Azido/tetrazole Equilibrium in the Thiazoloacridinone Series [1]

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Dedicated to the memory of Professor Nicholas Alexandrou

Compounds 2-azido-6*H*-thiazolo[5,4-*a*]acridin-11-one **3** and 2-azido-6-butylthiazolo[5,4-*a*]acridin-11-one **4** have been prepared for the first time. The azido/tetrazole equilibria of the most soluble compound **4** has been studied in six solvents. The resulting tautomeric equilibrium constants have been compared with those of 2-azido-4,5-dimethylthiazole **1** and 2-azidobenzothiazole **2**. The rather insoluble NH derivative **3** when dissolved in DMSO contains 66% of tetrazole **3b** while the corresponding anion (obtained by adding sodium hydride) is all in the tetrazole **13b** form.

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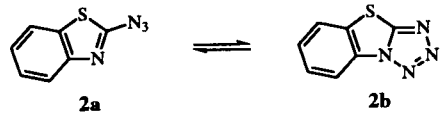
We are interested in the problem of the azido/tetrazole equilibrium in azides derived from aromatic five-membered rings [2-7]. Since for the following discussion some of these results are required we will summarize here the two main conclusions concerning the influence of solvents on the azido/tetrazole equilibria of 2-azido-4,5-dimethylthiazole **1** [4] and 2-azidobenzothiazole **2** [6]:

1) The position of the equilibrium (K = [A]/[T]) depends essentially on the polarity of the solvent.

2) For different 2-azidothiazoles (for instance **1** and **2**) in a series of solvents there is a proportionality of the equilibrium constant. In other words, solvent and substituent effects are independent.

1a **1b**



2a **2b**

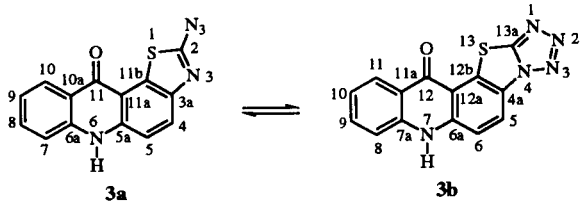
Results and Discussion.

Chemistry.

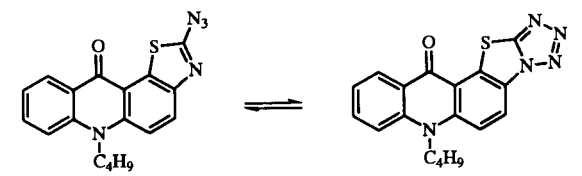
Synthesis of **3** {2-azido-6*H*-thiazolo[5,4-*a*]acridin-11-one (**3a**); 7*H*-tetrazolo[1',5':1,5]thiazolo[5,4-*a*]acridin-12-one (**3b**)} and **4** {2-azido-6-butylthiazolo[5,4-*a*]-acridin-11-one (**4a**); 7-butyltetrazolo[1',5':1,5]thiazolo[5,4-*a*] acridin-12-one (**4b**)} was achieved starting from 2-chlorobenzothiazole **5** (Scheme 1). The sequence (nitration, reduction, anthranilic acid **8**) to obtain the 'bent' tetracycle [8] is the usual procedure for these acridinones.

NMR Spectroscopy.

The nmr spectra are reported in Tables 1 (^{1}H nmr) and 2 (^{13}C nmr).



