

S. M. Hussain [a], A. A. El-Barbary [b] and S. A. Mansour [b]

[a] Department of Chemistry, Faculty of Science,  
University of Cairo, Giza, A. R. Egypt[b] Department of Chemistry, Faculty of Science and Faculty of Education,  
University of Tanta, A. R. Egypt

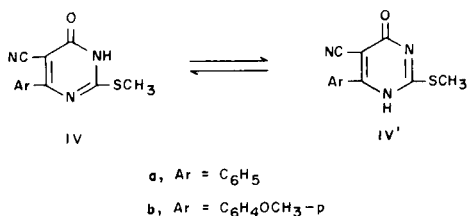
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Condensation of a ternary mixture of ethyl cyanoacetate, *S*-methylisothiurea and aromatic aldehydes in pyridine afforded directly the 4-aryl-5-cyano-2-methylthio-6-oxypyrimidines IV in good yields. Alkylation of IV with alkyl halides in alkaline medium yielded the 1-alkyl derivatives V. The methylthio group in IV and V could be eliminated by aniline, hydrazine and phenylhydrazine and the corresponding 2-anilino, VII, 2-hydrazino, VIIIa,b, and 2-phenylhydrazino, VIIIc,d, derivatives were obtained. Compounds VIIIa,b could be cyclised with nitrous acid to give the 3-cyano-4-phenyltetrazolo[1,5-*a*]pyrimidine-2-one (Xa) and the 1-methyl analogue Xb, respectively. Some derivatives of VIII were prepared to help in elucidating the structures.

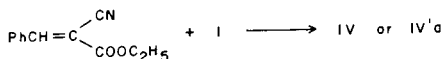
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In continuation of our interest in the synthesis of pyrimidine derivatives with expected medicinal and microbiological uses [1], we report in this paper a simple synthesis of the title compounds by the direct condensation of *S*-methylisothiurea sulphate (I), aromatic aldehydes II and ethyl cyanoacetate (III). The condensation products have been used in the preparation of fused pyrimidinones.

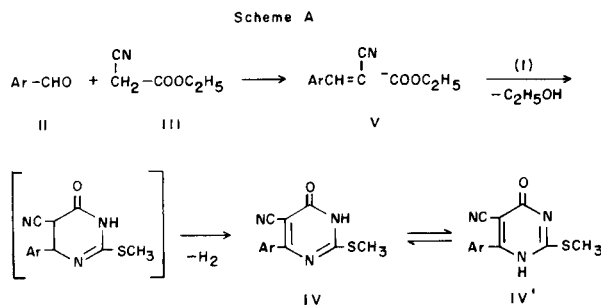
When a mixture of equimolecular amounts of I, II and III was heated under reflux in pyridine in presence of anhydrous fused sodium acetate, there were obtained 4-aryl-5-cyano-2-methylthio-6-oxypyrimidines IV or their isomeric structures IV'.



The assignment of structure IV, or IV' to the reaction products is based on the facts that (a) the ir spectrum of IVa, as a typical example, displayed absorption bands at 1660 cm<sup>-1</sup> (CO), 2220 cm<sup>-1</sup> (CN) and 3160 cm<sup>-1</sup> (NH), (b) the nmr spectrum (DMSO-d<sub>6</sub>) of IVa showed signals at δ 2.60 ppm (s, 3H, CH<sub>3</sub>), δ 7.65 ppm (m, 3H, aromatic protons) and δ 7.95 ppm (m, 2H, aromatic protons) and (c) compound IVa or IV'a could also be prepared from I and α-carbethoxycinnamionitrile (V) by refluxing in pyridine in presence of anhydrous sodium acetate.

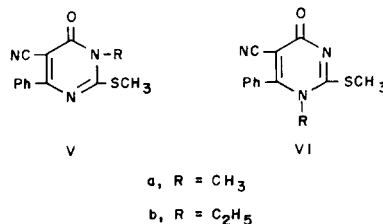


The formation of IV may be assumed to be formed as in Scheme A.



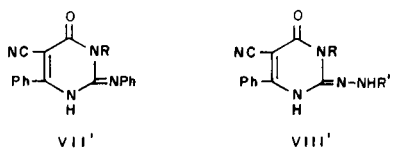
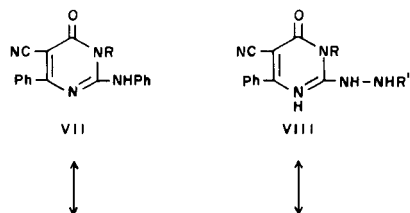
The absence of any chemical shifts at the higher field region up to 7 ppm, except for CH<sub>3</sub> protons, in the pmr spectrum of IVa proves the autoxidation of the reaction intermediate and hence the formation of IVa. Similar oxidation is reported in our previous publication [1] and by Kambe *et al* [2].

