Reaction of *N*-Substituted Acetohydrazides with 2-Substituted Cinnamonitriles. Competitive Cyclizations to Pyrazolo[3,4-*b*]pyridinones and [1,2,4]Triazolo[1,5-*a*]pyridinones

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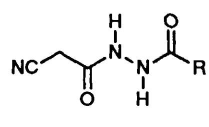
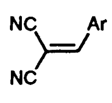
A novel synthesis of pyrazolo[3,4-*b*]pyridinones **9** from 2′-acyl-2-cyanoacetohydrazide **5** and arylidenecyanoacetates **6** is described. In the reaction, an alternative cyclization leading to [1,2,4]triazolo[1,5-*a*]pyridinones takes place. Compounds **9** were isolated from the reaction mixture as the corresponding piperidinium salts due to the high stability of the heterocyclic anion. Acidification with dilute hydrochloric acid yielded the neutral pyrazolo[3,4-*b*]pyridinone. Depending on the reaction conditions, the corresponding intermediate dihydropyridinone **12** and pyrazolo derivatives **16** were also obtained.

We have very recently reported the reaction of 2′-acetyl-2-cyanoacetohydrazide **1** and 2′-benzoyl-2-cyanoacetohydrazide **2** with arylidenemalononitriles **3** as a very convenient, one-step method to synthesize the very important [1,2,4]triazolo[1,5-*a*]pyridinones **4**[1] which have proved their usefulness in many applications such as pharmaceuticals, complexing agents or fluorescent brighteners.[1b]



1 R = Me
2 R = Ph



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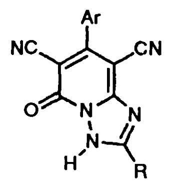


4 R = Me, Ph,

The synthesis of compounds **4** involves the formation of the pyridine ring by attack by an amide nitrogen on a cyano group of the arylidenemalononitrile, followed by a second cyclization leading to the five-membered ring of the [1,2,4]triazolo[1,5-*a*]pyridinone system.[1]

In this paper we describe the reaction of *N*-phenylacetyl-substituted cyanoacetohydrazides **5** with substituted cinnamonitriles **6** in which an alkoxycarbonyl group has been substituted for a cyano group in arylidenemalononitrile **3**. Now, an alternative cyclization can take place and, in addition to the [1,2,4]triazolo[1,5-*a*]pyridinones **10**, the novel pyrazolo[3,4-*b*]pyridinones **9** are obtained as the corresponding piperidinium salts (Scheme 1).

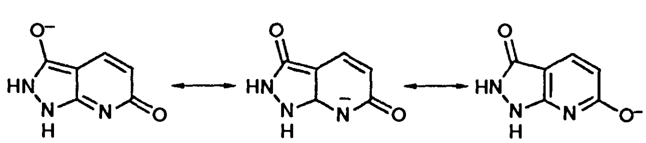
The synthesis of pyrazolo[3,4-*b*]pyridinones has attracted attention in recent years due to the wide variety of their biological and pharmacological properties.[2] The methods described in the literature to obtain pyrazolo[3,4-*b*]pyridinones usually involve several steps and, although some procedures starting from the pyridine ring are known,[3] most of them involve the construction of the pyrazole ring first, from which the pyrazolo[3,4-*b*]pyridinone is formed by subsequent cyclization.[4]

In contrast to the previous methods, the synthesis presented here generates the pyrazolo[3,4-*b*]pyridinone fused system in one single step from easily available 2′-acyl-2-cyanoacetohydrazides **5** and arylidenecyanoacetates **6** in moderate to good yields. To the best of our knowledge, there is only one precedent in the literature in which a condensation of cyanoacetohydrazide with 1,3-dicarbonyl compounds gave pyrazolo[3,4-*b*]pyridinones under certain conditions.[5]

Formation of the novel compounds **9a–d** and **10a–j** can be accounted for as depicted in Scheme 1, in which all the compounds obtained are shown. Thus, conjugate addition of 2-cyano-2′-phenylacetylacetohydrazide **5**, obtained by careful acylation of 2-cyanoacetohydrazide, to arylidenecyanoacetates **6** in alcoholic solution and in the presence of a stoicheiometric amount of piperidine at reflux temperature, afforded a mixture of pyrazolo[3,4-*b*]pyridinone **9**, as its piperidinium salt, and triazolo[1,5-*a*]pyridinone **10** obtained from the non-isolated intermediate piperidinium salt **8** by acid treatment (see Scheme 1). Formation of the salt **8** involves the construction of the pyridine ring in a 6-*exo-dig* cyclization[6] from intermediate **7** and subsequent ring closure to the [1,2,4]triazolo[1,5-*a*]pyridinone by nucleophilic attack on the amide carbonyl group and spontaneous aromatization.

