NITROGEN BRIDGEHEAD COMPOUNDS. PART 58[1]. NUCLEOPHILIC RING CLEAVAGE OF 1-THIA-2a,5a-DIAZAACENAPHTHENE RING

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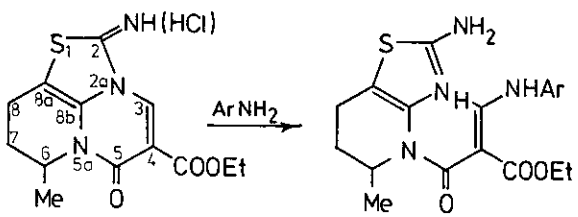
Abstract-1-Thia-2a,5a-diazaacenaphtene ring is cleaved by amines affording thiazolo[4,5-b]pyridine derivatives which undergo degenerate ring transformation.

In our previous paper[2] we reported on the synthesis of the 1-thia-2a,5a-acenaphtene ring system. Certain derivatives of this new condensed heterocycle are unusually sensitive towards nucleophiles. Compound 1 (or its HCl salt 1b) can react even with aromatic amines at room temperature in a few minutes suffering cleavage of the pyrimidine ring.

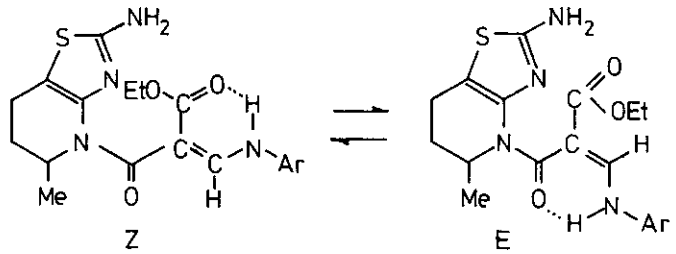


1a: base 1b: HCl salt 2a-g

Ar	Ar
a: C_6H_5	e: 4-Cl-C_6H_4
b: 2-Me-C_6H_4	f: 2-pyridyl
c: 4-Me-C_6H_4	g: $CH_2C_6H_5$
d: 4-$MeOC_6H_4$	

X-ray crystallogram of compound 2b (Fig.1.)[3] reveals that C(3)-C(4) double bond has Z geometry stabilized by intramolecular hydrogen bonding moreover two molecules are associated in a dimer by the hydrogen bonding of the -N=C-NH_2 moieties of the thiazole rings. Compounds 2a and 2f are supposed of the same structure (Z) in solid state owing to their similar IR spectra (νNH chelated 3150-3210 cm^{-1}, ν CO chelated 1672-1685 cm^{-1}). Compounds 2c,d,e, however, have different IR

spectra containing non-chelated ν NH and ν CO bonds 3200, 3170, 3180 cm^{-1} and 1700, 1700, 1710 cm^{-1}, respectively beside the chelated ones 3160, 3140, 3140 cm^{-1} and 1664, 1662, 1664 cm^{-1}, respectively .



Z E

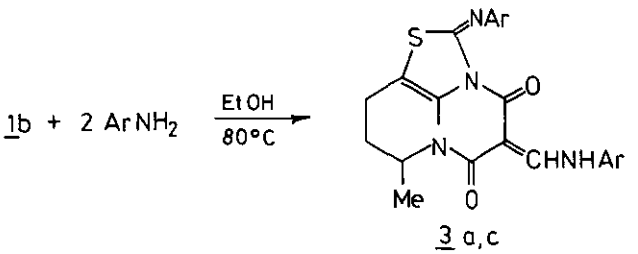
^{1}H NMR investigation also indicated that every compound existed in two isomeric forms in solution $CDCl_3$, DMSO-d_6 . The spectral data can be explained by the supposition of Z/E isomers which could be distinguished by the different rates of the deuterium exchange of the chelated and non-chelated protons (Z/E ratios are calculated on the intensity of the ester methyl and CH= signals as well).

