# SYNTHESIS OF NEW 3-(AZOLYLTHIOACETAMIDO)-ACRIDINYL-9-THIOETHERS

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**Abstract :** A new series of acridinic compounds has been prepared alkylating several different mercapto azolylheterocycles with an acridinic thioether branched in position 3 with an aminoacylhalide group. Compounds obtained are now under investigation as potential trypanocidal drugs.

## Introduction.

Within the framework of our research on new drugs to be used as antiprotozoal agents, acridinyl-9-thioethers have demonstrated a promising *in vitro* activity against *Trypanosoma cruzi* (1,2) and *Leishmania donovani* (3) as well. One of the most efficient compounds is the 3-amino-9-[2'-(diethylamino)-ethylthio]-acridine (4) but to optimize this derivative is strictly needed owing its cell toxicity (5). With the aim of doing that, we intended to prepare a new series (figure 1) by substituting the 3-amino function. With this intention, we selected some 2-mercapto-azoles because of the well known antimicrobial properties of the parent aza heterocycles like imidazoles, oxazoles, and thiazoles (6-8).

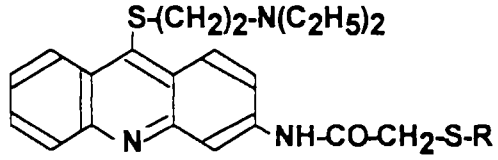


Figure 1. General formula of the acridinyl-9-thioethers prepared

## Results and Discussion.

At first, 3-amino-9-[2'-(diethylamino)-ethylthio]-acridine ***1*** was prepared according to the method previously described (9).

In a second stage, ***1*** was acylated with either bromacetyl bromide or chloracetyl chloride. Reaction was achieved in acetone at room temperature but molecular nature of the product obtained, chiefly depends upon the reaction time as shown in figure 2. Compounds obtained were identified with the help of $^1$H NMR spectroscopy.

Finally, 3-chloracetamido-9-[2'-(diethylamino)-ethylthio]-acridine hydrochloride ***2*** and 2-mercaptobenzimidazole dissolved in pyridine in the presence of potassium carbonate, reacted at room temperature for 24h to yield one of the title-compounds (***3a***). The 2-thiosubstituted-5-mercapto-1,3,4-thiadiazole reacted with ***2*** under the same experimental conditions to yield ***3b***. In contrast, we never succeeded in purifying the crude obtained by using 2-mercaptobenzothiazole as starting material under these experimental conditions. Therefore, we prepared *3c* by dissolving reagents in dimethylsulfoxide in the presence of potassium

