NITROGEN BRIDGEHEAD COMPOUNDS. PART 56.[1] REACTION OF 2,6a-DIAZA-3a-AZONIAPHENALENE QUATERNARY SALTS WITH N-NUCLEOPHILES AND CARBANIONS

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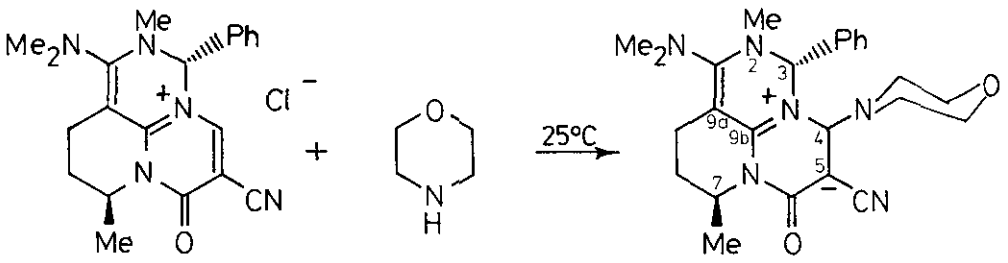
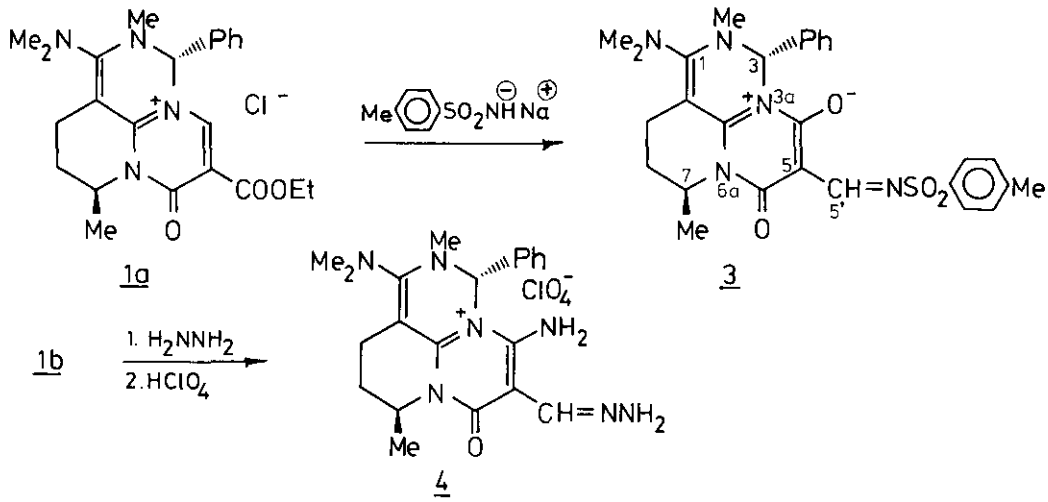
Abstract - 2,6a-Diaza-3a-azoniaphenalene chlorides (1) smoothly condense with strong N-nucleophiles and carbanions generated from malonic ester derivatives affording tri- and tetracycles by ring transformation.

In our previous papers[2,3] we reported on the reactions of 2,6a-diaza-3a-azoniaphenalene chlorides with simple nucleophiles e.g. HSO_3^-, CN^-, OH^-. We established that in case of the first former anions Michael addition took place on the C4-C5 double bond while the OH^- ion caused degenerated ring transformation resulting in stable mesomeric betaines. Now we are presenting our new results concerning first N- and C-nucleophilic reactions of the quaternery salts (1 a,b)[4]. Compounds 1b reacts with morpholine to afford a similar betaine as CN^-.



Degenerated ring transformation of 1a,b was brought about with hydrazine and p-toluenesulfonamide-Na[4].



1a

3

1b

4

^1H and ^{13}C NMR data are in accordance with the structures which have been correctly assigned in our recent papers[2,3] for a few similar examples.