^{1}H NMR chemical shifts of compounds 2 ppm

Comp.	Z			E				E/Z
	Me-6	H-3	Ar-NH	Me-6	H-3	Ar-NH	Solvent	ratio %
2a	1.06t	7.89d	9.98d	1.09t	8.04d	9.85d	$CDCl_3$	69:31
	1.03t	7.92d	10.03d	1.05t	7.94d	9.72d	DMSO-d_6	66:34
2b	1.07t	7.90d	9.96d	1.15t	8.04d	9.85d	$CDCl_3$	64:36
	1.00t	7.85d	9.97d	1.01t	7.87d	9.62d	DMSO-d_6	66:34
2c	1.03t	8.00d	-	1.03t	8.12d	10.17d	$CDCl_3$	83:17
	1.02t	7.95d	10.20d	1.02t	8.04d	10.16d	DMSO-d_6	80:20
2e	1.05t	7.88d	10.05d	1.09t	8.02d	9.90d	$CDCl_3$	58:42
	1.01t	7.89d	10.04d	1.01t	8.00d	9.69d	DMSO-d_6	75:25

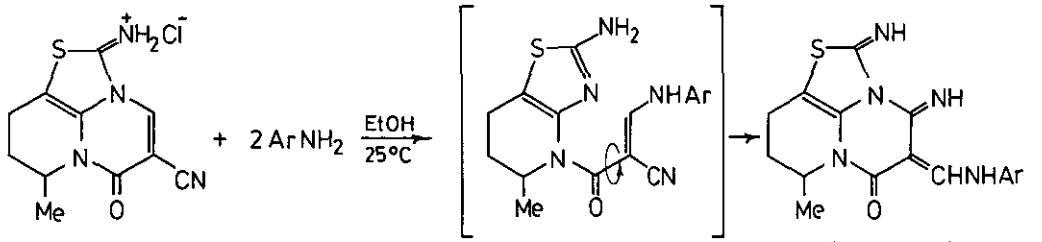
$J_{=CH-NHAr}$=12.5 Hz trans coupling

If the reaction of 1 with two equivalents of amine is carried out at 80°C,a reclosure by the ester group takes place after the ring cleavage meanwhile one more mole of amine is incorporated in the product:



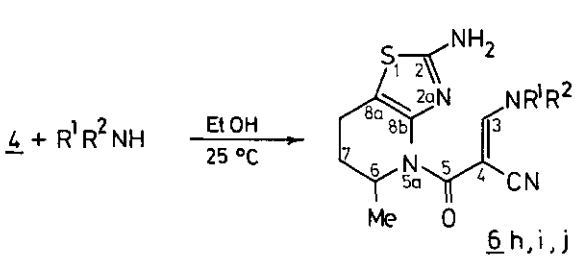
3 a,c

This kind of degenerate ring transformation is very quick with compound 4[2]. In this case the ring cleaved product could not be isolated owing to the very fast recyclization of the nitrile group:



4 → 5 a,c,e,d,g

Aliphatic primary amines are too reactive resulting in some unstable unidentified compounds. Secondary amines, however, behave similarly as described for 4, but the ring cleaved intermediates do not recyclize at ambient temperature. It is due to the decreased reactivity of the nitrile group caused by the strong electronreleasing dialkylamino substituents.



6 h,i,j

h: R^1, R^2 = CH_2=CH-CH_2

i: C_6H_5-CH_2

j: $(-CH_2CH_2)_2O$

^{1}H NMR chemical shifts of compounds 6h,6i,6j solvent: $CDCl_3$ ppm

Comp.	Me-6,H-6,H_2-7,8	CH_2N	Ar	H-3	CH_2=CH-	CH_2O	NH_2
6h	1.19d,4.65m	3.9 b	-	7.73s	5.0-5.4m	-	5.4b
	1.7-2.8m	4.24 b			5.6-6.1m		
6i	1.19d,4.69m	4.38b	7.1-7.5m	7.99s	-	-	5.2b
	1.7-2.8m	4.68b					
6j**	1.07d,4.50m	overlapped	-	7.67s	-	overlapped	6.98s
	1.7-2.7m	by DMSO				by DMSO	

