NITROGEN BRIDGEHEAD COMPOUNDS PART 57[1]. SYNTHESIS OF NEW 1-THIA-2a,5a-DIAZAACENAPHTHENES

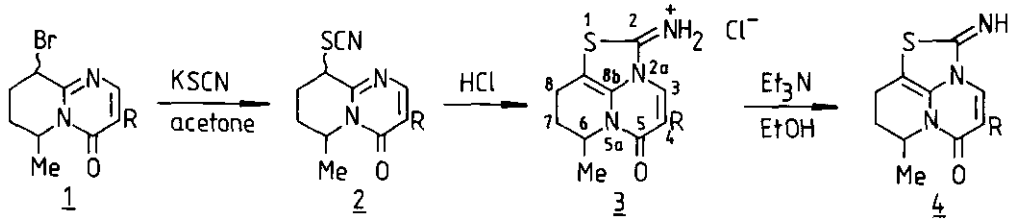
István Bitter[a1], Gábor Tóth[a2], Béla Pete[a1], Attila Almásy[a2], István Hermecz[b], and Zoltán Mészáros[b]

a1 Technical University, Depertment of Organic Chemistry and Technology, H-1111 Budapest, Hungary
a2 NMR Laboratory of the Institute of General and Analytical Chemistry, H-1111 Budapest, Hungary
b CHINOIN Pharmaceutical and Chemical Works, H-1325, Budapest Hungary

Abstract – The first representatives of a new ring system, the 1-thia-2a,5a-diazaacenaphthenes are prepared by the reaction of 9-bromo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-ones with alkali thiocyanates.

During our studies on synthesis of new annellated derivatives of biologically active[2] pyrido[1,2-a]pyrimidin-4-ones recently the first derivatives of 2,3a,6a-triazaphenalenes were prepared[3]. As a continuation of this work we wish to describe herein the first synthesis of 1-thia-2a,5a-diazaacenaphthenes.

For this purpose the reactivity of 9-bromo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]-pyrimidin-4-ones[4] was utilized. With nitrogen bases a very smooth S_N reaction[5] and sometimes subsequent oxidation[5a-c] have been observed. Making use of extreme reactivity of the 9-bromo derivatives further substitutions with other nucleophiles, e.g. CN^-, N_3^-, NO_2^-, I^-, SH^-, R_2NCSS^-, and thioureas have also been accomplished[6].



a) R=COOEt ; b) R=CN ; c) R=$CONH_2$; d) R = COOH

Compounds 1 (ca. 1:4 cis-trans mixture)[4c] readily reacted with equimolar potassium thiocyanate in acetone at room temperature affording 2 which without isolation[7] immediately cyclized by equimolar amount of aqueous hydrochloric acid and

the yellow hydrogen chloride salts (3)[8] were precipitated from the solvent. The free bases of red colour (4) could be liberated from the salts (3) by triethylamine[9]. The structure of the new tricyclic ring system is unambigously proved by correct elemental analysis, IR and NMR spectra of compounds 3 and 4. Although the fact of the ring closure is nicely indicated by the IR spectrum not containing νSCN band, ^{1}H and rather ^{13}C NMR spectra give strong evidences for the cyclization.

In ^{1}H NMR spectra of compounds 3 remarkable downfield shifts ($\Delta\delta \sim 1$ ppm) of the H-3 signal occur comparing with that of the starting material (1)[10]. It is due to the deshielding effect the neighbouring iminium group. ^{13}C NMR show three signals characteristic of the new thiazoline ring: C-2 at 164 ppm, C-8b at 127 ppm and C-8a at about 90 ppm. Deprotonation of salts 3 to compounds 4 caused a pronounced upfield shift on C-2, C-4, C-8a, and C-8b.

^{1}H NMR Chemical shifts JEOL FX-100 solvent DMSO-d_6 δ(TMS)= 0 ppm

Comp.	6-Me	H-6	CH_2-7,8		H-3	CH_3	CH_2O	NH(HCl)
3a	1.14d	4.74m	1.7-2.2m	2.4-2.8m	9.31s	1.32t	4.27q	10.30 13.30
4a*	1.25d	4.85m	1.95m	2.35m	8.55s	1.35t	4.25q	
3b	1.15d	4.72m	1.6-2.2m	2.4-2.9m	9.42s			5.85
4b	1.12d	4.61m	1.6-2.1m	2.2-2.5m	8.57s			9.70
3c	1.10d	4.82m	1.7-2.3m	2.6-2.8m	9.10s			7.87 8.42
4c	1.14d	4.70m	1.7-2.2m	2.3-2.8m	8.59s			9.52

* in $CDCl_3$

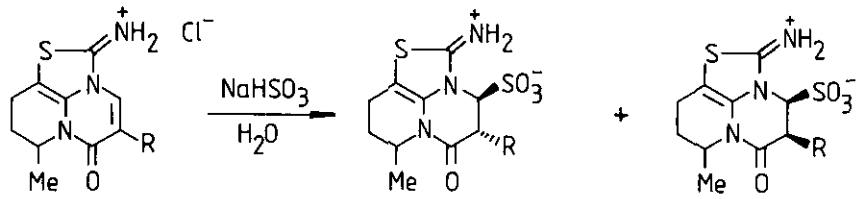
^{13}C NMR Chemical shifts JEOL FX-100 solvent DMSO-d_6

