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On the Problem of the Cyclisation of Benzothiazolyl-Anthranilic Acids into Thiazolo-Acridinones. The Case of Thiazolo[4,5-*a*]Acridines

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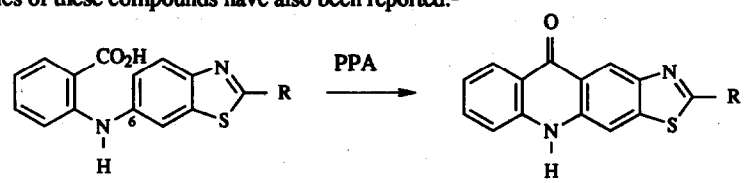
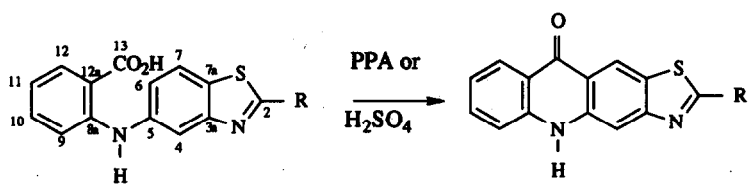
Abstract. *The cyclization of benzothiazolyl-anthranilic acids always yields 'bent' tetracycles. This has been verified in the case of benzothiazol-5-yl derivatives where, contrary to a recent literature report, the only products found are thiazolo[4,5-a]acridine derivatives.*

Taraporewala has described that the cyclization of *N*-(2-substituted-benzothiazolyl)anthranilic acids by either PPA (compounds **1** and **3**) or sulfuric acid (compound **3**) led to 'linear' thiazolo-acridines **2** and **4**.[1] The biological properties of these compounds have also been reported.[2]



1

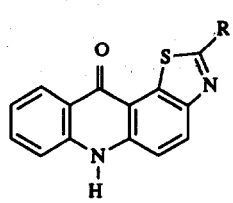
2, thiazolo[4,5-*b*]acridines
(R = H, $NHCOCH_3$)



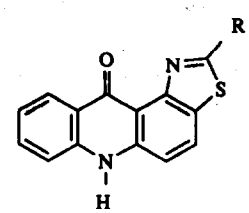
3

4, thiazolo[5,4-*b*]acridines
(R = CH_3)

In the benzothiazol-6-yl series, represented by **1**, a small amount (10-20%, depending on R) of the isomeric thiazolo[5,4-*a*]acridine, **5**, was formed, whereas in the 5-yl series (compound **3**) no thiazolo[4,5-*a*]acridine **6** was detected.



5



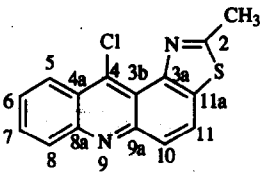
6

These were unexpected results since 'bent' isomers are usually obtained, when the synthesis of 6,6,6,5-tetracycles involves formation of the central six-membered ring as the last step. We have repeated the Taraporewala's synthesis of compounds **2** (R = H, CH_3, C_2H_5, Cl, NH_2) using H_2SO_4 and obtained exclusively the corresponding 'bent' isomers **5**.[3] It was not possible to compare our derivative **5a** (R = H) with the minor isomer (10%) obtained by Taraporewala, since no data (mp, ^1H NMR) were published.[1] Moreover, the role of PPA was not assessed.

We decided to repeat the results of the other series, since in this case i) both cyclization agents yield the same compound; ii) the reaction seemed to be cleaner (no formation of **6**),[1] and iii) for R = CH_3, the mps of **3** and **4** and the ^1H NMR spectrum of **4** were known.[1]

N-(2-substitutedbenzothiazol-5-yl)anthranilic acids **3a** (R = H) and **3b** (R = CH_3) were obtained by the Ullmann reaction between the corresponding 2-substituted-5-aminobenzothiazole[4] and potassium *o*-chlorobenzoate in pentanol with a small amount of powdered copper. The anthranilic acids were purified by repeated recrystallization in acetone. Yields are relatively fair: 24% for **3a** (mp 251°C) and 22% for **3b** (mp 233°C).