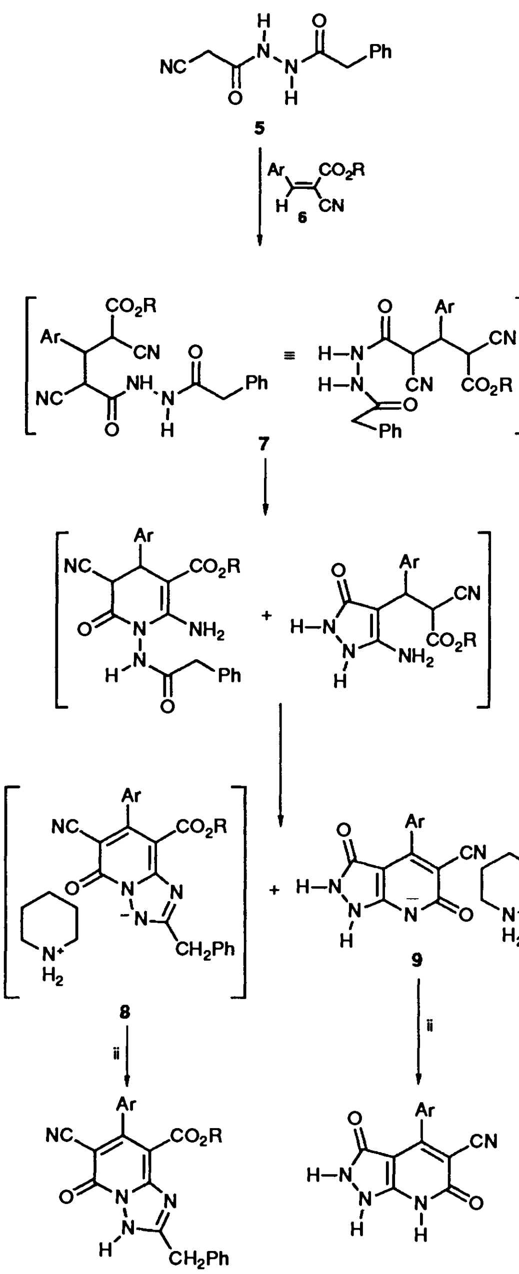
An inverse order sequence seems to be responsible for the formation of pyrazolo[3,4-*b*]pyridine **9**. It can be rationalized from the common intermediate, adduct **7**, by an alternative nucleophilic attack of the second amide nitrogen on the other cyano group in compound **7** by a 5-*exo-dig* process leading to the non-isolable aminopyrazole derivative which undergoes a second 6-*exo-trig* cyclization followed by spontaneous aromatization to the corresponding pyrazolo[3,4-*b*]pyridinone which was isolated as its piperidinium salt **9**. Formation of compound **9** is accompanied by loss of the acyl group attached to the nucleophilic nitrogen in intermediate **7**.

Formation of the piperidinium salt in the triazolo[1,5-*a*]pyridinone is due to the anion's stability, resulting from charge delocalization involving the two triazolo nitrogens and the pyridone oxygen in compounds **8**.[1a] Stabilization of the anion in the pyrazolo[3,4-*b*]pyridinone **9** involves a delocalization of the negative charge on the pyridone nitrogen and oxygen and the carbonyl oxygen on the five-membered ring.



The reaction of 2-cyano-2′-phenylacetylacetohydrazide **5** with arylidenemalononitriles **3** under the same reaction conditions (ethanol, piperidine, reflux temperature), afforded solely the corresponding piperidinium [1,2,4]triazolo[1,5-*a*]pyridine **13**, as no alkoxycarbonyl group is available in compound **3** (Scheme 2).

To show that neutral systems can be synthesized, the

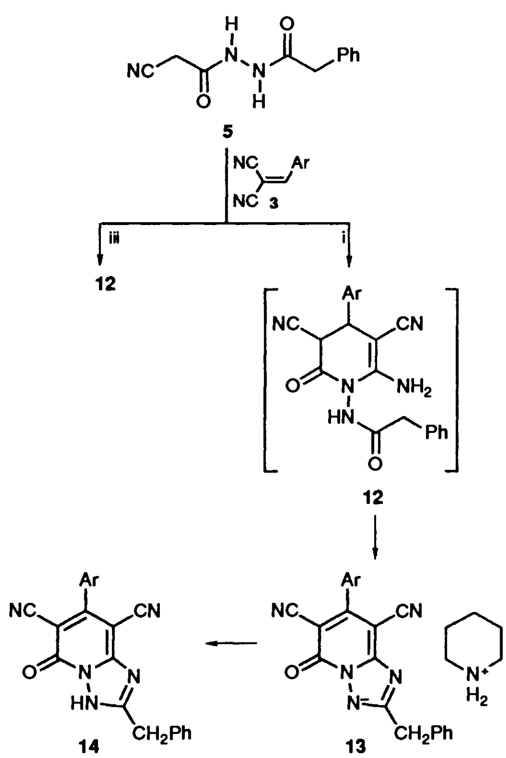


9a; Ar = Ph
b; Ar = p-MeC_6H_4
c; Ar = p-$MeOC_6H_4$
d; Ar = p-ClC_6H_4

10a; Ar = Ph, R = Me
b; Ar = p-MeC_6H_4, R = Me
c; Ar = p-$MeOC_6H_4$, R = Me
d; Ar = p-ClC_6H_4, R = Me
e; Ar = p-$NO_2C_6H_4$, R = Me
f; Ar = Ph, R = Et
g; Ar = p-MeC_6H_4, R = Et
h; Ar = p-$MeOC_6H_4$, R = Et
i; Ar = p-ClC_6H_4, R = Et
j; Ar = p-$NO_2C_6H_4$, R = Et

Scheme 1 *Reagents:* i, EtOH–piperidine; ii, 10% HCl.

neutralization of a few piperidinium salts was carried out. Thus, acidification of the salts **8a–j**, **9c** and **13a–d** with dil. hydrochloric acid produced the corresponding neutral molecules as stable, high melting white solids (**10**, **11** and **14**) in good yield (Schemes 1 and 2).



