

## Synthesis of new $\Delta^4$ -thiazolines. Part I

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**Abstract.** Interaction of aryl/alkyl isothiocyanates and  $\alpha$ -anilino benzylnitrile has been found to afford the corresponding 5-amino-4-phenyl-3-aryl-2-aryl/alkylimino thiazolines. These have been characterised. The reaction is found to be a general one. The thiazolines on hydrolysis with alkali afford hydrogen sulphide, benzaldehyde along with nonreacted products. Formation of these products, obtained by the hydrolysis, has been confirmed by thin layer chromatography.

**Keywords.** Isothiocyanates;  $\alpha$ -anilino benzylnitrile; thin layer chromatography; thiazolines.

### 1. Introduction and discussion

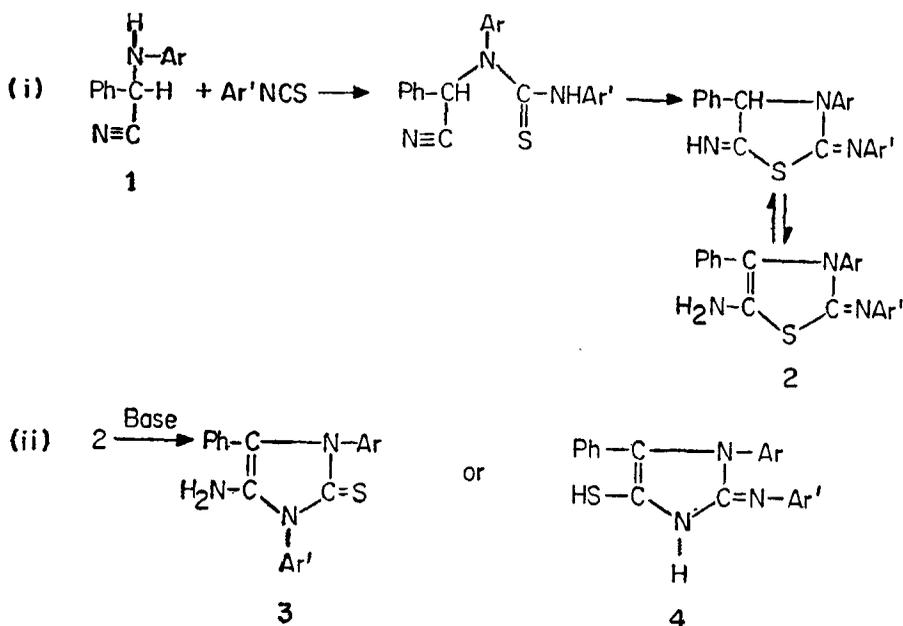
The thiazolines have been used as antimicrobial reagents as well as anaesthetics and sedatives (Takachicko *et al* 1971 *a-d*). A survey of the literature showed that the thiazolines of the type 5-amino-3,4-dialkyl/aryl-2-substitutedimino thiazoline have not been prepared and tested for their antimicrobial and pharmacological activity. Cook *et al* (1948) prepared 2,5-diaminothiazoles by the condensation of isothiocyanates and  $\alpha$ -aminonitrile. It was therefore considered worthwhile to attempt the condensation of  $\alpha$ -arylamino benzyl nitrile (1) with aryl isothiocyanates which would lead to the formation of 5-amino-4-phenyl-3-aryl-2-arylimino thiazolines (2). Thiazolines (2) on further treatment with a base could form 5-amino-4-phenyl-1,3-diaryl-2-thio imidazoline (3) or 5-mercapto-4-phenyl-3-aryl-2-arylimino imidazoline (4).

On mixing together equimolecular quantities of  $\alpha$ -anilinobenzyl nitrile (1, Ar = Ph) and aryl isothiocyanate in ethereal medium and using conditions of Cook *et al* (1948) and Capp *et al* (1948), no reaction was evident. However, when the reactants were mixed together in acetone in presence of alkali, a yellow colour developed which deepened further on standing. A product was isolated which did not desulphurise with alkali plumbite solution indicating the absence of thioureido ( $-\text{NH}-\overset{\text{||}}{\text{C}}-\text{NH}-$ ) group. Hence, it could be either 2, 3 or 4.