^1H NMR shifts of compounds 2,3,4 JEOL-FX-100 /TMS/

Comp.	Me-7,H-7,H_2-8,9	Me-2	Me_2N	Ph	O N	pTsA	H-5'	H-3	H-4
2	1.12d,5.31m	3.24s	3.06s	7.1-7.4m	2.2-2.8m	-	-	5.75s	4.84s
	1.2-2.8m				3.67t				
3	1.18d,4.82m	3.05s	3.10s	7.0-7.35m	-	2.35s	8.94s	6.95s	-
	1.6-2.7m					7.28d			
						7.60d			
4	1.18d,4.88m	3.36s	3.10s	7.0-7.4m	-	-	8.05s	7.06s	
	1.6-2.8m								

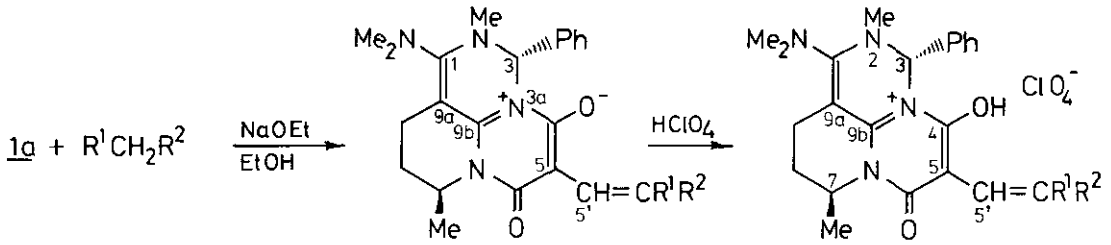
^{13}C NMR shifts of compounds 2,3,4 JEOL-FX-100 /TMS/

Comp.	C1	C3	C4	C5	C6	C7	C8	C9	C9a	C9b	Me_2N	Me-2	Me-7
2	151.6	76.4	77.3	42.5	159.2	47.2	26.6	18.1	83.4	158.2	41.4	42.5	16.5
3	149.5	67.5	164.4	92.7	158.8	45.3	29.6	18.5	84.7	158.8	41.2	41.2	15.6
4	148.3	70.8	166.7*	86.6	161.1*	46.6	25.0	18.8	85.9	152.3*	42.0	42.0	15.7

Additional ^{13}C NMR shifts of 2/C≡N/: 116.5, /C_6H_5/; 136.7, 128.0, 125,1;
3/CH=N/:161,5, /C_6H_5/; 136,7, 128,5, 125,0;
4/CH=N/:157.8*, /C_6H_5/; 135,3, 129,3, 126,0.

solvents: 2 $CDCl_3$; 3,4 DMSO-d_6 * interchangeable

Following our experiments with carbanions we have observed the same reaction pathway with compound 1a as the formation of 3. Carbanions generated from malonic acid derivatives proved to be excellent reagents capable for a very fast addition and recyclization after the ring opening.



5 b, c, d 5a

a: $R^1 = R^2 = COOEt$ c: $R^1 = CN$, $R^2 = COOEt$

b: $R^1 = R^2 = CN$ d: $R^1 = CN$, $R^2 = CONH_2$

Compounds 5a,b were insoluble in NMR solvents therefore ^1H NMR spectra have been taken only for 5c,d. *Both compounds exist in a single stereoisomeric form*, with respect to the exocyclic C=C double bond.

^1H NMR shifts of compounds 5a,5c JEOL-FX-100 /TMS/

Comp.	Me-7,H-7,H_2-8,9	Me-2	Me_2N	Ph	H-3	H-5'	COOEt	Solvent
5c	1.26d 5.05m 1.6-3.0m	3.32s	3.16s	6.9-7.35m	7.13s	8.53s	1.30t 4.24q	$CDCl_3$
5d	1.18d 4.82m 1.65-2.1m 2.3-2.8m	3.25s	3.04s	6.9-7.1m	6.99s	8.16s	-	DMSO-d_6