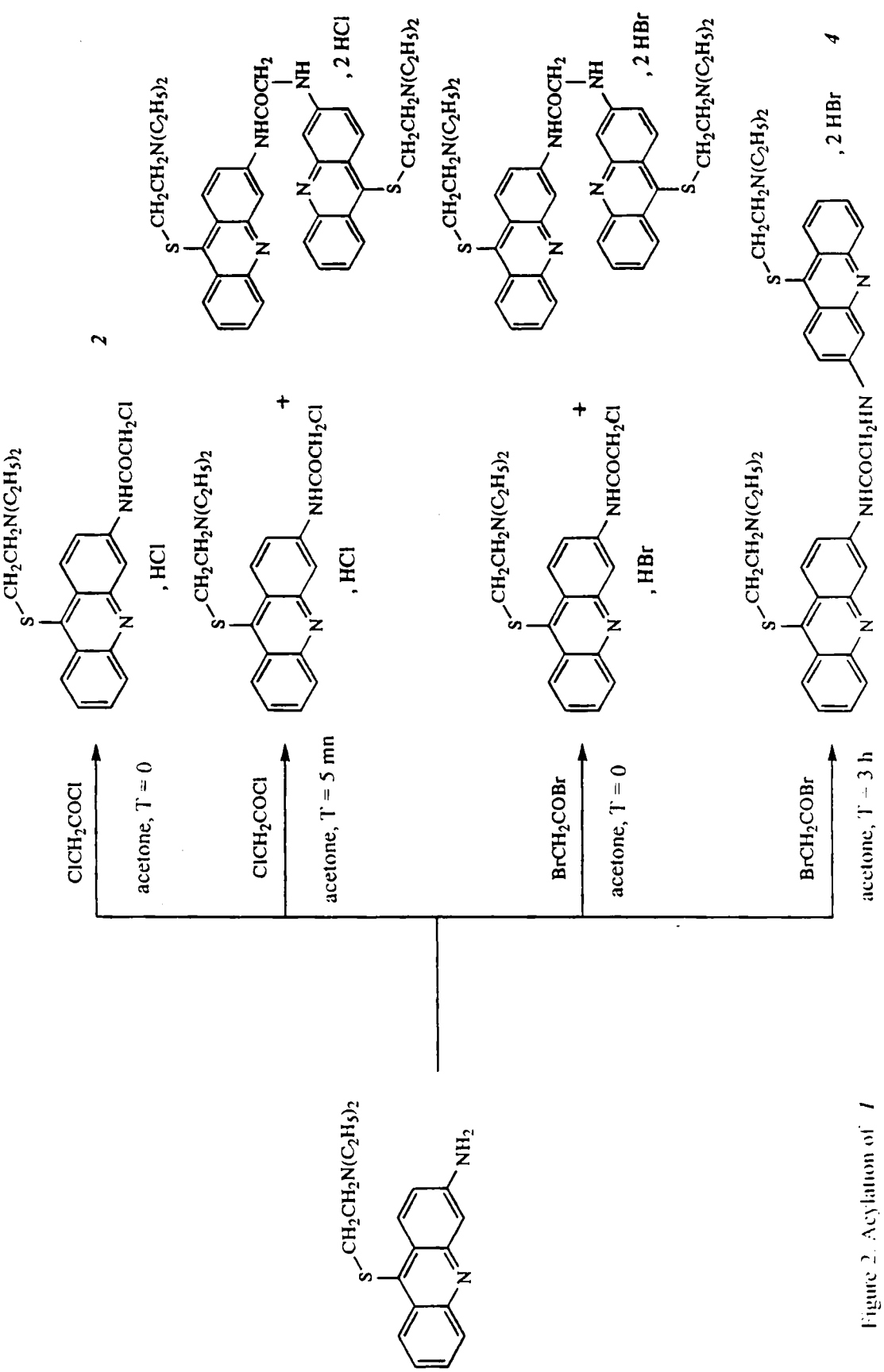


Figure 2. Acylation of *1*

hydroxide. Mixture was left at room temperature for 24h before the precipitate be washed with cold water. Compounds *3d* and *3e* were similarly obtained from 2-mercaptobenzoxazole and 2-mercapto-5-nitrobenzimidazole as starting materials.

The general synthetic pathway is portrayed in figure 3.

Chemical data of the compounds obtained are gathered in Table I.

By the way, one must note that mercapto azole heterocycles could react via two possible sites depending on the tautomeric form taken into account.

As the $^{13}C$ NMR spectra of the compounds obtained never show any signals over $\delta$180 ppm, this means that the sulfur atom is the reaction site owing to the $\delta$(C=S) value which usually falls between 185 and 200 ppm. This could be explained by the PEARSON principle (10), on the condition that the 3-chloracetamido-9-[2'-(diethylamino)-ethylthio]-acridine be considered as a soft electrophilic reagent.

**Experimental.**

Melting points have been measured on a Köfler heat bench and are given uncorrected. NMR spectra have been recorded on a Bruker ARX200 spectrometer at 20 ± 0.01°C with tetramethylsilane as internal standard. The solvents used are listed in Table I. Experimental values from microanalyses are within ± 0.4% of the theoretical ones.

***3-chloracetamido-9-[2'-(diethylamino)-ethylthio]-acridine hydrochloride 2.***

10 mmol (3.25g) of 3-amino-9-[2'-(diethylamino)-ethylthio]-acridine *1* are dissolved in acetone (150 ml) cooled in ice-bath. Chloracetyl chloride (10 mmol ; 0.8 ml)) is fastly dropped under vigourous stirring while temperature is maintained below 0°C. The red precipitate obtained is filtered before to be washed with acetone and ether. The compound is isolated in the hydrochloride form.