Comp.	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-8a	C-8b	Me	R	
3a	164.8	136.9	111.5	152.3	45.4	25.5	16.3	88.9	127.0	16.1	14.1	61.4 161.6
4a*	156.4	138.1	104.3	154.9	44.8	26.2	16.9	81.8	124.9	16.4	14.3	60.9 162.6
3b	164.3	141.3	95.6	151.7	46.1	25.2	16.4	91.0	126.1	16.2	112.1	
4b	152.8+	141.0	87.7	154.0+	45.0	25.1	16.3	83.9	123.4	16.0	114.5	
4c	154.2+	136.8	104.8	157.8+	44.7	25.4	16.2	82.1	124.5	16.0	162.8	

* in $CDCl_3$; + tentative assignment

We have investigated some nucleophilic reactions of the new tricyclic salts (3)

but in most cases only anion exchange (SCN^-, N_3^-, I^-) or the liberation of the free bases (4) (CN^-, OCN^-) have been observed. With HSO_3^- anion, however, Michael addition on the C-3 and C-4 double bond took place resulting in a fairly stable betaines (5+5')[11].



3 5 5'

The adducts are in all cases 1:1 mixtures of the cis (5') and trans (5) isomers. As both isomers have the SO_3^- group in pseudoaxial position owing to the peri effect of the neighbouring iminium group, the position of the R group is different. This is supported by the multiplicity and coupling constant of the H-3 and H-4 protons ($^3J_{3,4} \approx 1.0$Hz). The isomeric ratio can be determined by the intensity of the H-3 signals.

Recently we have described[12] a similar sensitivity towards nucleophiles in the case of the 2,3a,6a-triazaphenalenium salts where the site of the nucleophilic attack was the same carbon atom of the pyrimidine moiety as with compounds 3.

REFERENCES AND NOTES

1. Part 56: I. Bitter, B. Pete, G. Tóth, I. Hermecz, and Z. Mészáros, to be published.

2. I. Hermecz and Z. Mészáros, Adv. Heterocyclic Chem., 1983, 33, 241.

3. I. Bitter, B. Pete, I. Hermecz, G. Tóth, K. Simon, M. Czugler, and Z. Mészáros, Tetrahedron Lett., 1982, 23, 2891.

4. (a) I. Hermecz, T. Breining, Z. Mészáros, G. Tóth, and I. Bitter, Heterocycles, 1980, 14, 1953.

(b) Z. Mészáros, J. Knoll, P. Szentmiklósi, Á. Dávid, G. Horváth, and I. Hermecz, Arzneim. Forsch., 1972, 21, 815.

5. (a) I. Hermecz, T. Breining, Z. Mészáros, J. Kökösi, L. Mészáros, F. Dessy, and C. DeVos, J. Med. Chem., 1983, 26, 1126.

(b) I. Hermecz, T. Breining, L. Vasvári-Debreczy, Á. Horváth, Z. Mészáros, I.

Bitter, C. DeVos, and L. Rodriguez, J. Med. Chem., 1983, 26, 1494.

(c) T. Breining, I. Hermecz, B. Podányi, and J. Sessi, J. Heterocyclic Chem., in press.

(d) T. Breining, I. Hermecz, B. Podányi, Z. Mészáros, and G. Tóth, J. Chem. Soc., Perkin Trans. 1, in press.

6. I. Bitter, G. Tóth, I. Hermecz, and Z. Mészáros, to be published.

7. Only compound 2c could be isolated in pure form owing to its very poor solubility in acetone. Mp 190-192 °C, ^{1}H NMR (DMSO-d_6): Me 1.33d, H-6 4.56m, H-9 5.1-5.3m; H-2 8.63s; NH_2 7.80 and 8.40 ppm broad.

8. 3a: Yield 71%, mp 210 °C; 3b: Yield 57%, mp 244-245 °C; 3c: Yield: 75%, mp 243-245 °C; 3d: Yield 69%, mp 203-204 °C.

9. Reaction was carried out in methanol with a slight excess of triethylamine. 4a: mp 144-145 °C (EtOH); 4b: mp 166-168 °C (EtOH); 4c: mp 203-205 °C (EtOH).

10. G. Tóth, I. Hermecz, and Z. Mészáros, J. Heterocyclic Chem., 1979, 16, 1181.

11. To the yellow suspension of 3 in water excess of solid $NaHSO_3$ was added at 25 °C and stirred while the mixture became white. The precipitated crystals were filtered off, and washed with water. 5a and 5a': mp 196-198 °C; characteristic NMR data (DMSO-d_6): H-3 5.67d (^3J=1.0Hz) and 5.71d (^3J=1.2Hz); C-3 66.5 (^1J=157.0Hz) and 66.7 (^1J=157.0Hz); C-4 48.2 (^1J=141.6Hz) and 48.9 (^1J=141.6Hz). 5b and 5b': mp 250 °C; in solution it decomposed to 4b, 5c and 5c': mp 198-200 °C; H-3 5.44d (^3J=1.0Hz) and 5.48d (^3J=1.0Hz). 5d and 5d': mp 250 °C; H-3 5.24d (^3J=1.0Hz), and 5.30d (^3J=1.0Hz).

12. (a) I. Bitter, B. Pete, I. Hermecz, K. Simon, G. Tóth, and Z. Mészáros, Heterocycles, 1983, 20, 579.

(b) I. Bitter, B. Pete, G. Tóth, I. Hermecz, K. Simon, G. Náray-Szabó, and Z. Mészáros, Heterocycles, 1983, 20, 1891.

Received, 30th April, 1985