13, 14a; Ar = Ph
b; Ar = p-MeC_6H_4
c; Ar = p-$MeOC_6H_4$
d; Ar = p-ClC_6H_4

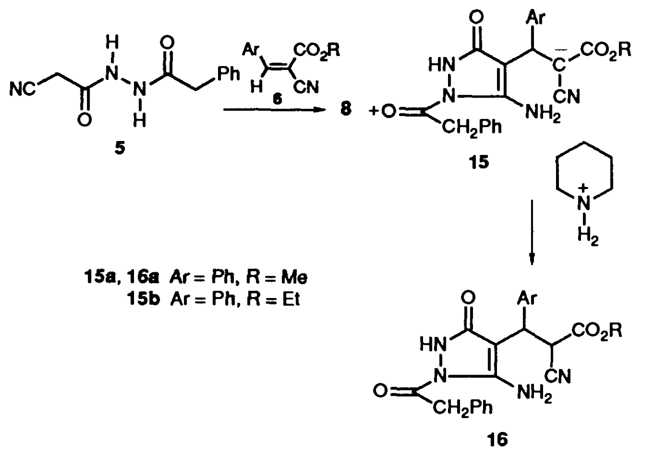
Scheme 2 *Reagents and conditions:* i, EtOH–piperidine, reflux; ii, 10% HCl; iii, EtOH, reflux.

When the reaction of hydrazide **5** with benzylidenemalononitrile (**3**, Ar = Ph) was carried out at reflux temperature but in the absence of piperidine, the corresponding *N*-acylated 1,6-diamino-3,4-dihydro-2-pyridone **12** was obtained as a mixture of diastereoisomers as the only reaction product (Scheme 2). This finding confirms that the driving force to give the second ring in the triazolo[1,5-*a*]pyridinone system **14** is the high stability of the heterocyclic anion of the salt (Scheme 2).

Recently, we have described how the regioselectivity of the reaction of unsubstituted cyanoacetohydrazides and ethoxycarbonylacetohydrazides with differently substituted propenones is dependent on the reaction temperature.[7,8] To check whether this is still true for *N*-acylated cyanoacetohydrazides, we have carried out the reaction of the acylated cyanoacetohydrazide **5** with arylidenecyanoacetates **6** in ethanol and piperidine at room temperature. Interestingly, some notable variations were observed. Thus, the piperidinium salt of the [1,2,4]triazolo[1,5-*a*]pyridinone **8a** was formed, together with the piperidinium pyrazolo derivative **15** which was obtained as the main product in good yield (Scheme 3). The mild reaction conditions used avoid the formation of the pyrazolo[3,4-*b*]pyridinide and, consequently, only the intermediate monocyclic pyrazolo derivative **15**, in which no hydrolysis of the amido group was observed, was obtained, in agreement with its role as the key intermediate in the two cyclizations to give intermediate **8**.

The neutral pyrazole ring system **16** was obtained from the salt(s) **15** by treatment with dil. hydrochloric acid.

In conclusion, we have developed a useful, one-step route for synthesizing, in addition to the important [1,2,4]triazolo[1,5-*a*]pyridinones, the pyrazolo[3,4-*b*]pyridinones obtained as their very stable piperidinium salts, from which the neutral heterocyclic system can be easily obtained. The influence of



Scheme 3 *Reagents and conditions:* i, EtOH–piperidine, room temp.; ii, 10% HCl.

both substituents and reaction temperature has been studied and the intermediate dihydropyridine derivative **12** and the pyrazolo derivative **16** were also isolated.

Experimental

M.p.s were determined in capillary tubes in a Gallenkamp apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 MHz on a Varian VXR 300S spectrometer. All NMR spectra were recorded for $(CD_3)_2SO$ solutions, chemical shifts being given as δ values with respect to $SiMe_4$ as the internal standard. IR spectra were measured with a Perkin-Elmer 781 instrument for KBr pellets. Mass spectra were obtained with a Varian MAT 711 machine. Microanalyses were performed by the Universidad Complutense Microanalytical Service. The reactions were monitored by TLC performed on silica gel plates (Merck 60-F) and using chloroform–methanol (1:1) or toluene–ethyl acetate (1:1) as the developer.