3a **3b**



4a **4b**

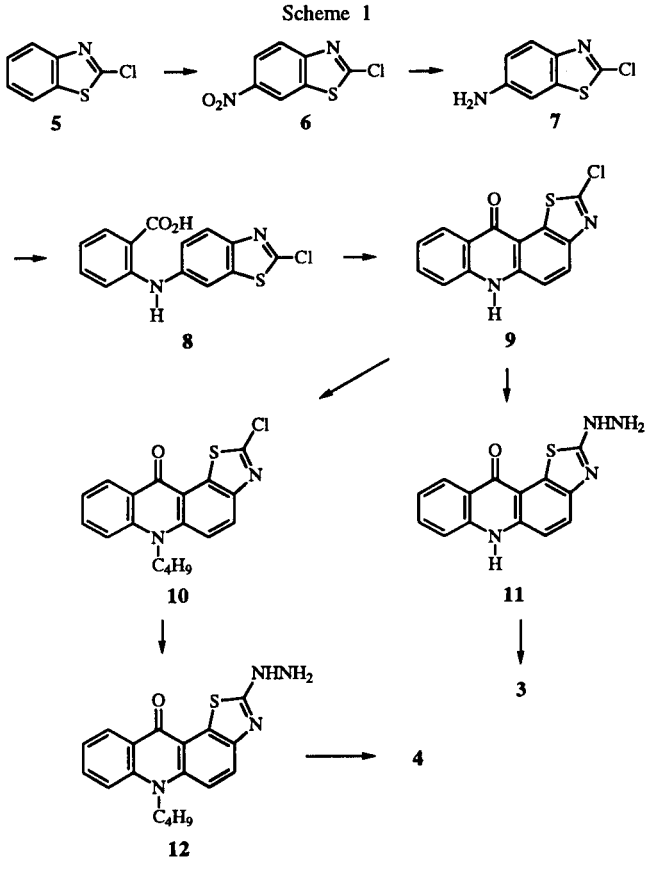
The following signals were used to determine the equilibrium constants of Table 3: DMSO-d_6 (8.28 and 8.67 ppm), acetone-d_6 (8.23 and 8.64 ppm); acetonitrile-d_3 (8.04 and 8.19 ppm); pyridine-d_5 (8.36 and 8.63 ppm); deuteriochloroform (8.15 and 8.43 ppm, see Table 1) and benzene-d_6 (7.55 and 7.95 ppm). The two other protons of the AB systems (H-4/H-5 of azide **4a**, H-5/H-6 of tetrazole **4b**, J = 9.0 to 9.3 Hz) when observable provide the same percentages but in several cases, they are overlapped by the protons of the benzene ring (H-7 to H-11).

The chemical shifts reported in Tables 1 and 2 for the anion **13** leaves no doubt that this compound exists in the tetrazole form **13b**.

Azido/Tetrazole Tautomerism.

We have reported in Table 3 the log K (K = [A]/[T]) values for compounds **1, 2** and **4** (compound **3** is too

Scheme 1



$$\log K(4) = 0.69\pm0.08 + 0.71\pm0.08 \log K(1), \quad n = 6, r^2 = 0.946 \qquad (2)$$

$$\log K(4) = 0.42\pm0.05 + 0.67\pm0.07 \log K(2), \quad n = 6, r^2 = 0.954 \qquad (3)$$

These linear relationships show:

1) Solvent effects are independent on the nature of the thiazole, in other words, there is no interaction term between the variables of solvent and structure in empirical models.

2) For the three cases, solvent effects on log K depend on the polarity of the solvent as described, for instance, by Koppel and Palm's Y parameter [Y = (ε-1)/(ε+2)] [4,9]. In the case of compound **4** the following equation is found:

$$\log K(4) = 1.2\pm0.2 - 1.5\pm0.2\ Y,\ n = 6,\ r^2 = 0.954 \qquad (4)$$

Recently [10,11] a new polarity scale called SPP has been proposed but it gives worse results for the present problem [see eq. (5)]:

$$\log K(4) = 2.8\pm0.5 - 3.1\pm0.6\ SPP,\ n = 6,\ r^2 = 0.868 \qquad (5)$$

If instead of compound **4** we use a combination of the log K of the three compounds [obtained using PCA (principal component analysis)] then equation (6) is obtained:

$$\log K(PCA) = 1.7\pm0.3 - 3.3\pm0.4\ Y,\ n = 6,\ r^2 = 0.946 \qquad (6)$$

Table 1

^{1}H NMR Chemical Shifts (ppm) and some ^{1}H-^{1}H Coupling,Constants (Hz) of Compounds **3**, **4** and **13**

