

Katsuhiko Nagahara\*, Hiroko Kawano, Shinji Sasaoka,  
Chisa Ukawa, Tamaki Hiram and Atsushi Takada

School of Pharmaceutical Sciences, Kitasato University,  
5-9-1, Shirokane, Minato-ku, Tokyo 108, Japan

Howard B. Cottam and Roland K. Robins

Department of Medicine 0663, University of California,  
San Diego, 9500 Gilman Drive,  
La Jolla, California 92093 USA

Received July 6, 1993

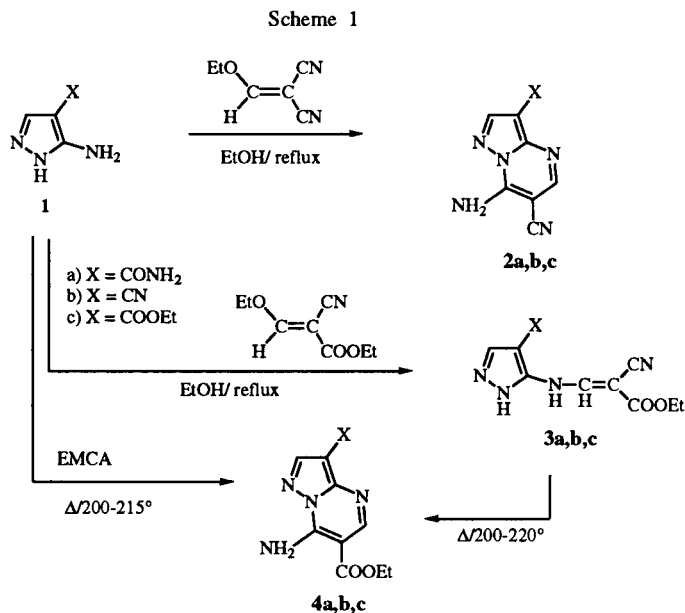
A one-pot synthesis using 5-aminopyrazole derivatives **1** with ethoxymethylenemalononitrile (EMMN), ethyl ethoxymethylenecyanoacetate (EMCA) or diethyl ethoxymethylenemalonate (DEMM) gave pyrazolo[1,5-*a*]pyrimidine compounds **2,4,8**. Also, the one step reaction of EMCA with hydrazine hydrate afforded ethyl(4-ethoxycarbonyl-5-pyrazolyl)aminomethylenecyanoacetate **3c**. On the other hand, the reaction of 1-substituted 5-aminopyrazole-4-carboxamide **9** with EMMN afforded pyrazolo[3,4-*d*]pyrimidine compounds **10**.

*J. Heterocyclic Chem.*, **31**, 239 (1994).

In a previous papers [1-3] from our laboratory we described a new synthesis of 3,4-dihydro-4-quinazolone derivatives by the reaction of 2-aminobenzamides with EMMN or EMCA. We have now found a one step synthesis of pyrazolo[1,5-*a*]pyrimidine derivatives **2,4,8** by the reactions of 5-aminopyrazole compounds **1** with EMMN, EMCA or DEMM, and a one-pot synthesis of **3c** by the treatment of EMCA with hydrazine hydrate. We have also found that the reaction of 1-substituted 5-aminopyrazole-4-carboxamide **9** with EMMN afforded pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-ones **10**.

The reaction of 5-aminopyrazole-4-carboxamide **1a** [4] with an equivalent amount of EMMN afforded 7-amino-6-cyanopyrazolo[1,5-*a*]pyrimidine-3-carboxamide **2a**. Similarly, treatment of 5-amino-4-cyanopyrazole **1b** [4] or ethyl 5-aminopyrazole-4-carboxylate **1c** [5] with EMMN under the same reaction conditions gave the corresponding 7-amino-3,6-dicyanopyrazolo[1,5-*a*]pyrimidine **2b** and ethyl 7-amino-6-cyanopyrazolo[1,5-*a*]pyrimidine-3-carboxylate **2c**, respectively (Scheme 1). Also, **2b** was prepared by the reaction of hydrazine hydrate with excess EMMN [6]. Next, heating of **1a** with an equivalent amount of EMCA afforded a mixture of two geometric isomers of ethyl (4-carbamoyl-5-pyrazolyl)aminomethylenecyanoacetate, *cis*- and *trans*-enamines **3a** (88%). The structure of **3a** was assigned by its ir spectrum [3160 cm<sup>-1</sup> (side chain NH) and 2240 cm<sup>-1</sup> (C≡N)] and mass spectrum (*m/z* 249), confirmed by the satisfactory elemental analysis. In particular, the nmr spectra of two isomeric enamines of **3a** show the doublet signal due to the vinyl proton coupled with the adjacent NH proton [7-10]. The vinyl proton of the *cis*-enamine is at higher field than that of the *trans*-enamine [7]. The downfield NH signal attributed to an intramolecular hydrogen bonding between the amino and ester groups

was assigned to that of the *cis*-enamine type (Table I). Similarly, refluxing of **1b,c** with EMCA under the same reaction conditions gave ethyl (4-cyano-5-pyrazolyl)aminomethylenecyanoacetate **3b** [8] and ethyl (4-ethoxycarbonyl-5-pyrazolyl)aminomethylenecyanoacetate **3c** [9].