Since our melting point for compound **3b** is very different from that reported previously, mp 183-186°C,[1] both anthranilic acids were carefully characterized (see Tables 1 and 2). Compound **3a** was cyclized[8] by PPA or H_2SO_4 and compound **3b**, by PPA, H_2SO_4 or $POCl_3$.[9] With PPA or H_2SO_4 only 'bent' derivatives **6a** (R = H) and **6b** (R = CH_3) were obtained (see Tables 1 and 2). Even though the yields were reasonably good, the reaction crude materials were checked by ^1H NMR spectroscopy to verify that other isomers, in particular the 'linear' ones, were not present. Compound **6b** is different (mp > 300°C, ^1H NMR, see Table 1 and 2) from compound **4** (mp = 278-281°C, ^1H NMR, two singlets at 8.06 and 8.50 ppm in DMSO).[1] Cyclization of **3b** by $POCl_3$ afforded the chloroacridine derivative **7** (mp 168°C), thus, the use of phosphorus oxychloride do not modify the orientation of the reaction.



7

In NMR spectroscopy the most characteristic feature of compounds **6** and **7** is the AB system formed by protons H-10 and H-11 (J_{AB} ~9 Hz). Series [5,4-*a*], **5**,[3] and [4,5-*a*], **6**, are very similar through their ^1H and in ^{13}C NMR spectroscopy, the major difference being the N-H proton which appears at 9.0 ppm in compound **5b** whilst that of compound **6b** was found at 11.9 ppm. In ^{13}C NMR spectroscopy, the 'bent' structure is characterized by the appearance of carbons C-10 and C-11 in the 120-130 ppm zone [in 'linear' isomers, the CH carbons of the corresponding ring appears between 100 and 110 ppm].[10] It could be that in compounds **6** a significant amount of the OH-tautomer, hydrogen-bridged to the N-3 nitrogen may explain the strong observed deshielding effect at 11.9 ppm (averaged N-H/O-H signal).

Table 1. Anthranilic acids and derivatives of thiazolo[4,5-*a*]acridine chemical and ^{1}H-NMR data

	R	Molecular formula	mp (°C)	^{1}H-NMR
3a	H	$C_{14}H_{10}N_2O_2S$	251	9.75 (s,1H,NH); 9.38 (s,1H,C-2/H); 8.12 (d,1H,C-7/H); 7.93 (dd,1H,C-12/H); 7.90 (d,1H,C-4/H); 7.4 (ddd,1H,C-10/H); 7.39 (dd,1H,C-6/H); 7.28 (dd,1H,C-9/H); 6.81 (ddd,1H,C-11/H).
3b	CH_3	$C_{15}H_{12}N_2O_2S$	233	9.71 (s, 1H, NH); 7.96 (d,1H,C-7/H); 7.91 (dd,1H,C-12/H); 7.75 (d,1H,C-4/H); 7.42 (ddd,1H,C-10/H); 7.30 (dd,1H,C-6/H); 7.25 (dd,1H,C-9/H); 6.78 (ddd,1H,C-11/H); 2.77 (s,3H,C-2/CH_3).
6a	H	$C_{14}H_8N_2OS$	>300	11.95 (s,1H,NH) ; 9.55 (s,1H,C-2/H); 8.46 (d,1H,C-11/H); 8.29 (dd,1H,C-5/H); 7.73 (ddd,1H,C-7/H); 7.65 (d,1H,C-10/H); 7.58 (dd,1H,C-8/H); 7.29 (ddd,1H,C-6/H); *J*(C-10H/C-11H) = 9,1 Hz.
6b	CH_3	$C_{15}H_{10}N_2OS$	>300	11.93 (s,1H,NH); 8.30 (d,1H,C-11/H); 8.29 (dd,1H,C-5/H); 7.72 (ddd,1H,C-7/H); 7.58 (d,1H,C-10/H); 7.57 (dd,1H,C-8/H); 7.28 (ddd,1H,C-6/H); 2.89 (s,3H,C-2/H) *J*(C-10H/C-11H) = 9,3 Hz.
7	CH_3	$C_{15}H_9N_2SCl$	168	8.61 (d,1H,C-5/H); 8.26 (d,1H,C-8/H); 8.13[a] (d,1H,C-10/H); 8,08[a] (d,1H,C-11/H); 7.82 (ddd,1H,C-7/H); 7,67 (ddd,1H,C-6/H); 2,96 (s,3H,C-2/CH_3); *J*(C-10H/C-11H) = 9.5 Hz.

