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2-Amino-5-phenyl-1,3,4-oxadiazole (**1a**) and 2-amino-1,3,4-thiadiazole (**1b**) reacted with acrylonitrile to yield β-cyanoethylamino derivatives. On the other hand, 2-amino-4-phenylthiazole (**2**) reacted with acrylonitrile under the same experimental conditions to yield a di-β-cyanoethylaminothiazole derivative. 3-Phenyl-Δ^2-1,2,4-triazoline-5-thione reacted with acrylonitrile to yield the corresponding adduct. The structure of the adduct was established by its conversion into the acid **13** which could be synthesised *via* another independent route.

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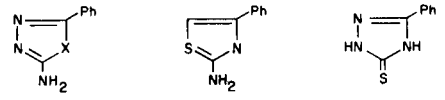
The chemistry of heterocyclic amidines has received considerable recent attention (1-4). As a part of our program directed for exploring the synthetic potentialities of this class of compounds we have previously demonstrated the possible utility of the reaction of 3-aminopyrazoles and 3-aminoisoxazoles with acrylic acid derivatives for the synthesis of 4,5,6,7-tetrahydropyrazolo-[1,5-*a*] and isoxazolo[2,3-*a*]pyrimidines (5-10). We have been particularly interested to study if reactions of this type might be extended to include a more general synthesis of fused pyrimidines. In the present paper we report the results of our investigation on the reaction of the cyclic amidine derivatives **1a,b**, **2** and **3** toward acrylonitrile. It has been found that 2-amino-5-phenyl-1,3,4-oxadiazole (**1a**) and 2-amino-5-phenyl-1,3,4-thiadiazole (**1b**) react with acrylonitrile to yield a 1:1 adduct. Two structures seemed possible for this product (*cf.* structures **4** and **5**). Structures **5a,b** were established for these products based on their ^{1}H nmr spectra. Thus, the ^{1}H nmr spectra revealed one methylene triplet at 2.75, a quartet for two protons at 3.5 ppm, a multiplet for five aromatic protons and a triplet for one proton at 8.20 ppm. Upon deuterium oxide exchange, the quartet at 3.5 ppm turned into a triplet and the triplet at 8.20 ppm disappeared completely. These data can be readily



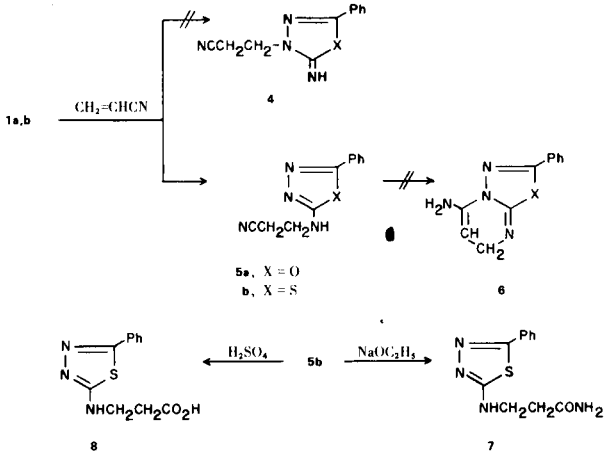
1a, X = O
b, X = S

2

3

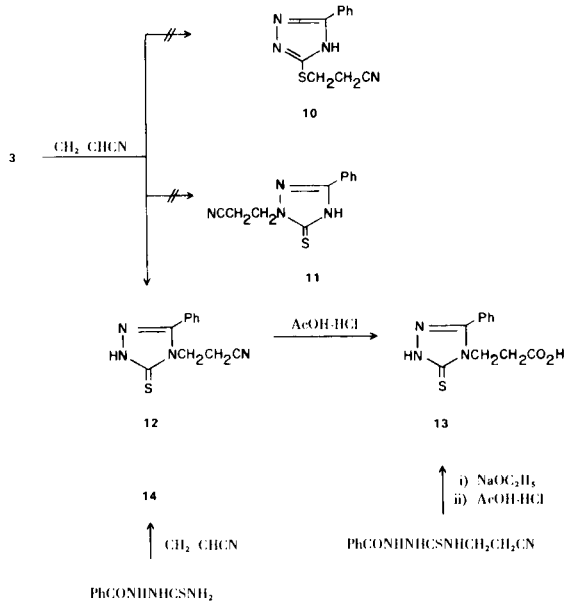
interpreted in terms of structure **5**. Attempted cyclisation of **5a,b** into the corresponding pyrimidine derivatives **6a,b** were unsuccessful. Benzoic acid was the only product isolated from the attempted cyclisation of **5a**. On the other hand, compound **5b** was converted into the amide **7** on treatment with sodium hydroxide and into the acid **8** on treatment with concentrated sulphuric acid.