Alkylation of IVa or IV'a gave most probably 1-alkyl-5-cyano-2-methylthio-4-phenyl-6-oxypyrimidines V rather than the isomeric compounds VI. The pmr spectrum of VI (DMSO-d<sub>6</sub>) showed signals at δ 2.65 ppm (s, 3H, S-CH<sub>3</sub>), δ 3.45 ppm (s, 3H, N-CH<sub>3</sub>), δ 7.6 ppm (m, 3H, Ar-H) and 7.9 ppm (m, 2H, Ar-H). That alkylation took place at the nitrogen atom far from the phenyl group in the pyrimidine nucleus was proved by comparing the pmr spectra of IVa and



Va, thus the pmr spectra revealed that the ortho phenyl protons in IVa and Va are deshielded by about 0.5 ppm relative to the meta and para protons, the phenyl group being coplanar with the pyrimidine ring and this indicates that the pyrimidine N-3, neighbouring to the phenyl group, is non-substituted [3,4]. (See below for compounds substituted at N-3).

Compounds IVa and Va reacted with aniline and hydrazines, with evolution of methyl mercaptan, to give the 2-anilino-5-cyano-4-phenyl-6-oxypyrimidine derivatives VII and the corresponding 2-hydrazino derivatives VIII, respectively. Compounds VII and VIII could also be present as the 2-phenylimino VII' and the 2-hydrazono derivatives VIII'.

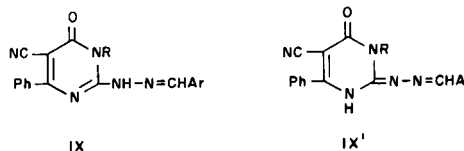


a, R = H  
b, R = CH<sub>3</sub>

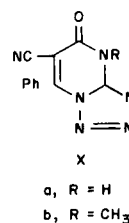
a, R = R' = H  
b, R = CH<sub>3</sub>, R' = H  
c, R = H, R' = C<sub>6</sub>H<sub>5</sub>  
d, R = CH<sub>3</sub>, R' = C<sub>6</sub>H<sub>5</sub>

Structures VII or VII' and VIII or VIII' were inferred from both elemental and spectral analyses, also compounds VIIIa,b gave the corresponding Schiff's bases, IXa-d or IX'a-d, with aromatic aldehydes.

When compounds VIIIa,b were treated with nitrous acid at 0°, there were obtained 3-cyano-4-phenyltetrazolo[1,5-a]pyrimidine-2-one (Xa) and 1-alkyl-3-cyano-4-phenyltetrazolo[1,5-a]pyrimidine-2-one (Xb), respectively.



a, R = H, Ar = C<sub>6</sub>H<sub>5</sub>  
b, R = H, Ar = C<sub>6</sub>H<sub>4</sub>OCH<sub>3</sub>-p  
c, R = CH<sub>3</sub>, Ar = C<sub>6</sub>H<sub>5</sub>  
d, R = CH<sub>3</sub>, Ar = C<sub>6</sub>H<sub>4</sub>OCH<sub>3</sub>-p



a, R = H  
b, R = CH<sub>3</sub>

The pmr spectrum of Xa (DMSO-d<sub>6</sub>) showed one signal at 7.75 ppm (m, 6H, Ar-H and NH) and that of Xb showed signals at 3.65 ppm (s, 3H, CH<sub>3</sub>) and 7.85 ppm (m, 5H, aromatic protons). The assignment of structure X to the reaction product is based on the comparison of the pmr spectra of IVa, Va, Xa and Xb. Thus, we reported before, while the ortho phenyl protons in IVa and Va are deshielded by 0.5 ppm relative to the meta and para protons. The phenyl protons of each Xa,b give compact signals and this indicates that the phenyl group is twisted out of plane of the pyrimidine nucleus because of steric interference due to the substituent at the pyrimidine N-3 (near from the phenyl group) and this is in favour of structure X [5,6].