[a]These assignments can be reversed.

Table 2 : ^{13}C-NMR data.

Carbon atoms	3a	3b	Carbon atoms	6a	6b	7
C-2	156.93	168.05	C-2	158.36	167.90	165.01
C-3a	154.21	154.14	C-3a	147.91	149.99	148.97
C-4	113.87[c]	113.72[c]	C-3b	114.15	113.77	**
C-5	146.91	147.14	C-4	174.12	174.87	134.30
C-6	120.79[d]	119.97[d]	C-4a	121.78	122.41	**
C-7	122.99	122.50	C-5	125.89	125.97	125.11
C-7a	127.89	129.61	C-6	121.38	121.12	127.30
C-8a	139.34	139.06	C-7	132.53	132.67	130.49
C-9	114.52[c]	114.03[c]	C-8	118.10	117.01	129.03
C-10	134.10	134.10	C-8a	141.27	141.27	147.55
C-11	117.67[d]	117.53[d]	C-9a	139.06	139.81	147.07
C-12	131.77	131.69	C-10	115.80	115.50	127.30
C-12a	112.93	112.79	C-11	127.04	126.50	123.74
C-13	169.73	169.92	C-11a	127.74	128.59	125.52
CH_3	-	19.74	CH_3	-	19.98	20.42

[a]Correct microanalytical results (± 0.3) were obtained for all the products.
[b]Always in DMSO-d_6, except for compound 7 ($CDCl_3$).
[c,d]These assignments can be reversed.
**Unobserved signal.

References and notes:

1 Taraporewala I.B., *Tetrahedron Lett..*, **1991,** *32*, 39-42.

2 Taraporewala I.B., Cessac J.W., Chanh T.C., Delgado A.V. and Schinazi R.F., *J. Med. Chem.*, **1992,***35*, 2744-2759.

3 Barbe J., Boyer G., Carignano I., Elguero J., Galy J.P., Morel S. and Oughedani R., *Tetrahedron Lett..*, **1991,** *32*, 6709-6710 .

4 The corresponding 5-amino benzothiazoles were prepared in a three-step procedure from 2-bromo-5-nitro-aniline; R = H series: 2-bromo-5-nitro-formanilide[5] ———> 5-nitrobenzothiazole[6] ———> 5-amino-benzothiazole;[5] R = CH_3 series: 2-mercapto-5-nitroaniline[7] ———> 2-methyl-5-nitrobenzothiazole[7] ———> 2-methyl-5-aminobenzothiazole.[7]

5 Spieler J. and Prijs B., *Helv. Chim. Acta .*, **1950,** *33*, 1429 -1433.

6 Shavyrina V.V. and Zhuravlev S.V., *Khim. Geterotsikl. Soedin.*, **1972,** *1*, 36-38.

7 Al'perovich M.A., Miroshnichenko Z.I. and Ushenko T.K., *Zhur. Obshchei. Khim.*, **1959,** *29*, 989-997.

8 Sulfuric acid procedure. A mixture of 0.3 g of the corresponding anthranilic acid and 3 ml of pure sulfuric acid was heated at 100°C with vigorous stirring during 2 h. Then ice was added carefully into the flask. The resulting solution was neutralized with dilute aqueous ammonia. The precipitate was filtered, washed with water and dried. After crystallization in methanol, the yields are: **6a** 85%; **6b** 64%. Polyphosphoric acid procedure. 4 g of polyphosphoric acid were heated at 90°C, then 0.3 g of anthranilic acid was added. The mixture was heated at 110°C for 2 h and ice was added. Diluted aqueous ammonia is used to neutralize the solution. The precipitate was filtered, washed with water, dried and crystallized in methanol. The yields are: **6a** 64%, **6b** 78%.

9 A mixture of 0.30 g (1.06 mmoles) of 2-methyl-5-(2'-carboxyphenyl-amino)benzothiazole **3b** and 2 ml of phosphorus oxychloride was heated at 80°C during 15 min and then 30 min at 120°C. After cooling, the excess of $POCl_3$ was extracted with petroleum ether. The sticky residue was neutralized with aqueous ammonia. The filtered green precipitate was washed with water, dried and crystallized in ethanol. Mp 168°C, yield 20%.

10 Mefetah, H., Barbe, J. Galy, A.M. and Galy, J.P. *unpublished results.*

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