products arising from **1b** and **1c** .

All the compounds have been analysed by ^{1}H and ^{13}C NMR spectroscopy using 1D and 2D standard methods . Enamines were not isolated but were characterised by their hydrolysis products . Benzylic hydrogens in **1a** are diastereotopic between 303 ° K and 473 ° K as a result of the reduced mobility of the methylene chain . Cooling **1c** below 272°K gave rise to two new spectra assigned to the nitrogen invertomers ; the calculation of the activation energy has been performed on different ^{1}H and ^{13}C signals and lead to a value of 53.6 KJoule/mole (12.8 KCal./mole) : this high value is due to the strain of the molecule .

Experimental

All melting and boiling points are uncorrected . Elemental analyses have been performed by the Microanalyses Center of CNRS (Vernaison, France) .^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 400, WP 80 or WP 60 instrument using standard pulse sequences . GLC were carried out on a GIRDEL 3000 instrument equipped with a 2 m x 3.17 mm column (for analyses ; x 9.51 mm for preparative purposes) packed with 10% OV 225 on Chromosorb W HP (100-120 mesh) or with 15 % Carbowax 20M and 5% potassium hydroxide on Chromosorb P (60-80 mesh) .

Procedures for the preparation of ammonium salts and their rearrangement were previously described [6] . The rearrangement products were first treated in aqueous acidic medium to hydrolyse the enamines into the corresponding aldehydes, which were extracted from aqueous medium with ether and distilled ; the amines were extracted from the aqueous layer, which has been made alkaline, and were separated by preparative GLC ; the yields were calculated from the amounts of recovered aldehyde and from analytical GC of the amines The formation of enamines was also confirmed by spectroscopic experiments on the crude mixture of ammonium ylide rearrangement : IR ν=1620 cm^{-1} ; ^{1}H NMR δ 4.2 (td, ^{3}J = 7 and 14.2 Hz), 5.9 (td, ^{4}J = 1 Hz) ; ^{13}C NMR δ 99.8 (d), 140.3 (d) .

Compound **1a** is known [9] ; **1b,c** , **3a-c**, **4a-c** are described in tables .

6-(N,N-Dimethylamino)-5,6,7,8,9,10-hexahydrobenzocyclooctene **5a** : ^{1}H NMR δ 0.5-2.3 (m, 6H, H-7, H-8, H-9), 2.32-2.7 (m with s at 2.38, 7H, NMe_2, H-6), 2.74-2.93 (m, 4H, H-5, H-10), 7.15 (m, 4H, aromatic hydrogens) ; ^{13}C NMR δ 21.9 (t), 28.6 (t), 31.0 (t), 31.1 (t), 35.1 (t), 41.4 (q), 68.0(d), 126.1 (d), 126.4 (d), 128.8 (d), 129.5 (d), 139.3 (s), 140.4 (s) . This compound was also obtained by reaction of a solution of benzocycloocten-2-one [10] (1.74g, 10mmol) with a 3M solution of dimethylamine (5ml, 15mmol) in ether and a solution of titanium (IV) chloride (1g, 5.5 mmol) in benzene (10 ml) at 0°C under a nitrogen stream ; the mixture was stirred for 5 h, filtered and the solvents were removed in vacuo . The crude oil was treated with formic acid (0.55g, 12mmol), refluxed for 2 h, cooled and made alkaline with a 6N aqueous solution of sodium hydroxide, extracted with ether, dried on magnesium sulfate and distilled to afford 1.68 g (yield 83 %) of **5a**; b.p. 91°C (1 Torr) .

6-(N,N-Dimethylamino)-1-methoxy-5,6,7,8,9,10-hexahydro benzocyclooctene **5c** : ^{1}H NMR δ 1.5-1.9 (m, 6H, H-7, H-8, H-9), 2.38 (s, 6H, NMe_2),2.39-2.65 (m, 1H,H-6), 2.71-3.12 (m, 4H, H-5, H-10), 2.80 (s, 3H, O-Me), 6.77 (m, 2H, H-2, H-4), 7.08 (m, 1H, H-3) ; ^{13}C NMR δ 22.6 (t), 23.1 (t), 28.5 (t), 29.2 (t), 35.4 (t), 41.2 (q), 55.4 (q), 68.2 (d), 108.3 (d), 122.1 (d), 126.4 (d),