Cyanoacetohydrazide, malononitrile, ethyl cyanoacetate, methyl cyanoacetate and piperidine were obtained from commercial sources (Aldrich and Merck) and were used without further purification. Aromatic aldehydes were distilled before use. Benzylidenemalononitrile was also a commercial product (Aldrich), but the remaining arylidenemalononitriles and arylidenecyanoacetates were prepared from aromatic aldehydes following standard procedures.[9]

2-Cyano-2'-phenylacetylacetohydrazide **5**.—To a stirred solution of 2-cyanoacetohydrazide (2.0 g, 20 mmol) in water (5 cm^3) at 0 °C was added phenylacetyl chloride (30 mmol) dropwise, followed by aq. potassium carbonate (1.29 g in 2.0 cm^3). After 30 min a precipitate had formed. The solid was collected by filtration and washed with plenty of water. Further purification was accomplished by recrystallization from ethanol to yield *crystals* (70%), m.p. 190–192 °C (Found: C, 60.75; H, 5.05; N, 19.45. $C_{11}H_{11}N_3O_2$ requires C, 60.85; H, 5.1; N, 19.35%); ν_{max}/cm^{-1} 3200 (NH), 2260 (CN), 1690 (CO) and 1640 (CO); δ_H 3.45 (2 H, s, CH_2), 3.74 (2 H, s, CH_2), 7.30 (5 H, m, ArH) and 10.31 (2 H, br, NH); δ_C 23.78 (CH_2), 30.74 (CH_2), 115.68 (CN), 126.61, 128.31 (2 C), 129.04 (2 C), 135.55 (*ipso* Ar), 161.31 (CO) and 168.92 (CO).

Piperidinium 4-Aryl-5-cyano-3,6-dioxopyrazolo[3,4-b]*pyridinides* **9** *and Alkyl-7-aryl-2-benzyl-6-cyano-5-oxo*[1,2,4]*triazolo*[1,5-a]*pyridine-8-carboxylates* **10**: *General Procedure*.—To a suspension of 2-cyano-2'-phenylacetylacetohydrazide **5** (2 mmol) and the corresponding arylidenecyanoacetate **6** (2 mmol) in dry ethanol (~ 10–15 cm^3) was added an equimolar amount of piperidine (2 mmol). The reaction mixture was refluxed until TLC showed the absence of starting material (4–7 h). The solid that precipitated in the reaction mixture was collected by filtration and recrystallized from the appropriate solvent. This compound was found to be the corresponding piperidinium 4-aryl-5-cyano-3,6-dioxopyrazolo[3,4-*b*]pyridinide **9**. To the mother liquors was added 10% hydrochloric acid (10–15 cm^3), and the mixture was stirred for 15 min and then left at room temperature. A white solid corresponding to the alkyl-7-aryl-2-benzyl-6-cyano-5-oxo[1,2,4]triazolo[1,5-*a*]pyridine-8-carboxylate **10** precipitated out. It was collected by filtration and washed with plenty of water (neutral pH). Further purification was accomplished by recrystallization from the appropriate solvent.

*Piperidinium 5-cyano-1,2,3,6-tetrahydro-3,6-dioxo-4-phenyl-7*H*-pyrazolo*[3,4-b]*pyridin-7-ide* **9a** was obtained in 38% yield, m.p. 230–232 °C (from EtOH) (Found: C, 62.5; H, 6.0; N, 20.05. $C_{18}H_{19}N_5O_2 \cdot \frac{1}{2}H_2O$ requires C, 62.45; H, 5.8; N, 20.25%); ν_{max} 3400, 3000–2300, 2220, 1670, 1600, 1540, 1510, 1450, 1400 and 1260; δ_H 1.60 (6 H, m, 3 × CH_2 piperidinium), 3.0 (4 H, m, 2 × CH_2 piperidinium), 7.05–7.69 (6 H, m, ArH, NH) and 10.7 (1 H, br s, NH).

Methyl 2-benzyl-6-cyano-3,5-dihydro-5-oxo-7-phenyl[1,2,4]*triazolo*[1,5-a]*pyridine-8-carboxylate* **10a** was obtained in 36% yield, m.p. 280–282 °C (from MeCN) (Found: C, 68.7; H, 4.2; N, 14.5. $C_{22}H_{16}N_4O_3$ requires C, 68.75; H, 4.15; N, 14.6%); ν_{max}/cm^{-1} 3100, 2220, 1700, 1660, 1590, 1500, 1430, 1340, 1270, 1200, 1170, 1140, 790 and 700; δ_H 3.46 (3 H, s, MeO), 4.34 (2 H, s, CH_2) and 7.32–7.44 (10 H, m, ArH); δ_C 31.10 (CH_2), 51.49 (MeO), 90.30, 92.00 (C-6, -8), 116.48 (CN), 127.03, 127.32 (2 C), 127.78 (2 C), 128.32 (2 C), 128.50 (2 C), 128.90, 135.24, 137.44 (Ar), 146.95, 153.96, 155.38 (C-7, -8a and -2), 157.23 (CO) and 163.23 (CO).