Table I

2-Anilino and 2-Hydrazino-5-cyano-4-phenyl-6-oxypyrimidine Derivatives

| Compound | Mp, °C | Yield % | Solvent        | Formula  | Analysis % |       |      | IR cm <sup>-1</sup>             |
|----------|--------|---------|----------------|--|------------|-------|------|---------------------------------|
|          |        |         |                |  | Calcd.     | Found |      |                                 |
| VIIa     | 286    | 80      | Ethanol        | C <sub>17</sub> H <sub>12</sub> N <sub>4</sub> O | 70.8       | 4.1   | 19.4 | 3310 (NH), 2218 (CN), 1690 (CO) |
|          |        |         |                |  | 71.0       | 4.2   | 19.5 |                                 |
| VIIb     | 248    | 85      | Dilute dioxane | C <sub>18</sub> H <sub>14</sub> N <sub>4</sub> O | 71.5       | 4.6   | 18.5 | 3310 (NH), 2218 (CN), 1690 (CO) |
|          |        |         |                |  | 71.2       | 4.5   | 18.6 |                                 |
| VIIIa    | 237    | 75      | Ethanol        | C <sub>11</sub> H <sub>9</sub> N <sub>5</sub> O  | 58.1       | 3.9   | 30.8 | 3330 (NH), 2225 (CN), 1680 (CO) |
|          |        |         |                |  | 58.2       | 3.8   | 30.7 |                                 |
| VIIIb    | 277    | 80      | Dioxane        | C <sub>12</sub> H <sub>11</sub> N <sub>5</sub> O | 59.7       | 4.5   | 29.0 | 3325 (NH), 2225 (CN), 1680 (CO) |
|          |        |         |                |  | 59.5       | 4.4   | 29.2 |                                 |
| VIIIc    | 262    | 84      | Acetic acid    | C <sub>17</sub> H <sub>13</sub> N <sub>5</sub> O | 67.3       | 4.3   | 23.1 | 3350 (NH), 2225 (CN), 1675 (CO) |
|          |        |         |                |  | 67.0       | 4.2   | 23.2 |                                 |
| VIIId    | 229    | 89      | Ethanol        | C <sub>18</sub> H <sub>15</sub> N <sub>5</sub> O | 68.1       | 4.7   | 22.1 | 3350 (NH), 2230 (CN), 1690 (CO) |
|          |        |         |                |  | 68.0       | 4.7   | 22.3 |                                 |

## EXPERIMENTAL

Melting points were taken on a Kofler apparatus and are uncorrected. Infrared (ir) spectra were determined as potassium bromide pellets with a Perkin-Elmer Infracord 137 instrument. The <sup>1</sup>H-nmr spectra were determined with a Perkin-Elmer R12A instrument.

## 4-Aryl-5-cyano-2-methylthio-6-oxypyrimidines IV.

A) A mixture of S-methylisothiourea sulphate (I) (0.005 mole), aromatic aldehyde II (0.01 mole), ethyl cyanoacetate (III) (0.01 mole) and 5 g of anhydrous fused sodium acetate in 50 ml of pyrimidine was heated under reflux for 4 hours. The reaction mixture was cooled and poured into cold water, then acidified with acetic acid. The precipitate formed was collected and crystallised from the proper solvent to give IVa,b.

Compound IVa was crystallised from ethanol in 78% yield, mp 275°; ir: 3150 (NH), 2220 (CN), 1660 (CO); <sup>1</sup>H-nmr (deuteriodimethylsulfoxide): δ 2.60 (s, 3H, CH<sub>3</sub>), 7.65 (m, 3H, aromatic protons), δ 7.95 (m, 2H, aromatic protons).

*Anal.* Calcd. for C<sub>12</sub>H<sub>9</sub>N<sub>3</sub>O<sub>2</sub>S: C, 59.2; H, 3.7; N, 17.3; S, 13.1. Found: C, 59.4; H, 3.8; N, 17.3; S, 13.0.

Compound IVb was crystallised from acetic acid in 82%, mp 299°; ir: 3150 (NH), 2220 (CN), 1660 (CO).

*Anal.* Calcd. for C<sub>13</sub>H<sub>11</sub>N<sub>3</sub>O<sub>2</sub>S: C, 57.1; H, 4.0; N, 15.4; S, 11.7. Found: C, 56.9; H, 3.9; N, 15.5; S, 11.6.

B) A mixture of 2.78 g of I, 4 g of α-carbethoxycinnamitrile and 1.7 g of anhydrous fused sodium acetate in 50 ml of pyridine was heated under reflux and treated as in method A to produce a substance identical with IVa prepared in method A, mp and mixed mp 275°.

## 1-Alkyl-5-cyano-2-methylthio-4-phenyl-6-oxypyrimidines V.

About 2 g of IVa were dissolved in 50 ml of 4% aqueous alcoholic sodium hydroxide solution. An excess (1.1 moles) of methyl or ethyl iodide was added, and the solution was refluxed for 3 hours, left to cool and poured into cold water. The precipitate was collected, dried and crystallised from ethanol.

The 1-methyl derivative Va was obtained in 80% yield, mp 187°; ir: 2220 (CN), 1670 (CO); <sup>1</sup>H-nmr (deuteriodimethylsulfoxide): δ 2.65 (s, 3H, S-CH<sub>3</sub>), δ 3.45 (s, 3H, N-CH<sub>3</sub>), δ 7.6 (m, 3H, Ar-H).

