NITROGEN BRIDGEHEAD COMPOUNDS. PART 54[1]. NEW ROUTE FOR THE PREPARATION OF 2,3a,6a-TRIAZAPHENALENE SKELETON

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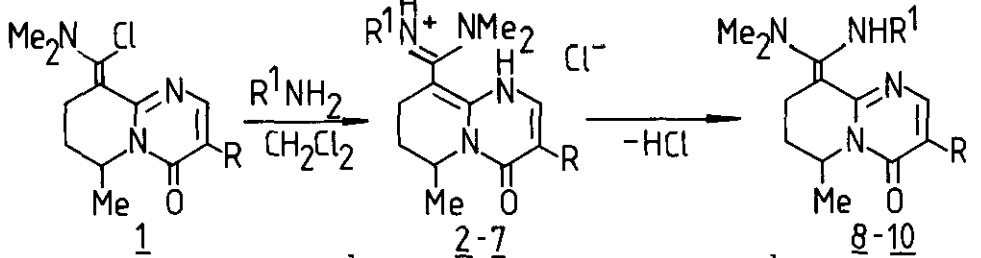
Abstract - A new approach for the synthesis of 2,3a,6a-triazaphenalene skeleton has been developed by the reaction of 9 with aldehydes.

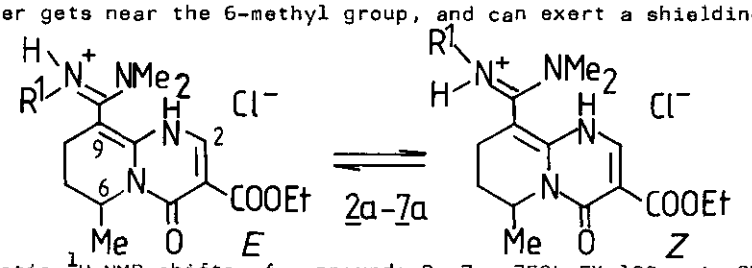
In our previous papers[1,2] we have reported the preparation of 2,3a,6a-triazaphenalenium quaternary salts and some representatives of the neutral species. These routes are not suitable for the syntheses of derivatives unsubstituted in position 3. Therefore we have developed a new method which can be widely used in the preparation of the title compounds. Compounds 1[3,4] smoothly react with ammonia and amines at room temperature affording compounds 2-7 and 8-10[5].



R	R^1	mp (°C)	R^1	mp (°C)
a: COOEt	2a: Ph	236-239 (EtOH)	8a: Ph	193-195 (i-PrOH)
b: CN	3a: 4-Me-Ph	225-226 (EtOH)	9a: H	215-218 (DMF)
c: H	4a: 4-MeO-Ph	222-224 (EtOH)	9b: H	220 (EtOH)
	5a: 4-Cl-Ph	230-232 (EtOH)	9c: H	203 (EtOH)
	6a: 4-NO_2-Ph	234-235 (EtOH)	10a: Me	252 ($EtOH+H_2O$)
	7a: 2-MeOOC-Ph	210-211 (EtOH)		

As shown by the ^1H NMR spectra compounds 2-7 are present as Z-E equilibrium mixtures. Assignment was made on the basis of the 6-methyl signals, which in one of the isomers exhibited an anomalous diamagnetic shift. Considering that the rotation of the exocyclic amidine group is strongly hindered, the N-phenyl group of

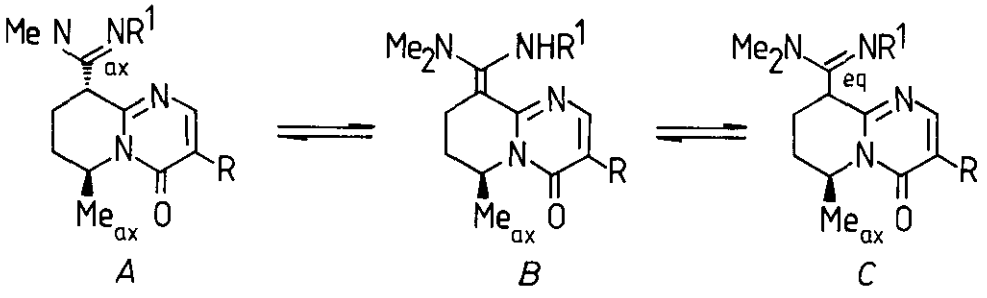
the E isomer gets near the 6-methyl group, and can exert a shielding effect.