Piperidinium 5-cyano-1,2,3,6-tetrahydro-4-(p*-methylphenyl*)*-3,6-dioxo-7*H*-pyrazolo*[3,4-b]*pyridin-7-ide* **9b** was obtained in 25% yield, m.p. 288–290 °C (from EtOH) (Found: C, 63.5; H, 5.8; N, 19.7. $C_{19}H_{21}N_5O_2 \cdot \frac{1}{2}H_2O$ requires C, 63.5; H, 6.1; N, 19.5%); ν_{max}/cm^{-1} 3300, 3200, 2980–2300, 2200, 1650, 1600, 1540, 1500, 1450, 1370, 1290, 790 and 690; δ_H 1.50 (2 H, m, CH_2 piperidinium), 1.57 (4 H, m, 2 × CH_2 piperidinium), 2.31 (3 H, s, Me), 2.94 (4 H, m, 2 × CH_2 piperidinium), 7.0–7.4 (4 H, m, ArH), 10.00 (1 H, br s, NH) and 10.74 (1 H, br s, NH); δ_C 21.19 (C-γ, piperidinium), 21.84 (C-β, piperidinium), 22.40 (Me), 43.94 (C-α, piperidinium), 83.55, 93.62 (C-3a, -5), 120.23 (CN), 127.95 (2 C), 129.25 (2 C), 131.49, 138.29 (Ar), 147.63, 156.92 (C-4, -7a), 161.92 (CO) and 163.46 (CO); *m*/*z* (relative intensity) 266 (M^+, 100).

Methyl 2-benzyl-6-cyano-3,5-dihydro-7-(p*-methylphenyl*)*-5-oxo*[1,2,4]*triazolo*[1,5-a]*pyridine-8-carboxylate* **10b** was obtained in 60% yield, m.p. 249–250 °C (from MeCN) (Found: C, 69.35; H, 4.65; N, 13.9. $C_{23}H_{18}N_4O_3$ requires C, 69.35; H, 4.5; N, 14.05%); ν_{max}/cm^{-1} 3100, 2220, 1700, 1650, 1590, 1560, 1500, 1370, 1330, 1260, 740 and 700; δ_H 2.38 (3 H, s, Me), 3.48 (3 H, s, MeO), 4.34 (2 H, s, CH_2) and 7.1–7.4 (9 H, m, ArH); δ_C 21.14 (Me), 31.30 (CH_2), 51.78 (MeO), 90.50, 92.54 (C-6, -8), 116.77 (CN), 127.26 (2 C), 127.57 (2 C), 128.51, 129.13 (2 C), 129.15 (2 C), 134.66, 135.44, 137.93 (Ar), 147.01, 154.00, 155.37 (C-7, -8a, -2), 157.76 (CO) and 163.44 (CO).

Piperidinium 5-cyano-1,2,3,6-tetrahydro-4-(p*-methoxyphenyl*)*-3,6-dioxo-7*H*-pyrazolo*[3,4-b]*pyridin-7-ide* **9c** was obtained in 41% yield, m.p. 295–297 °C (from EtOH) (Found: C, 61.95; H, 5.85; N, 18.85. $C_{19}H_{21}N_5O_3$ requires C, 62.1; H, 5.7; N, 19.0%); ν_{max}/cm^{-1} 3300, 3100, 2970–2300, 2200, 1650, 1540, 1500, 1450, 1370, 1250, 780 and 700; δ_H 1.53 (2 H, m, CH_2 piperidinium), 1.58 (4 H, m, 2 × CH_2 piperidinium), 2.94 (4 H, m, CH_2 piperidinium), 3.81 (3 H, s, MeO), 6.95 (2 H, d, ArH), 7.48 (2 H, d, ArH), 10.15 (1 H, br s, NH) and 10.80 (1 H, br s, NH); δ_C

21.67 (C-γ, piperidinium), 22.23 (C-β, piperidinium), 43.73 (C-α, piperidinium), 55.15 (MeO), 83.51, 93.27 (C-3a, -5), 112.59 (2 C, Ar), 120.46 (CN), 126.19 (Ar), 130.87 (2 C, Ar), 147.51, 156.57 (C-4, -7a), 159.83 (Ar), 161.73 (CO) and 163.39 (CO).

Methyl 2-benzyl-6-cyano-3,5-dihydro-7-(p-methoxyphenyl)-5-oxo[1,2,4]triazolo[1,5-a]pyridine-8-carboxylate **10c** was obtained in 35% yield, m.p. 253–255 °C (from aq. MeCN) (Found: C, 66.85; H, 4.45; N, 13.55. $C_{23}H_{18}N_4O_4$ requires C, 66.65; H, 4.35; N, 13.55%); ν_{max}/cm^{-1} 3100, 2220, 1700, 1660, 1580, 1560, 1500, 1430, 1370, 1320, 1290, 1250, 750 and 700; δ_H 3.49 (3 H, s, MeO), 3.82 (3 H, s, MeO), 4.33 (2 H, s, CH_2), 7.01 (2 H, d, ArH), 7.19 (2 H, d, ArH) and 7.25–7.40 (5 H, m, ArH); δ_C 31.14 (CH_2), 51.70 (MeO), 55.09 (MeO), 90.20, 92.20 (C-6, -8), 113.22 (2 C, Ar), 116.72 (CN), 127.04 (2 C), 128.56 (2 C), 128.94 (2 C), 129.90, 135.24, 139.86 (Ar), 146.96, 154.01, 155.30 (C-7, -8a, -2), 159.50, 159.60 (Ar, CO) and 163.58 (CO).