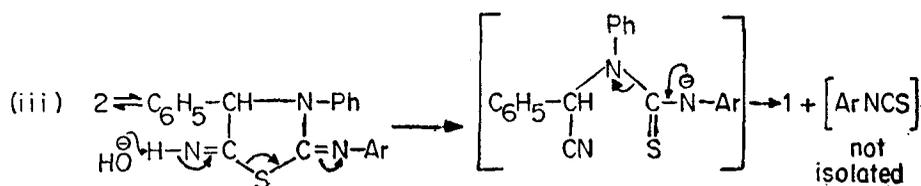
The compound did not react with benzyl chloride. This ruled out structure 4 for the compound.

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Infrared spectrum of the above compound showed the presence of a band at  $695\text{ cm}^{-1}$  due to  $-\text{C}-\text{S}-\text{C}$  linkage (Randall *et al* 1952),  $1590\text{ cm}^{-1}$  due to cyclic thiazoline structure (Colthup *et al* 1964) and at  $3225\text{ cm}^{-1}$  due to  $\text{NH}_2$  stretch (Colthup *et al* 1964). This confirms structure 2 for the above compound and rules out the imidazoline structure 3 or 4.

On heating with aqueous alkali, structure 2 afforded hydrogen sulphide, benzaldehyde, nonreacted 2 and very small quantities of a golden yellow silky product which on heating decomposed into the corresponding isothiocyanates. The formation of  $\alpha$ -anilino benzyl nitrile (1) from 2 could be shown by the following mechanism which is most likely to operate under the reaction conditions.



$\alpha$ -Anilino benzyl nitrile is known to decompose into benzaldehyde (von Walther and Hubner 1916). The examination of the yellow compound is in progress. Attempts to isomerise 2 into either 3 or 4 by using basic condition (Cook *et al* 1948) were unsuccessful as it decomposed into benzaldehyde.

## 2. Experimental

The required  $\alpha$ -anilino benzyl nitrile (1) was prepared as described by von Walther and Hubner (1916) by mixing together equimolar quantities of aniline, potassium cyanide and benzaldehyde in cold glacial acetic acid. The nitrile 1 and isothiocyanates were condensed together in acetic alkali to afford the thiazoline 2. The details of a typical experiment are as follows :

$\alpha$ -Anilinobenzyl nitrile (1, 0.01 M), phenyl isothiocyanate ( $\text{Ar}' = \text{Ph}$ , 0.01 M) and sodium hydroxide (0.01 M) were mixed together in acetone (20 ml) and the solution was refluxed for 30 min on a water bath, when a yellow colour developed which deepened further. After keeping overnight, the reaction mixture was poured into crushed ice and acidified with hydrochloric acid, when a product separated out which was filtered, washed with water followed by petroleum ether ( $40^\circ\text{--}60^\circ$ ) and dried (3 g), m.p.  $176^\circ$ . On crystallisation from alcohol, m.p.  $178^\circ$ ; found: C 72.75, H 5.13, N 12.05, S 9.1%;  $\text{C}_{21}\text{H}_{17}\text{N}_3\text{S}$  requires: C 73.47, H 4.9, N 12.24, S 9.32%. IR spectrum in nujol ( $\text{cm}^{-1}$ ): 3225, 1600s, 1500s, 1300m, 1250, 1160m, 1120s, 1080s, 1060, 1040, 1000, 918ms, 840, 795, 765 and 695vs. It did not easily desulphurise on warming with alkali plumbite solution and on heating with alkali, the smell of benzaldehyde was perceptible. It was stable to conc. HCl even on prolonged boiling. It was identified as 5-amino-3,4-diphenyl-2-phenylimino thiazoline (2;  $\text{Ar}/\text{Ar}' = \text{Ph}$ ). The compounds thus prepared are listed along with their relevant data in table 1 (m.ps are uncorrected).

#### *Attempted isomerisation of thiazoline 2*

2 (2 g) was suspended in aqueous alcoholic sodium carbonate solution (2.5 g in 50 ml 70% alcohol) and heated under reflux for 1 hr. On cooling the reaction mixture in ice followed by acidification, a small quantity of sticky red coloured solid was isolated. The acidified solution strongly smelt of benzaldehyde.

2 ( $\text{Ar}' = \text{Ph}$ , 2 g) and aqueous sodium hydroxide (20%, 30 ml) were refluxed together for 1 hr when a dark brown oil separated out which was extracted in benzene. Thin layer chromatography of the oil using silica gel and benzene as solvent gave two spots on development of the plate with iodine vapours. The first spot with  $R_f = 0.524$  was identified as due to  $\alpha$ -anilino benzyl nitrile (1) when chromatographed with an authentic sample prepared as described earlier. The second spot with  $R_f = 0.266$  was due to 5-amino-3,4-diphenyl-3-phenyliminothiazoline (2) when compared with an authentic sample.