***3 - [2"-(benzimidazolyl)-thioacetamido]-9-[2'-(diethylamino)-ethylthio] - acridine 3a, and 3- {2"-(5"-[2"'-(diethylamino)-ethylthio]-1",3",4"-thiadiazolyl)-thioacetamido} - 9 -[2'-(diethylamino)-ethylthio]-acridine 3b.***

A mixture of *2* (2 mmol ; 0.87 g), 2-mercaptobenzazole (2 mmol), and potassium carbonate (8.6 mmole ; 1.2 g),-water (5 ml), and pyridine (80 ml) is stirred at room temperature for 24h. A large excess of water (800 ml) is then added before the solution be kept in the fridge for one night. A yellow precipitate is separated and washed with water.

***3 - [2"-(benzothiazolyl)-thioacetamido] - 9 - [2'-(diethylamino)-ethylthio]-acridine 3c, and 3 - [2"-(benzoxazolyl)-thioacetamido] - 9 - [2'-(diethylamino)-ethylthio] - acridine 3d, and 3-[2"-(5"-nitrobenzimidazolyl)-thioacetamido]-9-[2'-(diethylamino)-ethylthio]-acridine 3e.***

A mixture of *2* (2 mmol ; 0.87 g), 2-mercaptobenzazole (2 mmol), and 10% aqueous potassium hydroxide (2 ml), and dimethylsulfoxide (20 ml) is stirred at room temperature for 24h. A large excess of water (800 ml) is then added before the solution be kept in the fridge for one night. A yellow precipitate is separated and washed with water. The crude is dissolved in warm ethanol (50 ml) before a large excess of water (800 ml) be added. The precipitate obtained is washed again with water.