Characteristic ^{1}H NMR shifts of compounds 2a-7a; JEOL-FX-100; in $CDCl_3$ (TMS)

Compound	E Isomer			Z Isomer			E : Z Ratio
	6-Me	H-2	NH	6-Me	H-2	NH	
2a	0.67d	8.08d J=4Hz	11.50d 10.58s	1.13d	8.12d J=4Hz	11.45 d 10.60 s	50:50
3a	0.64d	8.08d J=6Hz	11.56d 10.49s	1.09d	8.14d J=6Hz	11.50 d 10.60 s	45:55
4a	0.65d	8.09d J=5.5Hz	11.56d 10.54s	1.09d	8.15d J=5.5Hz	11.50 d 10.60 s	45:55
5a	0.74d	8.07d J=5.5Hz	11.56d 10.60s	1.12d	8.14d J=5.5Hz	11.50 d 10.68 s	45:55
6a	-	-	-	1.08d	8.05s	12.20br 11.00br	0:100
7a	0.82d	8.21d J=6Hz	12.55d 10.32s	1.17d	8.28d J=6Hz	13.00 d 10.57 s	40:60

Compounds 8a-10a may exhibit tautomerism between forms A, B, and C. According to their ^{1}H NMR and ^{13}C NMR spectra, compounds 9b and 9c really shows this equilibria but in 9b, B isomer (86%) predominates to such a great extent that we have failed in the correct assignment of isomers A (5%) and C (9%).



^{1}H NMR shifts of compound 9c JEOL-FX-100 in $CDCl_3$ (TMS)

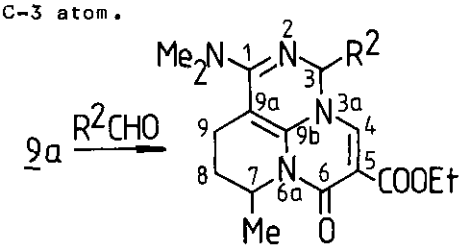
Isomer	6-Me	H-2	H-3	H-6	H_2-7,H_2-8	H-9	NMe_2	NH	Ratio
A	1.40d	7.81d ^3J=7Hz	6.35dd $^6J_{3,9}$=1Hz	5.02m	1.70-2.65m	4.13m	3.00s	8.60br	18%
B	1.28d	7.61d	5.78d	5.02m	1.70-2.65m	-	2.85s	8.60br	60%
C	1.46d	7.83d	6.38dd $^6J_{3,9}$=0.5Hz	5.02m	1.70-2.65m	4.10m	3.02s	8.60br	22%

^{13}C NMR shifts of compound 9c JEOL-FX-100 in $CDCl_3$ (TMS)

Isomer	C-2	C-3	C-4	C-6	C-7	C-8	C-9	C-9a	6-Me	NCN	$(CH_3)_2N$
A	152.2*	113.1	162.6	47.8+	24.1	20.0	43.9	158.8	19.3	164.3	38.5x
B	151.0	103.0	162.6	45.3	26.7	20.3	79.0	158.9	17.7	165.0	40.5
C	152.4*	112.9	162.6	47.9+	27.4	21.9	46.3	158.8	19.0	164.3	38.7x