Azides	Solvent	H-4	H-5	H-7	H-8	H-9	H-10
3a	DMSO-d_6	8.17 $J_{4,5}$ = 8.8 Hz	7.67	7.61	7.78	7.34	8.25
4a [a]	$CDCl_3$	8.15 $J_{4,5}$ = 9.2 Hz	7.61	7.57	7.75	7.35	8.58
Tetrazoles	Solvent	H-5	H-6	H-8	H9	H-10	H-11
3b	DMSO-d6	8.52 $J_{5,6}$ = 9.0 Hz	7.78	7.61	7.78	7.36	8.21
4b [a]	$CDCl_3$	8.43 $J_{5,6}$ = 9.0 Hz	7.74	7.61	7.81	7.41	8.53
13b [b]	DMSO-d_6	8.22 $J_{5,6}$ = 9.1 Hz	7.79	7.69	7.53	7.11	8.24

[a] *N*-Butyl **4a** and **4b**: 4.43 (NCH_2), 1.95 (CH_2), 1.59 (CH_2), 1.11 ppm (CH_3). [b] Plus NaH.

insoluble in most nmr solvents), some values for the first two compounds were already known [4,6].

These values are linearly related:

$$\log K(1) = -0.41\pm0.09 + 0.90\pm0.13 \log K(2), \quad n = 6, r^2 = 0.926 \qquad (1)$$

3) Equations (1)-(3) show that they are of similar quality and that the values of log K can be compared. For instance in deuteriochloroform the equilibrium constants (in parentheses the molar fractions for the azide and the tetrazole) are: **1** 0.398 (0.285/0.715), **2** 1.000 (0.500/0.500) and **4** 2.951 (0.747/0.253). Thus, the percentage of azide

Table 2

^{13}C NMR Chemical Shifts (ppm) of Compounds **3**, **4** and **13**

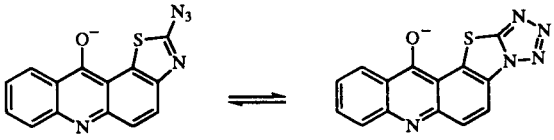
Azides	C-2	C-3a	C-4	C-5	C-5a	C-6a	C-7	C-8	C-9	C-10	C-10a	C-11	C-11a	C-11b
3a [a]	162.7	144.9	126.9	116.9	138.6	140.3	117.9	133.6	121.9	126.6	119.7	174.8	114.4	128.8
4a [b,c]	165.3	145.7	127.1	113.8	139.3	141.3	115.1	134.1	122.0	127.7	121.8	175.8	116.6	131.6
Tetrazoles	C-13a	C-4a	C-5	C-6	C-6a	C-7a	C-8	C-9	C-10	C-11	C-11a	C-12	C-12a	C-12b
3b [a]	159.5	122.3	122.6	118.1	140.1	140.4	117.7	134.4	119.9	125.4	119.7	175.8	114.6	130.9
4b [b,d]	N.o.	122.3	123.0	114.6	141.0	141.4	115.4	135.1	119.7	127.6	121.7	176.6	116.9	134.3
13b [a,e]	158.8	119.0	115.6	127.8	150.0	151.2	127.9	129.9	119.1	124.7	121.5	173.8	115.1	130.4

[a] DMSO-d_6. [b] $CDCl_3$. [c] *N*-Butyl: 46.9 (NCH_2), 29.5 (CH_2), 20.3 (CH_2), 13.9 ppm (CH_3). [d] *N*-Butyl: 47.3 (NCH_2), 29.4 (CH_2), 20.3 (CH_2), 13.9 ppm (CH_3). [e] Plus NaH.

increases from 4,5-dimethyl (28.5%) to benzothiazole (50%) to 6-butylthiazolo[5,4-*a*]acridin-11-one (74.7%).

We have shown that for thiazole derivatives log *K* depends on the Hammett σ constant of the substituents at positions 4 (σ_m) and 5 (σ_p) [6]. Assuming an average σ for the methyl group (-0.10) and taking into account the σ_m for benzo condensation (C_4H_4, 0.04) [12], then for the acridinone we found $\sigma_m = 0.20$, that is acridinone is much more electron-withdrawing than benzene.

In the case of compound **3** we have only obtained the ^1H nmr spectra in DMSO-d_6 and in DMSO-d_6 + NaH. In the first case both tautomers are present (log $K = 0.30$, 66% **3b**) while in the second one only tetrazole **5b** is observed.