NMR DATA OF COMPOUNDS 1,3 AND 4

1H	H-1a	H-1b	H-3a	H-3b	H-4a	H-4b	H-5a	H-5b	H-6a	H-6b	H-7a	H-7b	Me2N +	MeO	Ar
1a	4.46	5.08	2.60	3.32	1.36	1.65	1.75	2.18	1.51	2.18	2.75	2.94	3.03/3.25		7.25-7.5
1b	4.98	5.04	2.88	3.40	1.55	2.05	2.15	2.35	1.65	2.35	2.78	3.38	3.43/3.65	3.83	6.9-7.3
1c	5.00	5.04	2.94	3.56	1.55	2.06	2.15	2.35	1.65	2.35	2.86	3.42	3.38/3.67	3.93	6.9-7.3

1a	61.7	58.5	23.7	17.8	26.4	27.3	146.2	131.2	130.3	126.0	133.9	126.0	50.8/51.1	
1b	61.8	58.7	23.7	17.9	26.6	26.6	137.9	132.2	116.7	156.8	118.8	126.8	51.0	55.2
1c	61.5	58.2	20.3	17.6	24.5	23.6	134.3	157.5	112.7	126.9	125.7	126.8	50.7/51.2	55.8
13C	C-1	C-3	C-4	C-5	C-6	C-7	C-7a	C-8	C-9	C-10	C-11	C-11a	Me2N +	MeO

1H	H-1a	H-1b	H-3a	H-3b	H-4a	H-4b	H-5a	H-5b	H-6a	H-6b	H-7a	H-7b	H-9	H-10	H-11	MeN	MeO	MeAr
3a	4.17	3.00	2.10- 2.24		0.70	-1.91	1.19		1.83	0.8	3.0	2.60	6.92 - 7.20			2.32		2.57
3b	4.10	2.10 - 3.3			0.80	-1.55	0.80- 2.0				2.1- 3.3		6.57	6.89		2.31	3.73	2.90
3c	4.12	3.00	2.1- 2.35		0.75	-1.74	1.1 -1.3		1.75	0.90	3.17	2.70		6.52	6.88	2.32	3.77	2.54

3a	62.6	57.4	27.8	22.7	32.1	33.1	139.3	126.9	125.2	126.0	139.3	142.2	18.9	47.3	
3b	57.6	53.6	28.0	23.7	32.8	33.2	135.1	126.9	108.5	156.7	135.1	143.0	20.0	46.8	56.0
3c	62.6	57.5	28.2	23.4	30.3	27.0	131.6*	157.6	107.4	126.4	131.8*	141.1	19.9	46.9	55.8
13C	C-1	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-12	C-13	MeAr	MeN	MeO

1H	H - 1	H - 2	H-3, H-4	H - 5	Me2N	ArCH2N	MeO	Ar
4a	4.89 -5.17	5.62 -6.04	1.55 -2.32	2.58 -2.81	2.22	3.37		6.92- 7.32
4b	4.85 -5.11	5.60 -6.05	1.60 -2.00	2.50 -2.75	2.23	3.35	3.75	6.70- 7.25
4c	4.87 -5.11	5.60 -6.05	1.60 -2.00	2.62 -2.81	2.21	2.98	3.81	6.71- 7.22

4a	114.6	138.5	31.9	30.5	33.9	141.6	129.3	127.1	125.4	130.2	136.7	45.2	62.2	
4b	114.6	138.8	31.2	30.6	33.7	133.6	130.2	115.3	157.6	112.4	138.0	45.6	61.5	55.2
4c	114.2	139.1	34.2	29.1	25.4	130.7	157.8	109.2	125.9	122.6	138.1	45.6	61.7	55.4
13C	C-1	C-2	C-3	C-4	C-5	C-1'	C-2'	C-3'	C-4'	C-5'	C-6'	Me2N	ArCH2N	MeO

* can be inverted

ELEMENTAL ANALYSES OF 1b,c 3a-c AND 4a-c

	1b*	1c**	3a	3b	3c	4a	4b	4c
C	49.43(49.87)	49.81(49.87)	82.42(82.70)	76.74(77.20)	77.12(77.20)	82.85(82.70)	77.22(77.20)	76.87(77.20)
H	6.81(6.68)	6.48(6.68)	10.55(10.41)	9.87(9.93)	9.95(9.93)	10.38(10.41)	9.97(9.93)	9.92(9.93)
N	3.82(3.88)	3.81(3.88)	6.77(6.89)	6.07(6.00)	5.74(6.00)	6.81(6.89)	5.84(6.00)	5.81(6.00)
I	34.91(35.13	35.13(35.13)						