*Anal.* Calcd. for C<sub>13</sub>H<sub>11</sub>N<sub>3</sub>O<sub>2</sub>S: C, 60.7; H, 4.2; N, 16.3; S, 12.4. Found: C, 60.9; H, 4.3; N, 16.3; S, 12.2.

1-Ethyl derivative Vb was obtained in 88% yield, mp 165°; ir: 2220 (CN), 1670 (CO).

*Anal.* Calcd. for C<sub>14</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub>S: C, 62.0; H, 4.8; N, 15.5; S, 11.8. Found: C, 62.1; H, 4.9; N, 15.3; S, 11.9.

## 2-Anilino and 2-Phenylhydrazino-5-cyano-4-phenyl-6-oxypyrimidine Derivatives VIIa,b and VIIIc,d.

A mixture of 0.01 mole of IVa or Va and 0.011 mole of aniline or phenylhydrazine was gently heated in an oil bath, the temperature was raised gradually and kept at 170° for 3 hours and then cooled. The reaction product was triturated with ethanol and the solid which separated was crystallised to give VIIa,b and VIIIc,d (Table I).

## 5-Cyano-2-hydrazino-4-phenyl-6-oxypyrimidine Derivatives VIIIa,b.

A mixture of 0.02 mole of IVa or Va and 0.011 mole of hydrazine hydrate in 40 ml of ethanol was heated under reflux for 2 hours. The solid that separated while boiling was collected and crystallised from the proper solvent to give VIIIa,b respectively (Table I).

## Formation of the Schiff's Bases IX.

A mixture of 1 g of VIIIa,b, 20 ml of ethanol and an equimolecular amount of the appropriate aldehyde was refluxed for 2 hours. The solid separated was filtered off and crystallised to give IX. Compound IXa was purified by trituration several times with ethanol and obtained in 81% yield, mp 299°; ir: 3330 (NH), 2230 (CN) and 1690 (CO).

*Anal.* Calcd. for C<sub>18</sub>H<sub>13</sub>N<sub>5</sub>O: C, 68.6; H, 4.1; N, 22.2. Found: C, 68.9; H, 4.2; N, 22.3.

Compound IXb was also purified by trituration with ethanol and obtained in 85% yield, mp >300°; ir: 3320 (NH), 2220 (CN) and 1675 (CO).

The IXc derivative was recrystallised from ethanol in 80% yield, mp 220°; ir: 3330 (NH), 2220 (CN) and 1680 (CO).

*Anal.* Calcd. for C<sub>15</sub>H<sub>13</sub>N<sub>5</sub>O: C, 69.3; H, 4.5; N, 21.3. Found: C, 69.4; H, 4.5; N, 21.2.

The IXd derivative was crystallised from ethanol in 82% yield, mp 224°; ir: 3330 (NH), 2225 (CN) and 1680 (CO).

*Anal.* Calcd. for C<sub>20</sub>H<sub>17</sub>N<sub>5</sub>O<sub>2</sub>: C, 66.8; H, 4.7; N, 19.5. Found: C, 67.0; H, 4.9; N, 19.4.

## 3-Cyano-4-phenyltetrazolo[1,5-a]pyrimidine-2-ones Xa,b.

A solution of about 1 g of VIIIa,b in 10 ml of concentrated hydrochloric acid and 10 ml of water was cooled to 0° and a cold solution of 0.5 g of sodium nitrite in 10 ml of water was gradually added. The reaction mixture was kept at 0-5° with stirring for 2 hours and left overnight. The solid separated was collected and crystallised to give X.

Compound Xa was crystallised from ethanol in 70% yield, mp 234°; ir: 3230 (NH), 2218 (CN) and 1675 (CO); <sup>1</sup>H-nmr (deuteriodimethylsulfoxide): δ 7.75 (m, Ar-H + NH).

*Anal.* Calcd. for C<sub>11</sub>H<sub>8</sub>N<sub>6</sub>O: C, 55.4; H, 2.5; N, 35.3. Found: C, 55.5; H, 2.6; N, 35.4.

The Xb derivative was crystallised from dilute dimethylformamide in 60% yield, mp 215°; ir: 2220 (CN) and 1680 (CO); <sup>1</sup>H-nmr (deuteriodimethylsulfoxide): δ 3.65 (s, 3H, CH<sub>3</sub>) and 7.85 (m, 5H, Ar-H).

*Anal.* Calcd. for C<sub>12</sub>H<sub>8</sub>N<sub>6</sub>O: C, 57.1; H, 3.1; N, 33.3. Found: C, 57.2; H, 3.2; N, 33.5.

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