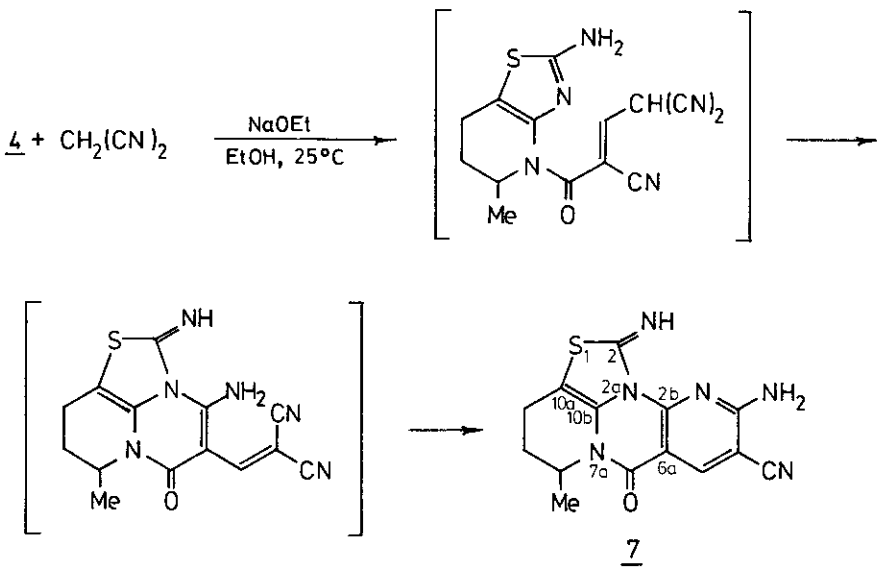
^{13}C NMR chemical shifts of compounds 6h, 6i solvent: $CDCl_3$ ppm

Comp.	C2	C3+	C4+	C5+	C6	Me-6	C7	C8	C8a	C8b	CN	R^1,R^2
6h	163.5*	156.4	98.5	165.9*	49.5	16.8	28.7	18.1	74.4	139.5	119.1	51.6 131.6 118.4
6i**	164.5*	155.7	99.0	165.6*	48.8	16.0	28.4	17.7	74.8	140.0	118.9	50.4 66.0

*: interchangeable +: numbered according to the 1-thia-2a,5a-acenaphtene ring

**: solvent: DMSO-d_6 b: broad

We have tried carbanions in order to obtain more informations on the unique behaviour of our compounds but the strong basic media NaOEt caused decomposition. Nevertheless, we succeeded in accomplishing a new reaction with malononitrile furnishing a new condensed tetracyclic compound:



Compound 7 is the result of three subsequent reactions: first ring cleavage then following two cyclizations caused by the original and one of the new nitrile groups.

EXPERIMENTAL

All melting points are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a JEOL FX-100 instrument using $SiMe_4$ as an internal standard, in $CDCl_3$ and DMSO-d_6 solutions.

Ring opening reaction of 1a with primary amines (General procedure).
1-Thia-2a,5a-diazaacenaphtene 1a (3.88 g, 10 mmol) or its HCL salt 1b (4.24 g, 10 mmol) was allowed to react with a primary amine (10 mmol or in the case of 1b 20 mmol) in ethanol (25 ml) at 25°C to give after 15 minutes' stirring the crystalline products 2 which were filtered off, washed with ethanol and recrystallized from ethanol. 2a: Yield 62%. Mp 159-160°C. Anal.Calcd.for $C_{19}H_{22}N_4O_3S$ (386.46): C, 59.05; H, 5.74; N, 14.50; Found: C, 59.15; H, 5.70; N, 14.45%. 2b: Yield 68%. Mp 144-145°C. Anal.Calcd. for $C_{20}H_{24}N_4O_3S$ (400.48): C, 59.98; H, 6.04; N, 14.00; Found: C, 59.90; H, 6.01; N, 14.08%. 2c: Yield 71%. Mp 164-167°C. Anal.Calcd.for $C_{20}H_{24}N_4O_3S$ (400.48): C, 59.98; H, 6.04; N, 14.00; Found: C, 59.84; H, 6.08; N, 14.08%. 2d: Yield 68%. Mp 152-153°C. Anal.Calcd. for $C_{20}H_{24}N_4O_4S$ (416.48): C, 57.67; H, 5.81; N, 13.45; Found: C, 57.60; H, 5.82; N, 13.40%. 2e: Yield 76%. Mp 186°C. Anal.Calcd.for $C_{19}H_{21}ClN_4O_3S$ (420.91): C, 54.21; H, 5.03; N, 13.31; Found: C, 54.20; H, 5.08; N, 13.27%. 2f: Yield 53%. Mp 148-150°C. Anal.Calcd. for $C_{18}H_{21}N_5O_3S$ (387.45): C, 55.79; H, 5.46; N, 18.08; Found: C, 55.82; H, 5.48; N, 18.00%. 2g Yield 51%. Mp 125°C. Anal.Calcd. for $C_{20}H_{24}N_4O_3S$ (400.48): C, 59.98; H, 6.04; N, 14.00; Found: C, 60.03; H, 6.03, N, 14.02%.