^{13}C NMR shifts of compounds 5c,5d JEOL-FX-100 /TMS/

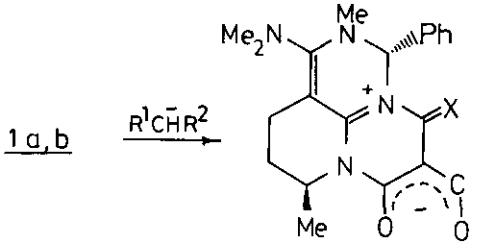
Comp.	C1	C3	C4	C5	C6	C7	C8	C9	C9a	C9b	Me-2	Me-7
5c	149.8	68.0	169.9	93.5	158.8	49.6	26.0	19.3	84.3	158.4	41.6	15.9
5d	143.2	67.7	166.1	93.1	158.8	45.7	25.9	19.8	84.1	158.6	41.6	16.1

Additional ^{13}C NMR shifts* of 5c/C=C,R^1,R^2/:149.1,92.0,117.5,161.1,60.7,14.3;
5d/C=C,R^1,R^2/:145.9,91.9,91.9,161.2.

solvents: 5c $CDCl_3$, 5d DMSO-d_6

* not informative concerning the geometry of exocyclic C=C double bond.

It is worth noting that β-ketoesters, and ketophosphonates did not react with 1a,b, and only the compounds (6a,b) described earlier[2] as a result of OH^- or EtO^- attack were formed.



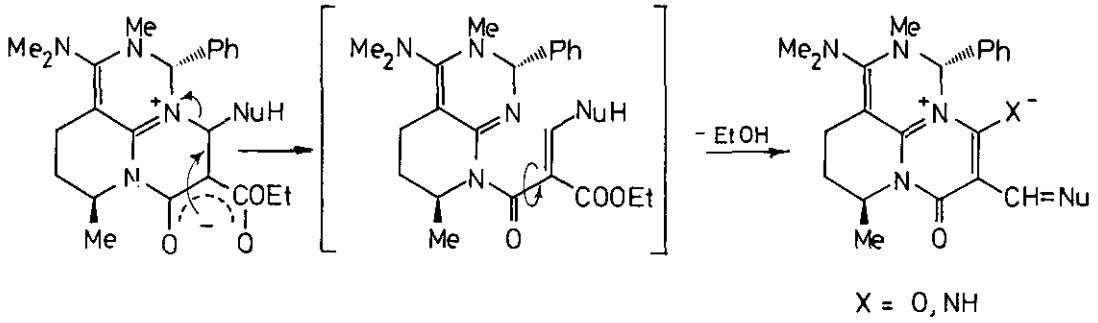
1a,b $\xrightarrow{R^1\bar{C}HR^2}$ 6a,b

R^1	R^2
CH_3CO	COOEt
PhCO	COOEt
COOEt	P O $(OEt)_2$

a: X= O

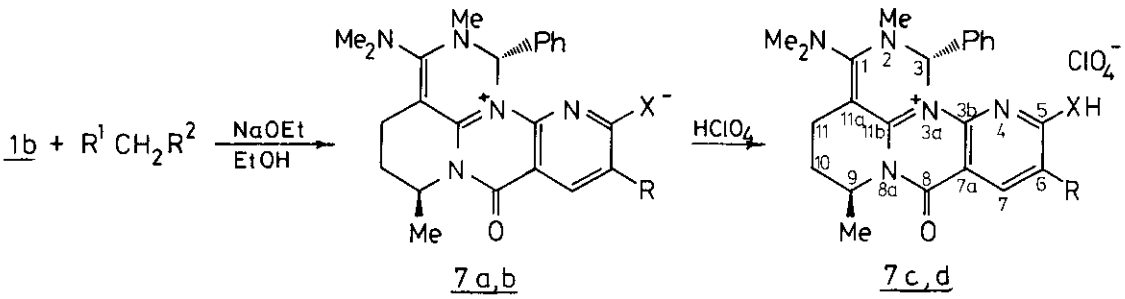
b: X= NH

Since the aldehyde group of compound 6a,b can also condense with hydrazine and pseudo acids, during the evaluation of the real reaction pathway this route is also to be considered. Condensation of 6a with ethyl cyanoacetate in the presence of NaOEt furnishes also 5c as a single isomer. This reaction, however, takes 1 h for completion whilst that of 1a requires some minutes only. Therefore the following mechanism seems to be probable:



X = O, NH

According to this mechanism if 1b is allowed to react with malonic acid derivatives another ring closure can be expected:



7a,b 7c,d

	R	X	R	X
R^1=R^2=CN or COOEt	a: COOEt	O	c: CN	NH
R^1=CN, R^2=COOEt	b: CN	O	d: COOEt	NH

Exactly, the pyridine ring is smoothly formed with diethyl malonate and malononitrile alike affording 7a,b tetracyclic mesomer betaines. With ethyl cyanoacetate, however, 7c and 7d simultanously formed in about 1:1 ratio indicating the similar reactivity of the ester and the nitrile group. After recrystallization 7c and 7d $HClO_4$ salt could be analysed separetely. Compounds(7) are mesomeric betaines and new types of the pyrido [4,5-b]-2,3a,6a-triazaphenalene ring system. Their preparation is a simple process in spite of their complicated structure.

^{1}H NMR shifts of compounds 7a-7d JEOL-FX-100 /TMS/

Comp.	Me-9,H-9,H_2-10,11	Me-2	Me_2N	Ph	H-3	H-7	COOEt	Solvent
7a	1.26d,4.85m 1.7-2.25m,2.4-2.9m	3.36s	3.14s	7.05-7.50m	7.42s	8.60s	1.23t 4.27q	DMSO-d_6
7b	1.26d,4.97m 1.7-2.15m,2.4-2.9m	3.39s	3.15s	7.2-7.6m	7.62s	8.16s	-	DMSO-d_6
7c	1.36d,5.04m 1.8-2.3m,2.5-3.1m	3.37s	3.17s	7.2-7.35m	7.78s	8.24s	-	$CDCl_3$+ CD_3OD
7d	1.30d,4.98m 1.7-2.2m,2.4-3.0m	3.46s	3.21s	7.2-7.6m	7.68s	8.79s	1.3t 4.28q	DMSO-d_6

^{13}C NMR shifts of compounds 7a-7d JEOL-FX-100 /TMS/

Cmp	C1	C3	C3b	C7a	C8	C9	C10	C11	C11a	C11b	Me-2	Me-9	C_6H_5	COOEt CN
7a	150.6	69.6	142.4	91.2	162.0	47.6	25.4	18.8	87.7	154.9	42.2	15.4	135.4	162.1
													129.1	61.5
													125.5	14.4
7b	148.6	68.7	151.1	98.8	161.8	47.0	25.4	18.7	87.0	155.8	42.0	15.5	135.7	116.7
											42.6		129.0	
													125.4	
7c	149.4	68.7	151.9	98.5	162.0	46.7	25.8	18.7	86.1	156.5	41.9	15.6	135.3	97.3
													128.8	
													124.7	
7d	148.7	69.1	161.9	107.6	161.9	47.2	25.6	18.8	87.0	156.8	42.7	15.5	135.6	167.5
													129.0	61.3
													125.3	14.3

Additional ^{13}C NMR shifts of 7a;7b;7c;7d in the order of C5,C6,C7:
169.2,91.2,148.5; 161.8,90.7,144.0; 171.2,97.3,143.7;
161.9,100.7,141.6.

solvents: 7a,7b,7d DMSO-d_6, 7c $CDCl_3$+CD_3OD

EXPERIMENTAL

All melting points are uncorrected.

Addition of morpholine on the 2,6a-diaza-3a-azoniaphenalene ring.

Morpholine (5 ml, 57 mmol) was used to solve 1b (0.40 g,1 mmol) at ambient temperature. Crystallization commences within a few hours, after 24 h the solid material was filtered off, washed with ethanol (5 ml) and dried to give 0.26 g of 2 (60%), mp 176°C. Anal. Calcd. for $C_{25}H_{25}N_6O_2$ (441.492) : C, 68.00; H, 5.71; N, 19.03. Found: C, 67.71; H, 5.80; N, 19.00 %.