On the other hand, the pyrolysis of **1a** with an equivalent amount of EMCA at 200-215° afforded only ethyl 7-amino-3-carbamoylpyrazolo[1,5-*a*]pyrimidine-6-carboxylate **4a** (76%), while the addition product of type **3** was not obtained. Also, the pyrolysis of compound **3a** at 200-220° gave product **4a** in 78% yield. Furthermore, the pyrolysis of **1b,c** with an equivalent amount of EMCA at 200-215° as well as the pyrolysis of **3b,c** at 200-220° gave the corre-

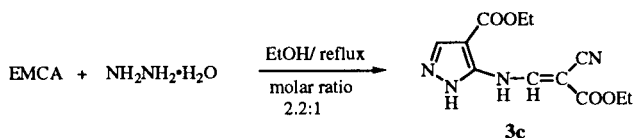
Table 1  
Characteristic NMR of 4-Substituted Ethyl 5-Pyrazolyl-aminomethylenecyanoacetates **3a,b,c** ( $\delta$  values in DMSO- $d_6$ )

| Compound  | <i>cis</i> -Enamine<br>=CH NH (Exo) |                  | <i>trans</i> -Enamine<br>=CH NH (Exo) |                  | Approximate<br>Ratio of <i>cis</i> - and<br><i>trans</i> -Enamine [a] |
|-----------|-------------------------------------|------------------|---------------------------------------|------------------|---|
| <b>3a</b> | 8.28<br>(1H, d)<br>J = 13.5 Hz      | 11.76<br>(1H, d) | 8.57<br>(1H, d)<br>J = 14.5 Hz        | 10.43<br>(1H, d) | 75:25   |
| <b>3b</b> | 8.21<br>(1H, d)<br>J = 13.0 Hz      | 11.52<br>(1H, d) | 8.37<br>(1H, d)<br>J = 13.0 Hz        | 10.87<br>(1H, d) | 80:20   |
| <b>3c</b> | 8.35<br>(1H, d)<br>J = 13.5 Hz      | 11.40<br>(1H, d) | 8.55<br>(1H, d)<br>J = 14.5 Hz        | 9.50<br>(1H, d)  | 83:17   |

[a] This number was measured by nmr spectroscopy and is probably accurate with  $\pm 5$ .

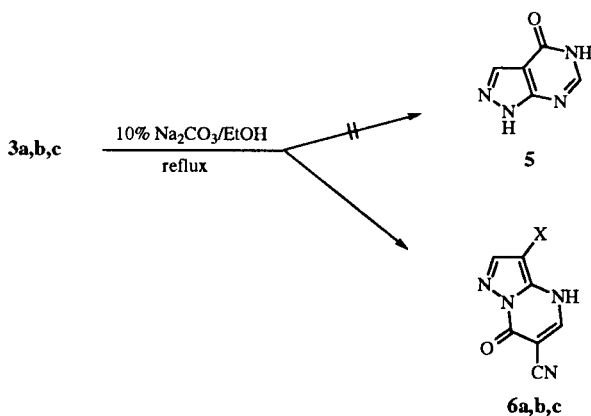
sponding ethyl 7-amino-3-cyanopyrazolo[1,5-*a*]pyrimidine-6-carboxylate **4b** [8] and diethyl 7-aminopyrazolo[1,5-*a*]pyrimidine-3,6-dicarboxylate **4c** [9], respectively. Moreover, the one step synthetic method using hydrazine hydrate with 2.2-fold molar amount of EMCA afforded **3c** (68%) (Scheme 2).

Scheme 2



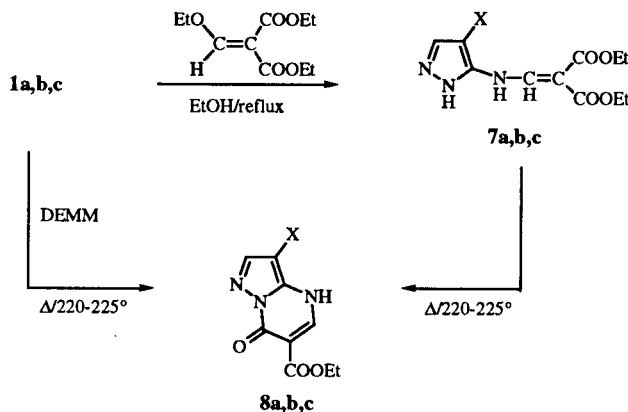
Next, when **3a** was treated with an aqueous solution of sodium carbonate, high yield (93%) of 6-cyano-4,7-dihydro-7-oxopyrazolo[1,5-*a*]pyrimidine-3-carboxamide **6a** was obtained instead of the expected pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one **5**. The structure of **6a** established by its satisfactory spectral data and elemental analysis. Also, treatment of **3b,c** under the same reaction conditions afforded the corresponding 3,6-dicyanopyrazolo[1,5-*a*]pyrimidin-7(4*H*)-one **6b** and ethyl 6-cyano-4,7-dihydro-7-oxopyrazolo[1,5-*a*]pyrimidine-3-carboxylate **6c**, respectively (Scheme 3).