2-Amino-4-phenylthiazole (**2**) reacted with acrylonitrile to yield a 1:2 adduct. All attempts to control this reaction to afford a 1:1 adduct were unsuccessful. Even when limited quantities of acrylonitrile were used under conditions favorable for monocyanoethylation, the products isolated were unreacted **2** and the di-adduct. Although several isomeric structures seemed possible for the di-adduct, structure **9** was established for the reaction product based on its ^{1}H nmr spectrum.

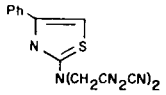


The behaviour of 5-phenyl-Δ^2-1,2,4-triazoline-5-thione (**3**) upon cyanoethylation was also investigated. It has been found that **3** reacts with acrylonitrile to yield a 1:1 adduct. Three structures seemed possible for the reaction product. Spectral data seemed to be of little value to be utilised for the discrimination between these structures (*cf.* structures **10-12**). Structure **10** was readily eliminated since the reaction product proved to have a free mercapto group as revealed by its solubility in sodium hydroxide solution. In order to establish structure **11** or isomeric **12** for the reaction product, synthesis of **12** *via* another route was attempted. Attempts to rearrange **5b** into **12** *via* a procedure similar to that reported (11) for the conversion of 2-amino-1,3,4-thiadiazoles into the corresponding Δ^2-1,2,4-triazoline-5-thiones were unsuccessful. Structure **12** could be, however, established for the reaction product by converting the latter into the carboxylic acid **13**. The acid **13** could be synthesised independently *via* cyclization of 1-benzoyl-4-β-cyanoethylthiosemicarbazide **14** (*cf.* Chart 1). The latter, in turn

Chart I



was prepared *via* cyanoethylation of 1-benzoylthiosemicarbazide.



9

EXPERIMENTAL

All melting points are uncorrected. Ir spectra were recorded in potassium bromide on a Bekman Ir 20. ^{1}H nmr were obtained on a Varian A-60 in DMSO with TMS as an internal indicator. Chemical shifts are expressed as δ ppm.

2-β-Cyanoethylamine-5-phenyl-1,3,4-oxadiazole (**5a**).

A solution of **1a** (5.0 g.) in pyridine (80 ml.) and water (20 ml.) was treated with acrylonitrile (2.0 ml.) and the reaction mixture was refluxed for eight hours. The solvent was then evaporated *in vacuo*. The remaining solid product was triturated with ethanol and collected by filtration. The formed solid product (3.0 g.) was crystallised from ethanol to yield pure sample of **5a**, m.p. 164°; ir: 1630 cm^{-1} (C=N), 2240 (CN), 2900-2940 (CH_2 groups) and 3250 (NH). ^{1}H nmr: 1.75 (t, 2H, CH_2), 3.50 (q, became a triplet after deuterium oxide exchange, 2H, CH_2), 7.5-7.8 (m, 5H, phenyl protons) and 8.20 (t, 1H, lost after deuterium oxide exchange, NH).

Anal. Calcd. for $C_{11}H_{10}N_4O$: C, 61.6; H, 4.7; N, 26.1. Found: C, 61.9; H, 5.0; N, 25.8.

2-β-Cyanoethylamino-5-phenyl-1,3,4-thiadiazole (**5b**).

Five grams of **1b** were treated with acrylonitrile (2.0 ml.) using the experimental procedure described for the cyanoethylation of **1a**. The product obtained after evaporation of the solvent was triturated with water, collected by filtration and crystallised from ethanol.

Compound **5b** formed colourless crystals, m.p. 167-170° (yield 3.8 g.); ir: 2240 cm^{-1} (CN), 2940-3050 (CH_2 groups) and 3300 (NH).

Anal. Calcd. for $C_{11}H_{10}N_4S$: C, 57.4; H, 4.4; N, 24.8; S, 13.9. Found: C, 57.3; H, 4.6; N, 24.4; S, 14.0.

2-β-Carboxamidoethyl-5-phenyl-1,2,4-thiadiazole (**7**).

To an ethanolic sodium ethoxide solution (prepared from 2.0 g. of sodium metal and 150 ml. of ethanol), compound **1b** (5.0 g.) was added. The reaction mixture was refluxed for seven hours then evaporated *in vacuo*. The remaining product was dissolved in water (100 ml.) and acidified with hydrochloric acid to *p*H 4. The solid product, formed on standing, was collected by filtration, washed several times with cold water and dried.

Compound **7** formed colourless crystals from ethanol, m.p. 155-159° (yield 3.0 g.); ir: 1630 cm^{-1} (δ NH_2), 1700 (CO), 3260 and 3400 (ν NH_2).