Piperidinium 4-(p-chlorophenyl)-5-cyano-1,2,3,6-tetrahydro-3,6-dioxo-7H-pyrazolo[3,4-b]pyridin-7-ide **9d** was obtained in 40% yield, m.p. 343–345 °C (from EtOH) (Found: C, 57.95; H, 5.05; N, 18.95. $C_{18}H_{18}ClN_5O_2$ requires C, 58.15; H, 4.85; N, 18.85%); ν_{max}/cm^{-1} 3300, 3100, 2980–2300, 2200, 1650, 1600, 1530, 1500, 1450, 1360, 1290, 780 and 680; δ_H 1.55 (2 H, m, CH_2 piperidinium), 1.60 (4 H, m, 2 × CH_2 piperidinium), 2.97 (4 H, m, 2 × CH_2 piperidinium), 7.48 (4 H, q, ArH), 10.10 (1 H, br s, NH) and 10.83 (1 H, br s, NH); δ_C 21.68 (C-γ, piperidinium), 22.26 (C-β, piperidinium), 43.77 (C-α, piperidinium), 83.29, 93.59 (C-3a, -5), 120.00 (CN), 127.40 (2 C, Ar), 130.99 (2 C, Ar), 132.98 (Ar), 133.48 (Ar), 147.36, 155.15 (C-4, -7a), 161.61 (CO) and 163.14 (CO).

Methyl 2-benzyl-7-(p-chlorophenyl)-6-cyano-3,5-dihydro-5-oxo[1,2,4]triazolo[1,5-a]pyridine-8-carboxylate **10d** was obtained in 35% yield, m.p. 284–286 °C (from EtOH) (Found: C, 63.15; H, 3.6; N, 13.25. $C_{22}H_{15}ClN_4O_3$ requires C, 63.1; H, 3.6; N, 13.4%); ν_{max}/cm^{-1} 3100, 2970, 2200, 1700, 1660, 1590, 1500, 1450, 1400, 1370, 1340, 1270, 800 and 700; δ_H 3.51 (3 H, s, MeO), 4.37 (2 H, s, CH_2), 7.25–7.40 (7 H, m, ArH) and 7.45 (2 H, m, ArH); δ_C 31.10 (CH_2), 51.65 (MeO), 90.20, 92.30 (C-6, -8), 116.20 (CN), 127.05, 127.95 (2 C), 128.56 (2 C), 128.90 (2 C), 129.31 (2 C), 133.16, 135.10, 136.40 (Ar), 147.00, 154.00, 155.50 (C-7, -8a, -2), 156.00 (CO) and 163.00 (CO).

Methyl 2-benzyl-6-cyano-3,5-dihydro-7-(p-nitrophenyl)-5-oxo[1,2,4]triazolo[1,5-a]pyridine-8-carboxylate **10e** was obtained in 56% yield, m.p. 272–274 °C (from EtOH or MeCN) (Found: C, 61.25; H, 3.6; N, 16.1. $C_{22}H_{15}N_5O_5$ requires C, 61.5; H, 3.5; N, 16.3%); ν_{max}/cm^{-1} 3300, 2220, 1710, 1680, 1590, 1530, 1490, 1440, 1350, 1290, 1250, 790 and 700; δ_H 3.50 (3 H, s, MeO), 4.37 (2 H, s, CH_2) and 7.25–7.65 (9 H, m, ArH).

Ethyl 2-benzyl-6-cyano-3,5-dihydro-5-oxo-7-phenyl[1,2,4]triazolo[1,5-a]pyridine-8-carboxylate **10f** was obtained in 48% yield from the corresponding ethyl arylidenecyanoacetate **6f**, m.p. 262–264 °C (from EtOH or Me_2SO) (Found: C, 69.1; H, 4.55; N, 14.05. $C_{23}H_{18}N_4O_3$ requires C, 69.35; H, 4.5; N, 14.05%); ν_{max}/cm^{-1} 3130, 2990, 2220, 1700, 1660, 1580, 1490, 1420, 1370, 1240, 790 and 710; δ_H 0.67 (3 H, t, Me), 3.88 (2 H, q, CH_2O), 4.34 (2 H, s, CH_2) and 7.22–7.50 (10 H, m, ArH); δ_C 13.07 (Me), 31.07 (CH_2), 60.13 (CH_2O), 90.32, 92.60 (C-6, -8), 116.48 (CN), 127.08, 127.35 (2 C), 127.80 (2 C), 128.30, 128.50 (2 C), 128.96 (2 C), 135.24, 137.78 (Ar), 146.92, 153.92, 155.28 (C-7, -8a, -2), 157.17 (CO) and 163.40 (CO).

Compound **9a** was isolated as the first product from this reaction, in 36% yield.