Scheme 3



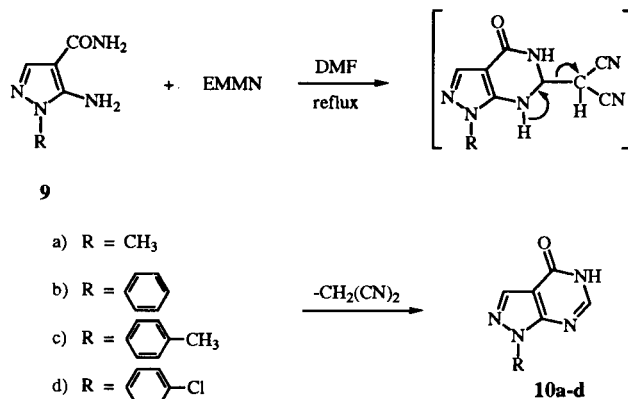
In view of the above facts, the reaction of compound **1** with an equivalent amount of DEMM gave the corresponding 4-substituted diethyl 5-pyrazolylaminomethylenemalonate [7]. Also, a one-pot synthesis using **1** with an equivalent amount of DEMM at 200-225° afforded 3-substituted ethyl 4,7-dihydro-7-oxopyrazolo[1,5-*a*]pyrimidine-6-carboxylate **8**. Similarly, the pyrolysis of **7** at 200-225° gave **8** (Scheme 4).

Scheme 4



On the other hand, heating of 1-alkyl(aryl)-5-aminopyrazole-4-carboxamide **9** [4] with an equivalent amount of EMMN in DMF at 140-150° afforded 51-61% yield of 1-alkyl(aryl)pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one **10** as the allopurinol derivatives, which was isolated by concentration of the reaction mixture and addition of water. The structure of **10** was established by its satisfactory spectral data and elemental analysis. In contrast with the above result, the EMCA or DEMM did not react with compound **9** and the starting material was recovered unchanged (Scheme 5).

Scheme 5



## EXPERIMENTAL

All melting points were determined on a Ishii melting point apparatus and are uncorrected. The ir spectra (potassium bro-

mide) were recorded with a JASCO IRA-1 spectrometer. The nmr spectra were measured in deuteriodimethyl sulfoxide with a Varian VXR-300 spectrometer. Chemical shifts are given in the  $\delta$  scale. The mass spectra (ms) were determined with a JEOL JMS-DX300 spectrometer. Elemental analyses were performed on a Perkin-Elmer 240B instrument.

#### 7-Amino-6-cyanopyrazolo[1,5-*a*]pyrimidine-3-carboxamide **2a**.

To a solution of 0.8 g (6.3 mmoles) of 5-aminopyrazole-4-carboxamide **1a** [4] in 15 ml of ethanol was added 0.8 g (6.3 mmoles) of ethoxymethylenemalononitrile (EMMN), and the mixture was refluxed on a water bath for 3 hours. The resulting precipitates were recrystallized from DMF-water to give 1.1 g (86%) of **2a** as a colorless powder, mp  $>300^\circ$ ; ir:  $\nu$  3340, 3380, 3300, 3160 ( $\text{NH}_2$ ), 2240 ( $\text{C}\equiv\text{N}$ ), 1670 ( $\text{C}=\text{O}$ )  $\text{cm}^{-1}$ ; ms: (EI)  $m/z$  202 ( $\text{M}^+$ );  $^1\text{H}$  nmr: 7.45 (2H, s,  $\text{CONH}_2$ ), 8.51 (1H, s,  $\text{C}_2\text{-H}$ ), 8.58 (1H, s,  $\text{C}_5\text{-H}$ ), 9.01 (2H, br,  $\text{NH}_2$ ).

*Anal.* Calcd. for  $\text{C}_8\text{H}_6\text{N}_6\text{O}$ : C, 47.52; H, 2.99; N, 41.57. Found: C, 47.28; H, 3.07; N, 41.28.

#### 7-Amino-3,6-dicyanopyrazolo[1,5-*a*]pyrimidine **2b**.

A mixture of 5-amino-4-cyanopyrazole **1b** [4] (0.8 g, 7 mmoles) and EMMN (0.9 g, 7 mmoles) in ethanol (15 ml) was refluxed on a water bath for 3 hours. The precipitates which resulted were collected and recrystallized from DMF-water to give 0.74 g (54%) of **2b**, mp  $>300^\circ$ . Compound **2b** was identified by mixed melting point test and comparison of the ir spectrum with that of the authentic samples prepared by the reported procedure [6].