Ring transformation of 1b with primary amines (General procedure).
A mixture of 1b (4.24 g, 10 mmol) and the primary amine (20 mmol) in ethanol (30 ml) was refluxed for 2 h. After cooling, the resulting precipitates were collected by filtration and washed with ethanol (10 ml) and dried to give compounds 3. 3a: Yield 65%. Mp 225-230°C. Anal.Calcd. for $C_{23}H_{20}N_4O_2S$ (416.48): C, 66.32; H, 4.84; N, 13.45; Found: C, 66.27; H, 4.90; N, 13.42%. ^{1}H NMR $CDCl_3$: $MeCHCH_2CH_2$ 1.29d, 5.04m, 1.85-2.15m, 2.15-2,8, ArH 6.95-7.50m, =CH-NH 8.53d (J_{trans} = 13Hz) , NH 11.53d (Fast exchange with D_2O).
3c Yield 72%. Mp 197-199°C. Anal.Calcd.for $C_{25}H_{24}N_4O_2S$ (444.53): C, 67.54; H, 5.44; N, 12.60; Found: C, 67.49; H, 5.48; N, 12.61%. ^{1}H NMR $CDCl_3$: $MeCHCH_2CH_2$ 1.25d, 5.02m, 1.7-2.1m, 2.3-2.6m, ArMe 2.33s, 6.80-7.20m, =CH-NH 8.55d (J_{trans} = 13Hz); NH 11.45d.

Ring transformation of 4 with primary amines (General procedure)

A mixture of 4 (3.78 g, 10 mmol) and a primary amine (20 mmol) was stirred in ethanol (30 ml) at ambient temperature for 0.5 h. The resulting crystalline material precipitated, was collected by filtration and washed with ethanol (10 ml) yielding the products 5. 5a: Yield 73%. Mp 210-212°C. Anal.Calcd.for $C_{17}H_{17}N_5OS$ (339.40): C, 60.15; H, 5.05; N, 20.63. Found: C, 60.10; H, 5.08; N, 20.61 %. ^{1}H NMR (DMSO-d_6): MeCHCH$_2$CH$_2$ 1.20d, 1.29d (Z/E=2:1) 1.7-2.6m, 4.8m, ArH 7.1-7.7 m, =CH-NH 9.05d (J_{trans}=12Hz), 12.6d. 5c: Yield 80%. Mp 212-214°C. Anal.Calcd.for $C_{18}H_{19}N_5OS$ (353.43): C, 61.17; H, 5.42; N, 19.81. Found: C, 61.20; H, 5.49; N, 19.80 %. 5d: Yield 76%. Mp 208-210°C. Anal.Calcd. for $C_{18}H_{19}N_5O_2S$ (369.43): C, 58.51; H, 5.18; N, 18.95. Found: C, 58.47; H, 5.24; N, 18.96 %. 5e: Yield 61%. Mp 228-230°C. Anal.Calcd. for $C_{17}H_{16}ClN_5OS$ (373.85): C, 54.61; H, 4.31; N, 18.73. Found: C, 54.57; H, 4.35; N, 18.70%. 5g: Yield 76%. Mp 195-197°C. Anal.Calcd. for $C_{18}H_{19}N_5OS$ (353.43): C, 61.16; H, 5.42; N, 19.81. Found: C, 61.13; H, 5.43; N, 19.83%.

Ring opening reaction of 4 with secondary amines (General procedure)

A mixture of 4 (3.78 g, 10 mmol) and the secondary amine (20 mmol) in ethanol (25 ml) was stirred for 30 min. at ambient temperature. The reaction mixture was filtered off and the solid residue was washed with ethanol (10 ml) and dried to give compounds 6. They were recrystallized from ethanol. 6h: Yield 70%. Mp 136-138°C. Anal.Calcd. for $C_{17}H_{20}N_5OS$ (342.43): C, 59.62; H, 5.88; N, 20.45. Found: C, 59.59; H, 5.93; N, 20.42%. 6i: Yield 81%. Mp 138-140°C. Anal. Calcd. for $C_{25}H_{24}N_5OS$ (442.54): C, 67.84; H, 5.46; N, 15.82. Found: C, 67.82; H, 5.51; N, 15.80%. 6j: Yield 85%. Mp 152-154°C. Anal.Calcd. for $C_{15}H_{18}N_5O_2S$ (332.39): C, 54.19; H, 5.46; N, 21.06. Found: C, 54.20; H, 5.49; N, 21.01%.