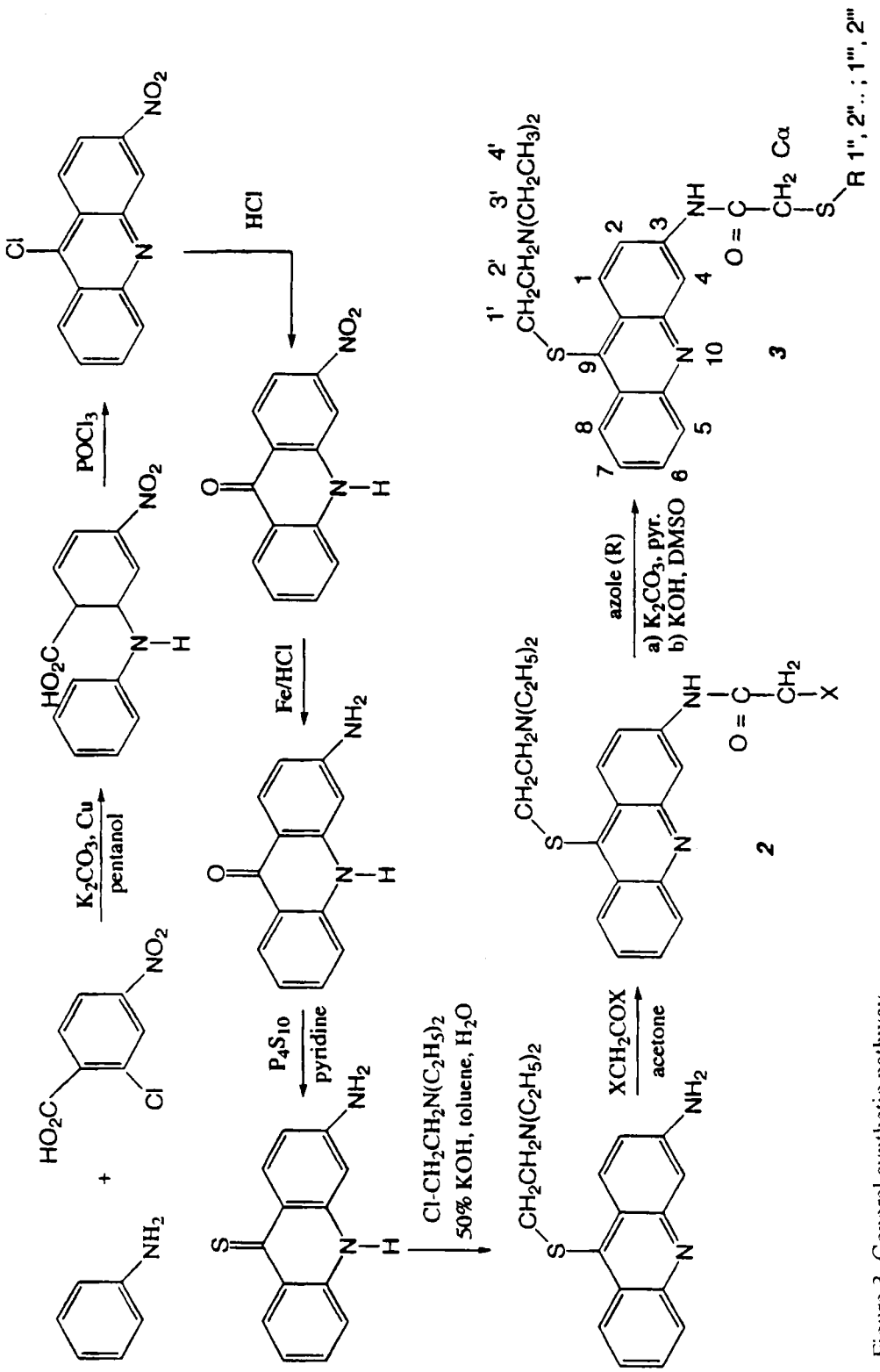


Figure 3. General synthetic pathway

Table I. Chemical data of compounds *2*, *3* and *4*.