#### Ethyl 7-Amino-6-cyanopyrazolo[1,5-*a*]pyrimidine-3-carboxylate **2c**.

To a solution of 3.1 g (2.0 mmoles) of ethyl 5-aminopyrazole-4-carboxylate **1c** [5] in 30 ml of ethanol was added 2.4 g (2.0 mmoles) of EMMN. The mixture was refluxed on a water bath for 3 hours. The solid product was recrystallized from DMF-water to give 2.9 g (63%) of **2c** as a colorless powder, mp  $301\text{-}302^\circ$ ; ir  $\nu$  3400, 3300 ( $\text{NH}$ ), 2240 ( $\text{C}\equiv\text{N}$ ), 1710 ( $\text{C}=\text{O}$ )  $\text{cm}^{-1}$ ; ms: (EI)  $m/z$  231 ( $\text{M}^+$ );  $^1\text{H}$  nmr: 1.29 (3H, t,  $\text{CH}_2\text{CH}_3$ ), 4.27 (2H, q,  $\text{CH}_2\text{CH}_3$ ), 8.54 (1H, s,  $\text{C}_2\text{-H}$ ), 8.57 (1H, s,  $\text{C}_5\text{-H}$ ), 9.19 (2H, s,  $\text{NH}_2$ ).

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_9\text{N}_5\text{O}_2$ : C, 51.94; H, 3.92; N, 30.29. Found: C, 51.98; H, 3.88; N, 30.33.

#### 4-Substituted Ethyl 5-Pyrazolylaminomethylenecyanoacetate **3a-c**.

##### General Procedure.

A mixture of **1a-c** (55 mmoles) and ethyl ethoxymethylenecyanoacetate (EMCA) (55 mmoles) in ethanol (50 ml) was refluxed on a water bath for 3 hours. The solid product was recrystallized from aqueous ethanol to give **3a-c**.

#### Ethyl (4-Carbamoyl-5-pyrazolyl)aminomethylenecyanoacetate **3a**.

This compound was obtained in 88% yield as a colorless powder, mp  $203\text{-}205^\circ$ ; ir:  $\nu$  3460, 3420, 3340, 3260, 3160 ( $\text{NH}_2$ ,  $\text{NH}$ ), 2220 ( $\text{C}\equiv\text{N}$ ), 1670, 1650 sh ( $\text{C}=\text{O}$ )  $\text{cm}^{-1}$ ; ms: (EI)  $m/z$  249 ( $\text{M}^+$ );  $^1\text{H}$  nmr 1.27 (3H, t,  $\text{CH}_2\text{CH}_3$ ), 4.21 (2H, q,  $\text{CH}_2\text{CH}_3$ ), 7.26, 7.74 (2H, s,  $\text{CONH}_2$ ), 8.24 (1H, s,  $\text{C}_3\text{-H}$ ), 13.01 (1H, s, ring NH).

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_{11}\text{N}_5\text{O}_3$ : C, 48.19; H, 4.45; N, 28.10. Found: C, 48.15; H, 4.32; N, 28.03.

#### Ethyl (4-Cyano-5-pyrazolyl)aminomethylenecyanoacetate **3b**.

This compound was obtained in 55% yield as a pale brown powder, mp  $198\text{-}199^\circ$ ; mp  $286^\circ$  [5]; ir:  $\nu$  3240, 3160 ( $\text{NH}$ ), 2260, 2220 ( $\text{C}\equiv\text{N}$ ), 1720, 1680 ( $\text{C}=\text{O}$ )  $\text{cm}^{-1}$ ; ms: (EI)  $m/z$  231 ( $\text{M}^+$ );  $^1\text{H}$  nmr: 1.25 (3H, t,  $\text{CH}_2\text{CH}_3$ ), 4.21 (2H, q,  $\text{CH}_2\text{CH}_3$ ), 8.55 (1H, s,  $\text{C}_3\text{-H}$ ), 13.60 (1H, br, ring NH).

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_9\text{N}_5\text{O}_2$ : C, 51.94; H, 3.92; N, 30.29. Found: C, 51.72; H, 4.02; N, 30.07.

#### Ethyl (4-Ethoxycarbonyl-5-pyrazolyl)aminomethylenecyanoacetate **3c**.

This compound was obtained in 81% yield as a colorless powder, mp  $178\text{-}179^\circ$ , *cis*-enamine mp  $178\text{-}182^\circ$ , *trans*-enamine, mp  $181.5\text{-}183^\circ$  [9]; ir:  $\nu$  3220, 3180 sh ( $\text{NH}$ ), 2220 ( $\text{C}\equiv\text{N}$ ), 1670 ( $\text{C}=\text{O}$ )  $\text{cm}^{-1}$ ; ms: (EI)  $m/z$  278 ( $\text{M}^+$ );  $^1\text{H}$  nmr: 1.30 (6H, t, 2  $\text{CH}_2\text{CH}_3$ ), 4.25 (4H, q, 2  $\text{CH}_2\text{CH}_3$ ), 8.34 (1H, s,  $\text{C}_3\text{-H}$ ), 13.38 (1H, br, ring NH).

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_{14}\text{N}_4\text{O}_4$ : C, 51.79; H, 5.07; N, 20.14. Found: C, 51.92; H, 5.05; N, 20.09.

#### One-pot Synthesis of **3c**.

To a solution of 10 g (5.9 mmoles) of EMCA in 50 ml of ethanol was added 1.3 g (2.6 mmoles) of hydrazine hydrate. The mixture was refluxed on a water bath for 5 hours. The solid product was treated by aqueous ethanol to give 11.4 g (68%) of **3c**.