Ethyl 2-benzyl-6-cyano-3,5-dihydro-7-(p-methylphenyl)-5-oxo[1,2,4]triazolo[1,5-a]pyridine-8-carboxylate **10g** was obtained in 35% yield from the corresponding ethyl arylidenecyanoacetate **6g**, m.p. 267–269 °C (from EtOH) (Found: C, 69.8; H, 4.85; N, 13.65. $C_{24}H_{20}N_4O_3$ requires C, 69.9; H, 4.85; N, 13.6%); ν_{max}/cm^{-1} 3210, 2980, 2220, 1710, 1670, 1590, 1490, 1410, 1370, 1320, 1240, 710 and 650; δ_H 0.67 (3 H, t, Me), 2.35 (3 H, s, Me), 3.85 (2 H, q, CH_2O), 4.29 (2 H, s, CH_2), 7.13 (2 H, d, ArH), 7.23 (2 H, d, ArH) and 7.33 (5 H, m, ArH).

Compound **9b** was isolated from the reaction product in 35% yield.

Ethyl 2-benzyl-6-cyano-3,5-dihydro-7-(p-methoxyphenyl)-5-oxo[1,2,4]triazolo[1,5-a]pyridine-8-carboxylate **10h** was obtained in 34% yield from the corresponding ethyl arylidenecyanoacetate **6h**, m.p. 268–269 °C (from EtOH or Me_2SO) (Found: C, 67.1; H, 4.75; N, 13.1. $C_{24}H_{20}N_4O_4$ requires C, 67.3; H, 4.65; N, 13.1%); ν_{max}/cm^{-1} 3100, 2220, 1700, 1660, 1590, 1560, 1500, 1430, 1370, 1320, 1260, 790 and 700; δ_H 0.71 (3 H, t, Me), 3.78 (3 H, s, MeO), 3.87 (2 H, q, CH_2O), 4.29 (2 H, s, CH_2), 6.98 (2 H, d, ArH), 7.18 (2 H, d, ArH) and 7.33 (5 H, m, ArH); δ_C 13.32 (Me), 31.10 (CH_2), 55.27 (MeO), 60.23 (CH_2O), 90.49, 92.82 (C-6, -8), 113.27 (2 C), 116.80 (CN), 127.13, 128.64 (2 C), 129.02 (4 C), 129.78, 135.31 (Ar), 146.94, 154.03, 155.24 (C-7, -8a, -2), 157.15 (CO), 159.56 (Ar) and 163.63 (CO).

Compound **9c** was also obtained, in 45% yield.

Ethyl 2-benzyl-7-(p-chlorophenyl)-6-cyano-3,5-dihydro-5-oxo[1,2,4]triazolo[1,5-a]pyridine-8-carboxylate **10i** was obtained in 56% yield from the corresponding ethyl arylidenecyanoacetate **6i**, m.p. 287–289 °C (from MeCN) (Found: C, 63.65; H, 3.95; N, 12.9. $C_{23}H_{17}ClN_4O_3$ requires C, 63.8; H, 3.95; N, 12.95%); ν_{max}/cm^{-1} 3220, 2220, 1710, 1680, 1590, 1490, 1420, 1400, 1370, 780 and 710; δ_H 0.74 (3 H, t, Me), 3.91 (2 H, q, CH_2O), 4.34 (2 H, s, CH_2), 7.25–7.40 (7 H, m, ArH) and 7.55 (2 H, d, ArH).

Compound **9d** was isolated from this reaction in 11% yield.

Ethyl 2-benzyl-6-cyano-3,5-dihydro-7-(p-nitrophenyl)-5-oxo-[1,2,4]triazolo[1,5-a]pyridine-8-carboxylate **10j** was obtained as the sole product in 69% yield, m.p. 299–301 °C (from EtOH) (Found: C, 62.2; H, 3.6; N, 15.85. $C_{23}H_{17}N_5O_5$ requires C, 62.3; H, 3.85; N, 15.8%); ν_{max}/cm^{-1} 3300, 2220, 1710, 1680, 1590, 1530, 1490, 1400, 1370, 1290, 790 and 700; δ_H 0.65 (3 H, t, Me), 3.86 (2 H, q, CH_2O), 4.32 (2 H, s, CH_2), 7.35 (5 H, m, ArH), 7.56 (2 H, d, ArH) and 8.32 (2 H, d, ArH); δ_C 13.11 (Me), 31.16 (CH_2), 60.43 (CH_2O), 89.40, 92.20 (C-6, -8), 116.25 (CN), 121.85, 123.14 (2 C), 127.09, 128.60 (2 C), 128.96 (2 C), 129.10 (2 C), 135.29, 144.80 (Ar), 147.39, 153.81, 154.79 (C-7, -8a, -2), 155.76 (CO) and 162.76 (CO).