Ring transformation of 1a with p-toluenesulfonamide-Na

To a suspension of p-toluenesulfonamide (1.71 g, 10 mmol) in ethanol (30 ml) sodium ethoxide (0.82 g, 12 mmol) and 1a (4.49 g,10 mmol) was added. After stirring for 15 min the mixture was evaporated to dryness, triturated with water (50 ml) and acidified with 5% HCl solution (10ml) to give 3 (5.03 g, 80 %). Mp > 260°C. Anal. Calcd. for $C_{28}H_{33}N_5O_4S$ (630.483): C, 53.33; H, 5.27; N, 11.11. Found: C, 53.38; H, 5.19; N, 11.13 %.

Ring transformation of 1b with hydrazine

A mixture of 1b (3.98 g, 10 mmol) in ethanol (30ml) and hydrazine hydrate (5 ml) was allowed to stand overnight then acidified with perchloric acid. The precipitated crystals were filtered off, washed with ethanol (10 ml) and dried.
Yield: 3.56 g (72 %) of 4. Mp 184-186°C. Anal. Calcd. for $C_{21}H_{29}ClN_7O_5$ (494.948): C, 50.96; H, 5.91; N, 19.81. Found: C, 51.01; H, 5.86; N, 19.88 %.

Ring transformation of 1a, 1b with malonic acid derivatives /General Procedure/
Ethanol (30 ml) was used to solve $R^1CH_2R^2$ (10 mmol) and sodium ethoxide (0.82 g, 12 mmol) and then 1a (4.49 g, 10 mmol) or 1b (3.98 g, 10 mmol) was added under stirring to the solution at room temperature. In the case of 5a and 7c, 7d, after stirring for 15 min the reaction mixture was acidified with perchloric acid (0.5 ml) and the perchlorate salts-(5a and 7c+7d)-were filtered off, washed with ethanol (10 ml) and dried. The mixture of 7c and 7d could be separated by multistep recrystallisation from ethanol:chloroform (3:2). In the case of 5b, 5c, 5d, 7a, 7b the products precipitated after stirring for 15 min, were filtered off, washed with ethanol (10 ml) and dried to give compounds 5 and 7.

5a Yield 53 %. Mp 240-242°C (dec.) Anal.Calcd.for $C_{28}H_{35}ClN_4O_{10}$ (623.041): C, 53.97; H, 5.66; N, 8,99. Found: C, 53.82; H, 5.76; N, 8.93 %.

5b Yield 60 %. Mp 218-220°C (dec.) Anal.Calcd.for $C_{24}H_{24}N_6O_2$ (428.474): C, 67.27; H, 5.65; N, 19.61. Found: C, 67.03; H, 5.78; N, 19.61 %.

5c Yield 65 %. Mp 270°C (dec.) Anal.Cald.for $C_{26}H_{29}N_5O_4$ (475.525): C, 65.66; H, 6.14; N, 14.73. Found: C, 65.55; H, 6.30; N, 14.66 %.

5d Yield 62 %. Mp>270°C. Anal.Calcd.for $C_{24}H_{26}N_6O_3$ (446.490): C, 64.55; H, 5.87; N, 18.82. Found: C, 64.50; H, 6.01; N, 18.70 %.

7a Yield 80 %. Mp > 270°C Anal.Calcd.for $C_{26}H_{29}N_5O_4$ (475.527): C, 65.67; H, 6.15; N, 14.73. Found: C, 65.61; H, 6.10; N, 14.70 %.

7b Yield 90 %. Mp > 270°C Anal.Calcd.for $C_{24}H_{25}N_7O$ (427.489): C, 67.43; H, 5.89; N, 22.93. Found: C, 67.38; H, 5.80; N, 22.88 %.

7c Yield 42 %. Mp > 270°C Anal. Calcd.for $C_{24}H_{25}ClN_6O_6$ (528.939): C, 54.49; H, 4.76; N, 15.89. Found: C, 54.46; H, 4.70; N, 15.85 %.

7d Yield 21 %. Mp > 270°C Anal.Calcd. for $C_{26}H_{31}ClN_6O_7$ (575.007): C, 54.30; H, 5.43; N, 14.61. Found: C, 54.32; H, 5.46; N, 14.57 %.

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