#### 3-Substituted Ethyl 7-aminopyrazolo[1,5-*a*]pyrimidine-6-carboxylate **4a-c**.

##### General Procedure.

##### Method A.

A mixture of **1a-c** (3 mmoles) and EMCA (3 mmoles) was heated on an oil bath for 10 minutes at  $210\text{-}215^\circ$ . After cooling, the solid product was recrystallized from DMF-water to give **4a-c**.

##### Method B.

One g of **3a-c** was heated on an oil bath for 10 minutes at  $200\text{-}220^\circ$ . After cooling, the solid product was treated as described in method A.

#### Ethyl 7-Amino-3-carbamoylpyrazolo[1,5-*a*]pyrimidine-6-carboxylate **4a**.

The yield by method A was 76% and it was a colorless powder, mp  $269\text{-}270^\circ$ ; the yield by method B was 78%; ir:  $\nu$  3360, 3300 ( $\text{NH}_2$ ), 1680, 1660 ( $\text{C}=\text{O}$ )  $\text{cm}^{-1}$ ; ms: (EI)  $m/z$  249 ( $\text{M}^+$ );  $^1\text{H}$  nmr: 1.34 (3H, t,  $\text{CH}_2\text{CH}_3$ ), 4.35 (2H, q,  $\text{CH}_2\text{CH}_3$ ), 7.44, 7.55 (2H, s,  $\text{CONH}_2$ ), 8.50 (1H, s,  $\text{C}_2\text{-H}$ ), 8.76 (1H, s,  $\text{C}_5\text{-H}$ ), 9.15 (2H, s,  $\text{NH}_2$ ).

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_{11}\text{N}_5\text{O}_3$ : C, 48.19; H, 4.45; N, 28.09. Found: C, 47.89; H, 4.41; N, 28.06.

#### Ethyl 7-Amino-3-cyanopyrazolo[1,5-*a*]pyrimidine-6-carboxylate **4b**.

The yield of **4b** by method A was 83% and by method B it was 89% and was obtained as a pale yellow powder, mp  $302\text{-}304^\circ$ , mp  $350^\circ$  [5]; ir:  $\nu$  3300, 3280 ( $\text{NH}_2$ ), 2240 ( $\text{C}\equiv\text{N}$ ), 1690 ( $\text{C}=\text{O}$ )  $\text{cm}^{-1}$ ; ms: (EI)  $m/z$  281 ( $\text{M}^+$ );  $^1\text{H}$  nmr: 1.35 (3H, t,  $\text{CH}_2\text{CH}_3$ ), 4.35 (2H, q,  $\text{CH}_2\text{CH}_3$ ), 8.76 (1H, s,  $\text{C}_2\text{-H}$ ), 8.78 (1H, s,  $\text{C}_5\text{-H}$ ), 9.00 (2H, br,  $\text{NH}_2$ ).

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_9\text{N}_5\text{O}_2$ : C, 51.94; H, 3.92; N, 30.29. Found: C, 52.23; H, 3.83; N, 30.28.

#### Diethyl 7-Aminopyrazolo[1,5-*a*]pyrimidine-3,6-dicarboxylate **4c**.

Compound **4c** was obtained in 79% yield by method A and in 75% yield by method B as a colorless powder, mp 244-245°, mp 243-244° [9]; ir:  $\nu$  3380, 3260 (NH<sub>2</sub>), 1710, 1680 (C=O) cm<sup>-1</sup>; ms: (EI) *m/z* 278 (M<sup>+</sup>); <sup>1</sup>H nmr: 1.33 (6H, t, 2 CH<sub>2</sub>CH<sub>3</sub>), 4.32 (4H, q, 2 CH<sub>2</sub>CH<sub>3</sub>), 8.58 (1H, s, C<sub>2</sub>-H), 8.80 (1H, s, C<sub>5</sub>-H), 9.06 (2H, br, NH<sub>2</sub>).

*Anal.* Calcd. for C<sub>12</sub>H<sub>16</sub>N<sub>4</sub>O<sub>5</sub>: C, 51.79; H, 5.07; N, 20.14. Found: C, 51.73; H, 4.84; N, 19.96.

3-Substituted 6-Cyano-4,7-dihydro-7-oxopyrazolo[1,5-*a*]pyrimidine **6a-c**.

General Procedure.

To a solution of **3a-c** (8 mmoles) in 100 ml of ethanol was added 100 ml of 10% sodium carbonate solution. The mixture was refluxed on a water bath for 6 hours. After evaporation of ethanol, the residue was acidified with hydrochloric acid to precipitate crystals, which were filtered off, washed with water and dried.

6-Cyano-4,7-dihydro-7-oxopyrazolo[1,5-*a*]pyrimidine-3-carboxamide **6a**.

This compound was obtained in 93% yield as a colorless powder, mp > 300°; ir:  $\nu$  3440, 3340, 3180 (NH<sub>2</sub>, NH), 2240 (C≡N), 1720, 1710, 1660 (C=O) cm<sup>-1</sup>; ms: (EI) *m/z* 203 (M<sup>+</sup>); <sup>1</sup>H nmr: 7.49, 8.02 (2H, s, CONH<sub>2</sub>), 8.45 (1H, s, C<sub>2</sub>-H), 8.49 (1H, s, C<sub>5</sub>-H), 10.00 (1H, br, NH).