Ring transformation of 4 with malononitrile

Into a solution of malononitrile (0.66 g, 10 mmol) and sodium ethoxide (0.82 g, 12 mmol) in ethanol (25 ml), 4 (3.98 g 10 mmol) was added and the reaction mixture was stirred for 30 min. at ambient temperature. The product 7 was filtered off and washed with ethanol and dried. Yield: 88%. Mp 220-222°C (ethanol). Anal. Calcd. for $C_{14}H_{12}N_6OS$ (312.34): C, 53.83; H, 3.87; N, 26.91. Found: C, 53.79; H, 3.91; N, 26.87%. ^{1}H NMR (DMSO-d_6): MeCHCH$_2$CH$_2$ 1.15d, 4.74m, 1.8-2.0m, 2.2-2.7m, CH= 8.10s, NH$_2$ 8.0 broad. ^{13}C NMR (DMSO-d_6); C2 151.7,*

C2b 160.3, C4 159.6, C5 101.4, CN-5 115.8, C6 143.3, C6a 101.4, C7 154.3*, C8 45.0, Me-8 16.5

REFERENCES

1. Part 57.: I. Bitter, G. Tóth, B. Pete, I. Hermecz and Z. Mészáros to be published.
2. I. Bitter, G. Tóth, B. Pete, I. Hermecz and Z. Mészáros: Heterocycles /in press/.
3. X-ray analysis of 2b. Emp. formula: $C_{20}H_{24}N_4O_3S$. a=10.900 /1/, b=28.388 /2/, c=13.653 /1/ Å, β =90.97 /1/°; space group $P2_1/n$, Z=8. Radiation Mo-K_α λ = 0.7107 Å; 5650 reflections. /$I \geq 3\sigma/I$// ; R index 0.047. Data were collected on an ENRAF NONIUS CAD4 diffractometer, all calculations were performed on a PDP 11/34 /64k/ minicomputer using EN.SDP program package. Relevant data are available from the authors on request.

There are two independent molecules A and B in the asymmetric unit that form a dimer by N-27A-H....N-3B and N-27B-H.....N-3A hydrogen bonds. N-6, C-10 and C-12 atoms are in the plane of the drawing, respectively.

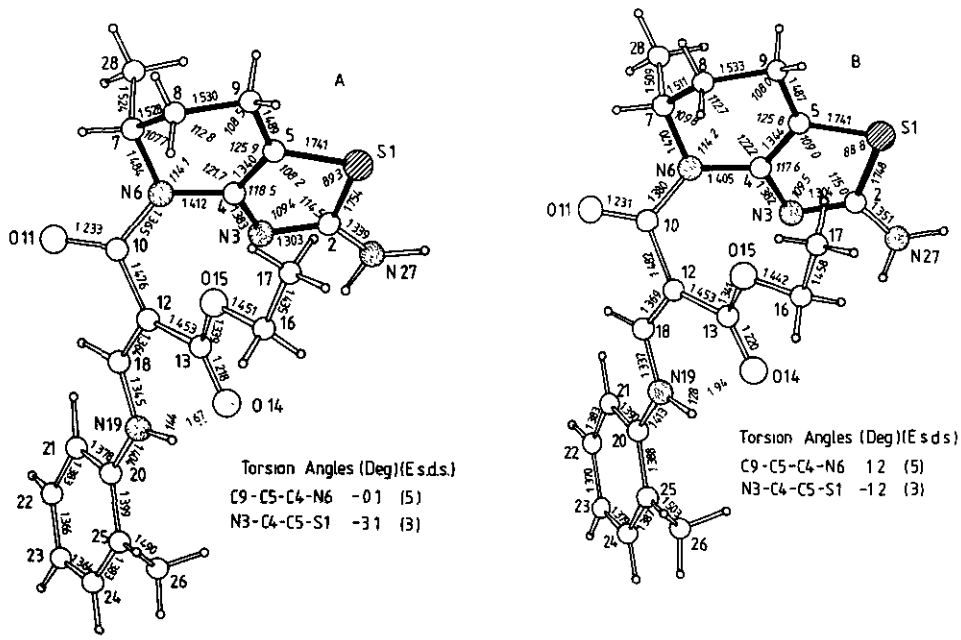


Fig.1. Molecular diagram of the structure of compound 2b showing atomic numbering, bond distance /Å/ /E.s.d.s are in the range of 0.003--0.006Å/,and bond angles /deg./ /E.s.d.s are in the range of 0.2-0.5 deg./.

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