Anal. Calcd. for $C_{11}H_{12}N_4OS$: C, 53.2; H, 4.9; N, 22.5; S, 12.9. Found: C, 52.9; H, 5.2; N, 22.5; S, 12.6.

2-β-Carboxyethyl-5-phenyl-1,3,4-thiadiazole (**8**).

To five grams of **1b**, concentrated sulphuric acid (2.0 ml., 98%) was added. The reaction mixture was left at room temperature for 24 hours then diluted with water and left to stand at room temperature. The solid product, so formed, was collected by filtration and crystallised from ethanol. Compound **8** formed colourless crystals, m.p. 162° (yield 3.0 g.); ir: 1700 cm^{-1} (carbonyl CO), 2700-3100 (OH dimer) and 3260 (NH).

Anal. Calcd. for $C_{11}H_{11}N_3O_2S$: C, 53.0; H, 4.4; N, 16.8 S, 12.8. Found: C, 53.4; H, 4.8; N, 16.6; S, 13.0.

2-di-β-Cyanoethylamino-4-phenylthiazole (**9**).

A solution of **2** (5.0 g.) in ethanol (100 ml.) and water (20 ml.) was treated with acrylonitrile (4.0 ml.) and concentrated potassium hydroxide solution (1.0 ml.). The reaction mixture was refluxed for three hours and then evaporated *in vacuo*. The remaining product was triturated with water and neutrallised with acetic acid.

Compound **9** formed colourless crystals, m.p. 121° (yield 6.5 g.); ^{1}H nmr: 3.00 (t, 4H, $2CH_2$), 3.83 (t, 4H, $2CH_2$), 7.25-8.00 (m, 6H, phenyl and pyrazole CH).

Anal. Calcd. for $C_{15}H_{14}N_4S$: C, 63.8; H, 5.0; N, 19.8; S, 11.3. Found: C, 63.7; H, 4.9; N, 20.0; S, 11.4.

4-β-Cyanoethyl-3-phenyl-Δ^2-1,2,4-triazoline-5-thione (**12**).

A solution of **3** (5.0 g.) in pyridine (80 ml.) and water (20 ml.) was treated with acrylonitrile (2.0 ml.) and concentrated solution of potassium hydroxide (1.0 ml.). The reaction mixture was heated for four hours and then evaporated *in vacuo*. The remaining oily product was dissolved in the least amount of aqueous sodium hydroxide. The insoluble resins were removed by filtration. Acidification of the filtrate afforded 3.5 g. of compound **12** which was further purified by crystallisation from acetone-water mixture.

Compound **12** formed colourless crystals, m.p. 185-188°; ir: 2250 cm^{-1} (CN), 2900-3050 (CH).

Anal. Calcd. for $C_{11}H_{10}N_4S$: C, 57.4; H, 4.4; N, 24.3. Found: C, 57.4; H, 4.5; N, 24.2.

4-β-Carboxyethyl-3-phenyl-Δ^2-1,2,4-triazoline-5-thione (**13**).

a From **12** and Acetic Acid/Hydrochloric Acid.

A solution of **12** (5.0 g.) in acetic acid (70 ml.) was treated with hydrochloric acid (3.0 ml., 37%). The reaction mixture was refluxed for six hours and then evaporated *in vacuo*. The remaining solid product was triturated with water and the solid product, formed on standing, was collected by filtration and crystallised from ethanol.

Compound **13** formed colourless needles, m.p. 194° (yield 4.5 g.); ir: 1700-1705 cm^{-1} (carboxyl CO), 2500-2900 (OH dimer),

2920-3050 (NH).

Anal. Calcd. for $C_{11}H_{11}N_3O_2S$: C, 53.0; H, 4.4; N, 16.8; S, 12.8. Found: C, 52.8; H, 4.7; N, 16.6; S, 13.0.

b From **14** and Ethanolic Sodium Hydroxide.

To a solution of benzoylthiosemicarbazide (5.0 g.) (prepared from benzoylhydrazine and ammonium thiocyanate as has been previously described), in pyridine (80 ml.) and water (20 ml.), acrylonitrile (2.0 ml.) and one ml. of concentrated potassium hydroxide were added. The reaction mixture was refluxed for seven hours then evaporated *in vacuo*. The remaining oily product was triturated with water, extracted by chloroform and chloroform extract evaporated to afford 5.0 g. of **14**. These were added to 150 ml. of ethanolic sodium ethoxide and refluxed for 10 hours. The reaction mixture was then evaporated *in vacuo* and the remaining product was acidified. The solid product, so formed, was collected by filtration and crystallised from ethanol.

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