*Anal.* Calcd. for C<sub>8</sub>H<sub>8</sub>N<sub>5</sub>O<sub>2</sub>: C, 47.29; H, 2.48; N, 34.48. Found: C, 47.23; H, 2.48; N, 34.46.

3,6-Dicyanopyrazolo[1,5-*a*]pyrimidin-7(4*H*)-one **6b**.

This compound was obtained in 86% yield (pale yellow powders); mp > 320° (mp 350° [8]); ir:  $\nu$  3420, 3180 (NH), 2240 (C≡N); 1710sh, 1690 (C=O) cm<sup>-1</sup>; ms: (EI) *m/z* 185 (M<sup>+</sup>); <sup>1</sup>H nmr: 8.45 (1H, s, C<sub>2</sub>-H), 8.75 (1H, s, C<sub>5</sub>-H), 10.62 (1H, br, NH).

*Anal.* Calcd. for C<sub>8</sub>H<sub>8</sub>N<sub>5</sub>O•1/4H<sub>2</sub>O: C, 50.66; H, 1.86; N, 36.93. Found: C, 50.70; H, 1.77; N, 37.22.

Ethyl 6-Cyano-4,7-dihydro-7-oxopyrazolo[1,5-*a*]pyrimidine-3-carboxylate **6c**.

This compound was obtained in 50% yield from aqueous ethanol as a colorless powder, mp 309-311°; ir:  $\nu$  3420, 3140 (NH), 2240 (C≡N), 1700, 1680sh (C=O) cm<sup>-1</sup>; ms: (EI) *m/z* 232 (M<sup>+</sup>); <sup>1</sup>H nmr: 1.31 (3H, t, CH<sub>2</sub>CH<sub>3</sub>), 4.31 (2H, q, CH<sub>2</sub>CH<sub>3</sub>), 8.28 (1H, s, C<sub>2</sub>-H), 8.62 (1H, s, C<sub>5</sub>-H), 10.60 (1H, br, NH).

*Anal.* Calcd. for C<sub>10</sub>H<sub>8</sub>N<sub>4</sub>O<sub>3</sub>•1/4H<sub>2</sub>O: C, 50.74; H, 3.62; N, 23.67. Found: C, 50.65; H, 3.37; N, 23.40.

4-Substituted Diethyl 5-Pyrazolylaminomethylenemalonates **7a-c**.

General Procedure.

A mixture of **1a-c** (2.6 mmoles) and diethyl ethoxymethylenemalonate (DEMM) (2.6 mmoles) in ethanol 50 ml was refluxed on a water bath for 3 hours. The solid product was recrystallized from a suitable solvent.

Diethyl (4-Carbamoyl-5-pyrazolyl)aminomethylenemalonate **7a**.

This compound was obtained in 51% yield from aqueous ethanol as a colorless powder, mp 243-245°; ir:  $\nu$  3460, 3320, 3260 (NH<sub>2</sub>, NH), 1730, 1690, 1650 (C=O) cm<sup>-1</sup>; ms: (EI) *m/z* 296 (M<sup>+</sup>); <sup>1</sup>H nmr: 1.25 (6H, t, 2 CH<sub>2</sub>CH<sub>3</sub>), 4.16 (4H, q, 2 CH<sub>2</sub>CH<sub>3</sub>), 7.22, 7.70 (2H, s, CONH<sub>2</sub>), 8.24 (1H, s, C<sub>3</sub>-H), 8.70 (1H, d, J = 14.0 Hz, -CH=), 11.52 (1H, d, J = 14.0 Hz, NH), 12.85 (1H, br, ring NH).

*Anal.* Calcd. for C<sub>12</sub>H<sub>16</sub>N<sub>4</sub>O<sub>5</sub>: C, 48.64; H, 5.44; N, 18.91. Found: C, 48.38; H, 5.43; N, 19.16.

Diethyl (4-Cyano-5-pyrazolyl)aminomethylenemalonate **7b**.

This compound was obtained in 46% yield from aqueous ethanol as pale brown needles, mp 213-215°; ir:  $\nu$  3300, 3140 (NH), 2240 (C≡N), 1700, 1660 (C=O) cm<sup>-1</sup>; ms: (EI) *m/z* 278 (M<sup>+</sup>); <sup>1</sup>H nmr: 1.25 (6H, t, 2 CH<sub>2</sub>CH<sub>3</sub>), 4.17 (4H, q, 2 CH<sub>2</sub>CH<sub>3</sub>), 8.49 (1H, s, C<sub>3</sub>-H), 8.53 (1H, s, -CH=), 10.73 (1H, br, NH), 13.54 (1H, br, ring NH).

*Anal.* Calcd. for C<sub>12</sub>H<sub>14</sub>N<sub>4</sub>O<sub>4</sub>: C, 51.79; H, 5.07; N, 20.14. Found: C, 51.60; H, 5.03; N, 20.10.