| Cpds | Yield (%) | Mp (°C) | | NMR data |
|---|---|---|---|---|
| *2* | 89 | 209-210 | ($D_2O$) | 8.10 (d,1H), 7.75 (d,1H), 7.55 (m,2H), 7.35 (t,1H), 7.20 (s,1H), 6.65 (dd,1H), 4.05 (s,2H), 2.95 (m,8H), 0.90 (t,6H). |
| | | | (DMSO-$d_6$) | 166.23 (CO), 150.23 (C-12), 149.67 (C-9), 148.45 (C-13), 142.58 (C-3), 130.22 (C-5), 129.61 (C-8), 128.93 (C-1), 127.89 (C-7), 126.58 (C-6), 122.35 (C-2), 121.94 (C-14), 118.74 (C-11), 112.86 (C-4), 52.48 (C-2'), 48.91 (Cα CO), 46.78 (C-3'), 35.62 (C-1'), 11.49 (C-4'). |
| *3a* | 78 | 204 | (DMSO-$d_6$) | 12.70 (s,1H), 11.05 (s,1H), 8.75 (d,1H), 8.70 (d,1H), 8.60 (s,1H), 8.15 (d,1H), 7.60 (unresol.,5H), 7.10 (unresol.,2H), 4.40 (s,2H), 3.05 (t,2H), 2.50 (unresol.,2H), 2.30 (q,4H), 0.70 (t,6H). |
| | | | ($CDCl_3$) | 168.42 (CO), 150.95 (C-12), 149.29 (C-9), 149.04 (C-13), 143.19 (C-3), 140.28 (C-2"), 130.52 (C-8",9"), 130.02 (C-5), 129.49 (C-8), 129.28 (C-1), 128.40 (C-7), 127.83 (C-6), 126.95 (C-5",6"), 126.63 (C-2), 126.13 (C-14), 122.83 (C-11), 121.83 (C-4",7"), 116.13 (C-4), 52.69 (C-2'), 46.64 (C-3'), 34.86 (C-1'), 31.05 (Cα CO), 11.53 (C-4'). |
| *3b* | 78 | 129 | (DMSO-$d_6$) | 10.90 (s,1H), 8.75 (d,1H), 8.60 (s,1H), 8.10 (d,1H), 7.75 (m,3H), 4.40 (s,2H), 3.30 (unresol.,2H), 3.05 (t,2H), 2.70 (t,2H), 2.50 (unresol.,2H), 2.40 (q,4H), 2.25 (q,4H), 0.90 (t,6H), 0.70 (t,6H). |
| | | | (DMSO-$d_6$) | 166.69 (CO), 166.29 (C-2"), 163.89 (C-5"), 149.04 (C-12), 148.72 (C-9), 142.54 (C-13), 140.13 (C-3), 130.61 (C-5), 130.21 (C-1), 129.73 (C-8), 127.67 (C-7), 126.63 (C-6), 126.11 (C-2), 125.73 (C-14),121.84 (C-11), 115.36 (C-4), 52.28 (C-2'), 51.13 (C-2'"), 46.16 (C-3'), 46.03 (C-3'"),35.83 (Cα CO), 35.04 (C-1'), 32.78 (C-1'"), 11.85 (C-4'), 11.62 (C-4"). |
| *3c* | 65 | 111-112 | (DMSO-$d_6$) | 11.00 (s,1H), 8.70 (t,2H), 8.55 (s,1H), 8.10 (d,1H), 8.00 (d,1H), 7.80 (unresol.,3H), 7.65 (t,1H), 7.50 (t,1H), 7.35 (t,1H), 4.55 (s,2H), 3.00 (t,2H), 2.45 (unresol.,2H), 2.25 (q,4H); 0.65 (t,6H). |
| | | | (DMSO-$d_6$) | 166.28 (CO), 166.04 (C-2"), 152.59 (C-9"), 149.03 (C-12), 148.69 (C-9), 142.42 (C-13), 140.16 (C-3), 134.89 (C-8"), 130.49 (C-5), 129.69 (C-8), 127.62 (C-1), 127.61 (C-7), 126.58 (C-6"), 126.46 (C-6), 126.26 (C-5"), 125.71 (C-7"), 124.61 (C-4"), 121.96 (C-2), 121.84 (C-14), 121.16 (C-11), 115.34 (C-4), 52.20 (C-2'), 45.99 (C-3'), 38.04 (C-1'), 34.91 (Cα CO), 11.51 (C-4'). |
| *3d* | 83 | 108-109 | (DMSO-$d_6$) | 11.00 (s,1H), 8.75 (t,2H), 8.60 (s,1H), 8.10 (d,1H), 7.80 (unresol.,5H), 7.35 (s,2H), 4.50 (s,2H), 3.05 (t,2H), 2.45 (unresol.,2H), 2.30 (q,4H), 0.70 (t,6H). |
| *3e* | 70 | 216 | (DMSO-$d_6$) | 11.15 (s,1H), 8.75 (dd,2H), 8.60 (s,1H), 8.30 (s,1H), 8.10 (dd,2H), 7.85 (dd,2H), 7.70 (d,1H), 7.60 (d,1H), 4.50 (s,2H), 3.05 (t,2H), 2.50 (unresol.,2H), 2.30 (q,4H), 0.65 (t,6H). |
| *4* | 80 | 218-220 | ($D_2O$) | 8.15 (d,1H), 8.05 (d,2H), 7.85 (dd,2H), 7.65 (dd,2H), 7.45 (d,2H), 7.35 (unresol.,3H), 7.15 (s,1H), 6.70 (d,2H), 6.00 (s,1H), 3.85 (s,2H), 2.95 (m,16H), 0.95 (m,12H) |

***N,N-{bis-3,3'-[9-(2''-diethylaminoethylthio)acridinyl]-μ-(1-aminoacetamide) 4.***

A solution of *1* (3 mmol ; 1 g) in 50 ml of acetone is stirred at room temperature. Bromacetyl bromide (4.5 mmol ; 0.4 ml) is added dropwise. The mixture is stirred continuously for 3h. The red precipitate obtained is filtered before to be washed with acetone and ether.

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