*, +, and x interchangeable

Compound 9a readily cyclizes with aldehydes affording the triazaphenalene derivatives 11-14. Compound 9a (3 mmole) was reacted with 38% aqueous CH_2O (0.5 ml) in CH_2Cl_2 (15 ml) at ambient temperature for 12 h to give compound 11 in yield 70%. Compound 9a (5 mmole) was reacted with aldehyde (25 mmole) in ethanol (20 ml) at reflux temperature for 5-10 h to give tricyclic compounds 12-14 in yield 65-75%. The cyclization proceeds highly stereoselectively, as ^{1}H and ^{13}C NMR spectra show in all cases the formation of single stereoisomer. We have recently described that in the thermodynamically more stable form the 2,3a,6a-triazaphenalenium salts contain the R^2 group in pseudo-axial position trans to the 7-Me group.[2] Compounds 12-14 are very likely to be the same structure but NMR data do not offer enough evidence for the determination of the geometry of the C-3 atom.



11-14

	R^2	mp (°C)	
11	H	160	(EtOH)
12*	i-Pr	186	(EtOH)
13	Pr	96-98	(Et_2O)
14**	Ph	146	(EtOH)

*: picrate salt, **: perchlorate salt

Characteristic ^1H NMR shifts of compounds 11-14; JEOL-FX-100 in $CDCl_3$ (TMS)

Compound	$(CH_3)_2N$	H-3	H-4	H-7	7-CH_3	$(C(8)H_2$-$C(9)H_2$
11	2.77s	4.90d+ 5.05d+	7.79s	5.06m	1.22d	1.6-2.6m
12*	3.24s	5.18d	8.03s	5.02m	1.28d	1.2-3.0m
13	2.76s	5.16t	7.81s	4.88m	1.21d	1.0-2.8m
14**	3.24s	6.82d	8.80s	4.90m	1.28d	1.7-3.0m

+ ^2J = 13Hz, * picrate salt, ** perchlorate salt

Characteristic ^{13}C NMR shifts of compounds 11-14; JEOL-FX-100 in $CDCl_3$ (TMS)

Compound	C-1	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-9a	C-9b	$(CH_3)_2N$	CH_3
11	141.8	68.2	147.7	101.0	163.7	45.3	25.8	18.8	86.8	156.3	40.4	15.2
12*	146.7	74.6	148.0	104.5	157.4	46.9	25.8	19.3	82.1	154.9	41.6	15.5
13	138.5	68.7	148.0	100.0	160.4	45.2	25.6	18.7	85.4	156.3	40.0	15.7
14**	146.0	67.7	148.6	104.4	156.8	46.8	25.3	18.8	83.3	154.4	41.7	15.3

* picrate salt, ** perchlorate salt

These new 2,3a,6a-triazaphenalene derivatives can be quaternized on the N-2 atom furnishing the same triazaphenelenium salts prepared by direct cyclization. Therefore this route is regarded as a structure proving synthesis of the 2,3a,6a-triazaphenalenium derivatives we have recently described.[2]

REFERENCES AND NOTES

1. Part 53, I. Bitter, B. Pete, G. Tóth, I. Hermecz, and Z. Mészáros, Heterocycles, in the press.
2. I. Bitter, B. Pete, I. Hermecz, G. Tóth, K. Simon, M. Czugler, and Z. Mészáros, Tetrahedron Letters, 1982, 23, 2891.
3. I. Hermecz, I. Bitter, Á. Horváth, G. Tóth, and Z. Mészáros, Tetrahedron Letters, 1979, 255.
4. G. Tóth, C. De la Cruz, I. Bitter, I. Hermecz, B. Pete, and Z. Mészáros, Org. Magn. Reson., 1982, 20, 229.

5. A solution of compound 1 (10 mmol) and aromatic amine (20 mmol) in CH_2Cl_2 (20 ml) was refluxed for 3 h. The precipitated amine hydrochloride was filtered off and the filtrate was evaporated to dryness in vacuo. The residue was recrystallized from ethanol. Yield 80-90%. The bases can be liberated with aqueous Na_2CO_3 solution. Compounds 9-10 can be prepared with excess of gaseous ammonia or methylamine in similar manner. Yield 80-85%.

Received, 28th January, 1985