13a **13b**

We have shown that the transformation of a neutral NH-azole into its anion (azolate) shifted the azido/tetrazole equilibrium from the azide to the tetrazole tautomer [3,7,13]. Thus, the present result is consistent with that finding which corresponds to the fact that anions are much more electron-releasing substituents than neutral azoles.

EXPERIMENTAL

Melting points were determined with a Reichert Jung microscope apparatus and are uncorrected. Reagent and solvents were purchased from common commercial suppliers. The nmr spectra were recorded on a Bruker AMX-400 spectrometer working at 400 and 100.6 MHz for ^1H and ^{13}C respectively. In all cases, TMS was used as an internal standard. 2-Chlorobenzothiazole (**5**) is a commercial compound; some others were previously described: 2-chloro-6-nitrobenzothiazole (**6**) [14], 2-chloro-6-aminobenzothiazole (**7**) [14], the anthranilic acid (**8**) [15] and 2-chloro-6*H*-thiazolo[5,4-*a*]acridin-11-one (**9**) [16].

2-Chloro-6-butylthiazolo[5,4-*a*]acridin-11-one (**10**).

This compound was prepared using a modification of the procedure used for the alkylation of acridin-9-ones [17]. In a two-necked flask 0.98 g (3.4 mmoles) of 2-chloro-6*H*-thiazolo[5,4-*a*]acridin-11-one (**9**) was dissolved in 10 ml of dimethyl formamide. Under stirring at room temperature, 0.28 g (10 mmoles) of sodium hydride was added under nitrogen stream. The mixture was then stirred at 45-50° for 40 minutes, then cooled with an ice bath. Butyl bromide (2.81 g, 20.5 mmoles) was added dropwise, then stirring at 95° was maintained for 8 hours under nitrogen atmosphere. The mixture was poured into cold water and the yellowish precipitate was filtered off and dried *in vacuo*. The residue was separated by column chromatography (silica gel-dichloromethane-ethanol 96:4). Compound **10** was crystallized in acetonitrile, golden flakes, 0.65 g, 55% yield, mp 186-188°; ^1H nmr (dimethyl sulfoxide-d_6): δ 8.14 (d, 1H, H-4), 7.54 (d, 1H, H-6, $J_{4,5}$ = 9.3 Hz), 4.36 (t, 2H, NCH_2), 1.79 (m, 2H, CH_2), 1.59 (m, 2H, CH_2), 1.07 (t, 3H, CH_3), 7.50 (dd, 1H, H-7), 7.72 (ddd, 1H, H-8), 7.29 (ddd, 1H, H-9), 8.48 ppm (dd, 1H, H-10); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 156.4 (C-2), 145.6 (C-3a), 128.1 (C-4), 114.0 (C-5), 139.9 (C-5a), 46.9 (NCH_2), 29.5 (CH_2), 20.3 (CH_2), 13.9 (CH_3), 141.2 (C-6a), 115.2 (C-7), 134.2 (C-8), 122.3 (C-9), 127.6 (C-10), 121.9 (C-10a), 175.6 (C-11), 116.1 (C-11a), 134.2 ppm (C-11b).

Anal. Calcd. for $C_{18}H_{15}N_2OSCl$: C, 70.33; H, 4.92; N, 9.11. Found: C, 70.21; H, 4.79; N, 9.34.

2-Hydrazino-6*H*-thiazolo[5,4-*a*]acridin-11-one (**11**).

A mixture of 1.43 g (5 mmoles) of 2-chloro-6*H*-thiazolo-[5,4-*a*]acridin-11-one (**9**) and 15 ml of hydrazine monohydrate were placed in a 50 ml flask and heated at 120-130° under stirring for 2 hours. Then 15 ml of ethanol was added and the mixture was allowed to cool down at room temperature. The precipitate was filtered off and washed with ethanol to give **11** in 96% yield (1.35 g), mp >300°, ^1H nmr (dimethyl sulfoxide-d_6): δ 4.96 (br, 2H, NH_2), 8.83 (br, 1H, NH), 7.79 (d, 1H, H-4), 7.47 (d, 1H, H-5, $J_{4,5}$ = 8.7 Hz), 11.92 (br, 1H, N6-H), 7.57 (dd, 1H, H-7), 7.72 (m, 1H, H-8), 7.25 (m, 1H, H-9), 8.25 ppm (dd, 1H, H-10); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 175.2 (C-2), 148.1 (C-3a), 124.7 (C-4), 114.7 (C-5), 136.2 (C-5a), 140.4 (C-6a), 117.5 (C-7), 133.0 (C-8), 120.8 (C-9), 125.8 (C-10), 119.6 (C-10a), 175.5 (C-11), 115.6 (C-11a), 126.0 ppm (C-11b).