Diethyl (4-Ethoxycarbonyl-5-pyrazolyl)aminomethylenemalonate **7c**.

This compound was obtained in 67% yield from ethanol as a colorless powder, mp 173-175°; ir:  $\nu$  3240 (NH), 1730, 1690, 1660 (C=O) cm<sup>-1</sup>; ms: (EI) *m/z* 325 (M<sup>+</sup>); <sup>1</sup>H nmr: 1.28 (9H, t, 3 CH<sub>2</sub>CH<sub>3</sub>), 4.23 (6H, q, 3 CH<sub>2</sub>CH<sub>3</sub>), 8.23 (1H, s, C<sub>3</sub>-H), 8.69 (1H, d, J = 13.5 Hz, -CH=), 11.31 (1H, d, J = 13.5 Hz, NH), 13.26 (1H, s, ring NH).

*Anal.* Calcd. for C<sub>14</sub>H<sub>19</sub>N<sub>3</sub>O<sub>6</sub>: C, 51.68; H, 5.89; N, 12.92. Found: C, 51.63; H, 5.66; N, 12.87.

3-Substituted Ethyl 4,7-Dihydro-7-oxopyrazolo[1,5-*a*]pyrimidine-6-carboxylates **8a-c**.

General Procedure.

Method A.

A mixture of **1a-c** (3.6 mmoles) and DEMM (3.6 mmoles) was heated on an oil bath for 10 minutes at 200-225°. After cooling, the solid product was recrystallized from DMF-water to give **8a-c**.

Method B.

One g of **7a,b,c** was heated on an oil bath 10 minutes at 200-225°. After cooling, the solid product was treated as described in method A.

Ethyl 3-Carbamoyl-4,7-dihydro-7-oxopyrazolo[1,5-*a*]pyrimidine-6-carboxylate **8a**.

This compound was obtained in 55% yield by method A and in 61% yield by method B as a colorless powder, mp 318-320°; ir:  $\nu$  3380, 3180 (NH<sub>2</sub>, NH), 1730, 1690, 1650 (C=O) cm<sup>-1</sup>; ms: (EI) *m/z* 250 (M<sup>+</sup>); <sup>1</sup>H nmr: 1.28 (3H, t, CH<sub>2</sub>CH<sub>3</sub>), 4.24 (2H, q, CH<sub>2</sub>CH<sub>3</sub>), 7.45, 7.96 (2H, s, CONH<sub>2</sub>), 8.36 (1H, s, C<sub>2</sub>-H), 8.39 (1H, s, C<sub>5</sub>-H), 12.60 (1H, br, NH).

*Anal.* Calcd. for C<sub>10</sub>H<sub>10</sub>N<sub>4</sub>O<sub>4</sub>: C, 48.00; H, 4.02; N, 22.39. Found: C, 47.78; H, 3.97; N, 22.43.

Ethyl 3-Cyano-4,7-dihydro-7-oxopyrazolo[1,5-*a*]pyrimidine-6-carboxylate **8b**.

This compound was obtained in 57% yield by method A and in 67% yield by method B as a colorless powder, mp 309-310°, mp 315° [8]; ir:  $\nu$  3440, 3160 (NH), 2240 (C≡N), 1730, 1700, 1670 (C=O) cm<sup>-1</sup>; ms: (EI) *m/z* 232 (M<sup>+</sup>); <sup>1</sup>H nmr: 1.29 (3H, t, CH<sub>2</sub>CH<sub>3</sub>), 4.25 (2H, q, CH<sub>2</sub>CH<sub>3</sub>), 8.44 (1H, s, C<sub>2</sub>-H), 8.55 (1H, s, C<sub>5</sub>-H), 8.96 (1H, br, NH).

*Anal.* Calcd. for C<sub>10</sub>H<sub>8</sub>N<sub>4</sub>O<sub>3</sub>: C, 51.73; H, 3.43; N, 24.12. Found: C, 51.78; H, 3.50; N, 23.94.

Diethyl 4,7-Dihydro-7-oxopyrazolo[1,5-*a*]pyrimidine-3,6-dicarboxylate **8c**.

This compound was obtained in 80% yield by method A and in 70% yield by method B as a colorless powder, mp 303-304°; ir:  $\nu$  3400, 3180 (NH), 1730, 1670 (C=O)  $\text{cm}^{-1}$ ; ms: (EI)  $m/z$  279 ( $M^+$ );  $^1\text{H}$  nmr: 1.30 (6H, t, 2  $\text{CH}_2\text{CH}_3$ ), 4.29 (4H, q, 2  $\text{CH}_2\text{CH}_3$ ), 8.25 (1H, s,  $\text{C}_2\text{-H}$ ), 8.36 (1H, s,  $\text{C}_5\text{-H}$ ), 12.77 (1H, br, NH).

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_{13}\text{N}_3\text{O}_2$ : C, 51.61; H, 4.69; N, 15.05. Found: C, 51.45; H, 4.63; N, 15.18.