Calculated values in brackets * Yield 97 % ; mp 229°C ** Yield 94 % ; mp 239°C

128.5 (s), 141.2 (s), 157.2 (s) . Anal. Calcd for $C_{15}H_{23}NO$: C, 77.20 ; H, 9.93 ; N, 6.00 . Found C, 77.19 ; H, 9.94 ; N, 5.77 .

3-Methyl -1,2,3,4,5,6,7,8-octahydro-3-benzazecine **6a** : ^1H NMR [11] . ^{13}C NMR δ 20.1 (t), 28.1 (t), 30.1 (t), 31.0 (t), 44.2 (q), 53.0 (t), 59..6 (t), 125.5 (d), 125.7 (d), 128.3 (d), 129.1 (d), 140.2 (s), 141.2 (s) .

3-Methyl-9-methoxy-1,2,3,4,5,6,7,8-octahydro-3-benzazecine **6c** : ^1H NMR δ 1.21-1.59 (m, 6H, H-5, H-6, H-7), 2.08 (s, 3H, N-Me), 2.34-2.55 (m, 4H, H-2, H-4), 2.65-3.01 (m, 4H, H-1, H-8), 3.80 (s, 3H, O-Me), 6.78 (m, 2H, H-10, H-12), 7.08 (m, 1H, H-11) ; ^{13}C NMR δ 21.9 (t), 26.5 (t), 27.8 (t), 28.4 (t), 31.4 (t), 44.8 (q), 53.4 (t), 55.3 (q), 59.7 (t), 107.7 (d), 121.5 (d), 126.0 (d), 130.1 (s), 141.9 (s), 158.2 (s) . Anal. Calcd for $C_{15}H_{23}NO$: C, 77.20 ; H, 9.93 ; N, 6.00 . Found: C, 76.43 ; H, 9.91 ; N, 5.58 .

5- (2-Methyl-4-methoxy phenyl) pentanal : b.p. 142°C (0.7 Torr) ; ^1H NMR δ 1.40-1.70 (m, 4H, H-3, H-4), 2.25 (s, 3H, ArMe), 2.25-2.81 (2t, 4H, H-2, H-5), 3.75 (s, 3H, OMe), 6.70-6.90 (m, 2H, H-3', H-5'), 7.10-7.25 (d, 1H, H-6'), 9.76 (t, 1H, H-1) ; ^{13}C NMR δ 19.6 (q) ,22.0 (t), 30.0 (t), 32.2 (t), 43.8 (t), 55.1 (q), 111.0 (d), 115.8 (d), 129.6 (d), 132.3 (s), 137.0 (s), 157.7 (s), 202.4 (d) . Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69 ; H, 8.79 . Found : C, 75.50 ; H, 8.79 . DNPH (ethanol) m.p. 107.5 °C [12] . This compound was also obtained by treatment of 5-(2-methyl-4-methoxyphenyl)-1-pentanol [12] (1g, 4.8 mmol) with 15 g of chromic anhydride / pyridine complex supported on alumina [13] in ether (30 ml) . The solution was stirred at room temperature for 1.5 hour, filtered and distilled to give 0.71 g of aldehyde (yield 72 %) .

5-(2-Methyl-6-methoxy phenyl) pentanal : b.p. 154°C (1 Torr) ; ^1H NMR δ 1.55-1.71 (m, 4H, H-3, H-4), 2.28 (s, 3H, ArMe), 2.49 (dt, 2H, H-2), 2.66 (t, 2H, H-5), 3.79 (s, 3H, OMe), 6.68-6.81 (m, 2H, H-3', H-5'), 7.03 (m, 1H, H-4'), 9.78 (t, 1H, H-1) ; ^{13}C NMR δ 19.4 (q), 22.3 (t), 25.8 (t), 28.7 (t), 43.7 (t), 55.4 (q), 108.1 (d), 122.7 (d), 126.0 (d), 129.0 (s), 137.2 (s), 157.6 (s), 202.5 (d) . Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69 ; H, 8.79 . Found : C, 75.83 ; H, 8.82 .

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