Anal. Calcd. for $C_{14}H_{10}N_4OS$: C, 59.56; H, 3.57; N, 19.85. Found: C, 60.02; H, 3.44; N, 20.01.

2-Hydrazino-6-butylthiazolo[5,4-*a*]acridin-11-one (**12**).

In a 50 ml flask containing preheated hydrazine hydrate (at 120°) were added 0.35 g (1 mmole) of **10**. After 3 hours of stirring at 120° the mixture is cooled at room temperature and the precipitate filtered off. After washing with ethanol and drying *in vacuo* compound **12**, a yellowish powder, was obtained in 87% yield (0.30 g), mp 239-241°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 4.98 (2H, NH_2), 8.92 (1H, NH), 7.80-7.88 (m, 3H, H-4, H-7, H-8), 7.71 (d, 1H, H-5, $J_{4,5}$ = 9.2 Hz), 4.49 (t, 2H, NCH_2), 1.78 (m, 2H, CH_2), 1.51 (m, 2H, CH_2), 0.96 (t, 3H, CH_3), 7.31 (m, 1H, H-9), 8.38 ppm (dd, 1H, H-10); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 174.9 (C-2), 148.4 (C-3a), 124.6 (C-4), 113.2 (C-5), 136.5 (C-5a), 45.5 (NCH_2), 29.0 (CH_2), 19.4 (CH_2), 13.8 (CH_3), 140.8 (C-6a), 115.9 (C-7), 133.8 (C-8), 120.9 (C-9), 126.6 (C-10), 120.6 (C-10a), 176.2 (C-11), 116.4 (C-11a), 127.2 ppm (C-11b).

Anal. Calcd. for $C_{18}H_{18}N_4OS$: C, 63.88; H, 5.36; N, 16.56. Found: C, 63.81; H, 5.41; N, 16.39.

2-Azido-6*H*-thiazolo[5,4-*a*]acridin-11-one (**3**).

This compound was prepared by a modification of the procedure of Dehuri *et al.* [18]. Thus, compound **11** (0.58 g, 2 mmoles) was dissolved in a mixture of 20 ml of concentrated sulfuric acid and 5 ml of water. The resulting yellow solution was cooled below 0° and a solution of 0.28 g (3 mmoles) of sodium nitrite in 5 ml of water was added dropwise. The mixture was stirred for 1 hour, poured into ice and neutralized with a 5*N* sodium hydroxide solution. The orange precipitate was filtered off, washed with water and dried *in vacuo*. Compound **3** was obtained with 85% yield (0.51 g) as a brown-orange powder, mp about 150° dec; ir (potassium bromide): ν 2121 cm^{-1} (N_3).

Anal. Calcd. for $C_{14}H_7N_5OS$: C, 57.33; H, 2.41; N, 23.88. Found: C, 57.40; H, 2.33; N, 24.05.

2-Azido-6-butylthiazolo[5,4-*a*]acridin-11-one (**4**).

Compound **12** (0.35 g, 1 mmole) was dissolved in a mixture of 9 ml of concentrated sulfuric acid and 7 ml of water. The yellow solution was cooled between 0 and -10°, then a solution of 0.10 g (1.5 mmoles) of sodium nitrite in 2 ml of water was added dropwise. Stirring was maintained for 1 hour at 0° then the mixture was poured into ice followed by neutralization with a 3*N* sodium hydroxide solution. The precipitate was filtered off, washed with water and dried *in vacuo*. Compound **4** was obtained with 97% yield (0.35 g) as a beige powder, mp 159-160° dec; ir (potassium bromide): ν 2125 cm^{-1} (N_3).

Anal. Calcd. for $C_{18}H_{15}N_5OS$: C, 61.88; H, 4.33; N, 20.04. Found: C, 61.77; H, 4.39; N, 19.88.

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