#### 1-Alkyl(aryl)pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-ones **10a-d**.

##### General Procedure.

To a solution of 15 mmoles of 1-alkyl(aryl)-5-aminopyrazole-4-carboxamide **9a-d** [4] in 40 ml of DMF was added of 15 mmoles of EMMN. The mixture was refluxed on an oil bath for 6 hours at 140-150°. The reaction mixture was concentrated *in vacuo* and the residue was added with water to precipitate crystals, which were filtered off, washed with water and dried.

#### 1-Methylpyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one **10a**.

This compound was obtained in 56% yield from aqueous ethanol, mp 287-288°, mp >300° [4]; ir:  $\nu$  3420, 3140 (NH), 1670 (C=O)  $\text{cm}^{-1}$ ; ms: (EI)  $m/z$  150 ( $M^+$ );  $^1\text{H}$  nmr: 3.89 (3H, s,  $\text{CH}_3$ ), 8.02 (1H, s,  $\text{C}_2\text{-H}$ ), 8.06 (1H, s,  $\text{C}_6\text{-H}$ ), 12.13 (1H, br, NH).

*Anal.* Calcd. for  $\text{C}_6\text{H}_8\text{N}_4\text{O}$ : C, 48.00; H, 4.03; N, 37.32. Found: C, 47.92; H, 4.07; N, 37.46.

#### 1-Phenylpyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one **10b**.

This compound was obtained in 61% yield from acetonitrile, mp 302-303°, mp 299° [4]; ir:  $\nu$  3440, 3160 (NH), 1730, 1650 (C=O)  $\text{cm}^{-1}$ ; ms: (EI)  $m/z$  212 ( $M^+$ );  $^1\text{H}$  nmr: 7.35-8.06 (5H, m, Ph), 8.19 (1H, s,  $\text{C}_2\text{-H}$ ), 8.32 (1H, s,  $\text{C}_6\text{-H}$ ), 12.44 (1H, br, NH).

*Anal.* Calcd. for  $\text{C}_{11}\text{H}_8\text{N}_4\text{O}$ : C, 62.25; H, 3.80; N, 26.40. Found: C, 62.29; H, 3.77; N, 26.70.

#### 1-(*p*-Chlorophenyl)pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one **10c**.

This compound was obtained in 59% yield from DMF-water,

mp >300°, mp >300° [4]; ir:  $\nu$  3440, 3160 (NH), 1670 (C=O)  $\text{cm}^{-1}$ ; ms: (EI)  $m/z$  246 ( $M^+$ ), 248 ( $M^+ + 2$ );  $^1\text{H}$  nmr: 7.65 (2H, d,  $J = 8.5$  Hz, Ph), 8.11 (2H, d,  $J = 8.5$  Hz, Ph), 8.22 (1H, s,  $\text{C}_3\text{-H}$ ), 8.35 (1H, s,  $\text{C}_6\text{-H}$ ), 12.50 (1H, br, NH).

*Anal.* Calcd. for  $\text{C}_{11}\text{H}_7\text{N}_4\text{OCl}$ : C, 53.56; H, 2.86; N, 22.72. Found: C, 53.35; H, 3.07; N, 23.00.

#### 1-(*p*-Tolyl)pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one **10d**.

This compound was obtained in 51% yield from DMF-water, mp 302-304°; ir:  $\nu$  3420, 3140 (NH), 1660 (C=O)  $\text{cm}^{-1}$ ; ms: (EI)  $m/z$  226 ( $M^+$ );  $^1\text{H}$  nmr: 2.36 (3H, s, Me), 7.34 (2H, d,  $J = 8.5$  Hz, Ph), 7.90 (2H, d,  $J = 8.5$  Hz, Ph), 8.17 (1H, s,  $\text{C}_3\text{-H}$ ), 8.29 (1H, s,  $\text{C}_6\text{-H}$ ), 2.41 (1H, s, NH).

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_{10}\text{N}_4\text{O}$ : C, 63.70; H, 4.46; N, 24.77. Found: C, 63.59; H, 4.53; N, 25.05.

#### REFERENCES AND NOTES

- [1] K. Nagahara, A. Takagi and T. Ueda, *Chem. Pharm. Bull.*, **24**, 1310 (1976).
- [2] K. Nagahara and A. Takada, *ibid.*, **25**, 2713 (1977).
- [3] K. Nagahara and A. Takada, *Heterocycles*, **19**, 1565 (1982).
- [4] C. C. Cheng and R. K. Robins, *J. Org. Chem.*, **21**, 1240 (1956).
- [5] P. Schmidt and J. Drucey, *Helv. Chim. Acta*, **39**, 986 (1956).
- [6] K. Nagahara, K. Takagi and T. Ueda, *Chem. Pharm. Bull.*, **24**, 2880 (1976).
- [7] S. Nishigaki, M. Ichiba, K. Shinomura and F. Yoneda, *J. Heterocyclic Chem.*, **8**, 759 (1971).
- [8] S. V. Sunthakar and S. D. Vaidya, *Indian J. Chem.*, **15B**, 349 (1977).
- [9] K. Saito, I. Hori, M. Igarashi and H. Midorikawa, *Bull. Chem. Soc. Japan*, **47**, 476 (1974).
- [10] A. Takamizawa, Y. Hamashima, S. Sakai and S. Nagakura, *ibid.*, **41**, 2141 (1968).