The aqueous alkaline filtrate, on dilution with water and acidification with dilute hydrochloric acid, afforded light, shining yellow needles (40 mg) which were filtered and washed with water, m.p.  $95^\circ$ . On purification by reprecipitation from its aqueous alkaline solution with dilute HCl, m.p.  $97^\circ\text{C}$  ( $R_f = 0.338$  in benzene). It desulphurised with lead plumbite solution and on heating decomposed into phenyl isothiocyanate. It was not examined.

Examination of the gaseous products evolved during the hydrolysis of 2, revealed the presence of hydrogen sulphide. The smell of benzaldehyde was also perceptible indicating further hydrolysis of  $\alpha$ -anilino benzyl nitrile.

### 3. Conclusion

It can be concluded that the  $\Delta^4$ -thiazolines, although formed readily, are very unstable in basic medium and decompose rapidly affording  $\alpha$ -anilino benzyl nitrile and other products. They are, however, very stable in acidic medium.

Table 1. Interaction of  $\alpha$ -arylimino benzyl nitrile with aryl isothiocyanates

| $\alpha$ -arylimino<br>benzyl nitrile<br>Ar (0.01 M) | Aryl<br>isothiocyanate<br>Ar'<br>(0.01 M) | Thiazoline<br>isolated  | M.P.<br>°C | Yield<br>% | Analysis |      |       |         |  |  |
|--|---|---|------------|------------|----------|------|-------|---------|--|--|
|  |   |   |            |            | Found %  |      |       | Calc. % |  |  |
|  |   |   |            |            | N        | S    | N     | S       |  |  |
| 1. Phenyl  | Phenyl                                    | 5-amino-3,4-diphenyl-2-phenylimino thiazoline*<br>(2, Ar = Ar' = Ph),<br>C <sub>21</sub> H <sub>17</sub> N <sub>3</sub> S   | 170d       | 90         | 12.05    | 9.1  | 12.24 | 9.32    |  |  |
| 2. Phenyl  | <i>o</i> -Tolyl                           | 5-amino-3,4-diphenyl-2- <i>o</i> -tolylimino thiazoline*<br>(2, Ar = Ph, Ar' = <i>o</i> -tolyl),<br>C <sub>22</sub> H <sub>19</sub> N <sub>3</sub> S                | 154d       | 58         | 11.38    | 8.42 | 11.76 | 8.96    |  |  |
| 3. Phenyl  | <i>p</i> -Tolyl                           | 5-amino-3,4-diphenyl-2- <i>p</i> -tolylimino thiazoline*<br>(2, Ar = Ph, Ar' = <i>p</i> -tolyl),<br>C <sub>22</sub> H <sub>19</sub> N <sub>3</sub> S                | 172d       | 98         | 11.66    | 8.96 | 11.76 | 8.96    |  |  |
| 4. Phenyl  | <i>m</i> -Tolyl                           | 5-amino-3,4-diphenyl-2- <i>m</i> -tolylimino thiazoline*<br>(2, Ar = Ph, Ar' = <i>m</i> -tolyl),<br>C <sub>22</sub> H <sub>19</sub> N <sub>3</sub> S                | 108d       | 70         | 11.34    | 8.29 | 11.76 | 8.96    |  |  |
| 5. Phenyl  | <i>p</i> -Bromo-phenyl                    | 5-amino-3,4-diphenyl-2- <i>p</i> -bromophenylimino thiazoline*<br>(2, Ar = Ph, Ar' = <i>p</i> -bromophenyl),<br>C <sub>21</sub> H <sub>15</sub> N <sub>3</sub> S Br | 181d       | 68         | 9.78     | 7.06 | 9.95  | 7.58    |  |  |
| 6. Phenyl  | <i>p</i> -Chloro-phenyl                   | 5-amino-3,4-diphenyl-2- <i>p</i> -chlorophenylimino thiazoline* (2, Ar = Ph, Ar' = <i>p</i> -chlorophenyl),<br>C <sub>21</sub> H <sub>14</sub> N <sub>3</sub> S Cl  | 108        | 65         | 10.85    | 7.78 | 11.12 | 8.47    |  |  |

\* C, H determinations for these are in agreement : Super-imposable IR spectra.

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