2,3,6,7-Tetrahydro-4-(p-methoxyphenyl)-3,6-dioxo-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile **11c**.—To a solution of the piperidinium salt **9c** (0.1 g, 0.25 mmol) in ethanol (~20 cm^3) was added 10% aq. HCl (20 cm^3). The reaction mixture was stirred for 10 min and then left at room temperature overnight. The ethanol was removed under reduced pressure, and a solid precipitated out. This was collected by filtration and was recrystallized from methanol to give the *title nitrile* (65%), m.p. 309–311 °C (Found: C, 57.35; H, 4.1; N, 18.8. $C_{14}H_{10}N_4O_3 \cdot \frac{1}{2}H_2O$ requires C, 57.7; H, 3.8; N, 19.25%); ν_{max}/cm^{-1} 3200–2300, 2220, 1650, 1600, 1550, 1520, 1480, 1420, 1360, 1270, 1210, 1180, 780 and 700; δ_H 3.83 (3 H, s, MeO), 7.05 (2 H, d, ArH) and 7.52 (2 H, d, ArH); δ_C 55.53 (MeO), 93.27 (C-3a or -5), 113.48 (2 C, Ar), 115.83 (C-5 or -3a), 117.51 (CN), 125.13 (Ar), 131.11 (2 C, Ar), 146.72, 156.22 (C-4, -7a), 156.84 (CO), 160.92 (Ar) and 162.09 (CO).

6-Amino-1,2,3,4-tetrahydro-2-oxo-4-phenyl-1-(phenylacetamido)pyridine-3,5-dicarbonitrile **12a**.—2-Cyano-2′-phenylacetylacetohydrazide **5** (0.81 g, 4 mmol) and benzylidenemalononitrile **3a** (1.08 g, 7 mmol) were suspended in dry ethanol (10 cm^3). The mixture was refluxed for 30 h until TLC showed the absence of starting material. The precipitate that separated out was filtered off and washed with ethanol to obtain a solid (0.5 g). From the concentrated mother liquors, a second crop was obtained (0.1 g). Recrystallization from ethanol yielded *compound* **12a** (46%), m.p. 241–243 °C (Found: C, 67.65; H, 4.65; N, 18.95.

$C_{21}H_{17}N_5O_2$ requires C, 67.95; H, 4.6; N, 18.85%); ν_{max}/cm^{-1} 3440, 3300, 3200, 3020, 2260, 2200, 1730, 1700, 1640, 1600, 1540, 1500, 1450, 1250 and 1200; δ_H(diastereoisomeric mixture) 3.64 and 3.36 (2 H, s, CH_2), 4.06 (1 H, m, CH), 5.36 (1 H, m, CH), 7.0–7.6 (10 H, m, ArH), 8.9 (1 H, br s, NH) and 10.7 (2 H, br s, NH_2).

Piperidinium 7-Aryl-2-benzyl-6,8-dicyano-3,5-dihydro-5-oxo-[1,2,4]triazolo[1,5-a]pyridin-3-ides **13**: *General Procedure.*—A mixture of equimolar amounts of 2-cyano-2′-phenylacetylacetohydrazide **5** (2 mmol) and the corresponding arylidenemalononitrile **3** (2 mmol) was suspended in dry ethanol (~15 cm^3). Piperidine (2 mmol) was added and the reaction mixture was refluxed for a variable time (3–7 h) until TLC showed the absence of starting material. The resulting solution was concentrated to half its volume and left in a refrigerator overnight. The solid that precipitated out was collected by filtration and recrystallized from a suitable solvent.

Piperidinium 2-benzyl-6,8-dicyano-3,5-dihydro-5-oxo-7-phenyl[1,2,4]triazolo[1,5-a]pyridin-3-ide **13a** was obtained in 88% yield, m.p. 204–206 °C (from EtOH) (Found: C, 71.7; H, 5.6; N, 19.0. $C_{26}H_{24}N_6O$ requires C, 71.5; H, 5.5; N, 19.25%); ν_{max}/cm^{-1} 3100–2400, 2200, 1640, 1550, 1520, 1420, 1390, 1250, 750, 720 and 690; δ_H 1.61 (2 H, m, CH_2 piperidinium), 1.63 (4 H, m, 2 × CH_2 piperidinium), 3.00 (4 H, m, 2 × CH_2 piperidinium), 4.08 (2 H, s, CH_2), 7.2–7.55 (10 H, m, ArH) and 8.2 (2 H, br s, NH_2); δ_C 21.59 (C-γ, piperidinium), 22.22 (C-β, piperidinium), 34.42 (CH_2), 43.78 (C-α, piperidinium), 77.07, 82.77 (C-6, -8), 116.97 (CN), 118.37 (CN), 126.29 (2 C), 128.30 (2 C), 128.32 (2 C), 128.54, 128.82 (2 C), 129.28, 135.99, 138.08 (Ar), 153.19, 154.64, 156.26 (C-7, -8a, -2) and 164.42 (CO).

Piperidinium 2-benzyl-6,8-dicyano-3,5-dihydro-7-(p-methylphenyl)-5-oxo[1,2,4]triazolo[1,5-a]pyridin-3-ide **13b** was obtained in 73% yield, m.p. 264–266 °C (from EtOH) (Found: C, 71.85; H, 5.95; N, 18.5. $C_{27}H_{26}N_6O$ requires C, 72.0; H, 5.80; N, 18.7%); ν_{max}/cm^{-1} 3100–2400, 2200, 1650, 1550, 1500, 1450, 1420, 1380, 1250, 740, 720 and 690; δ_H 1.50 (2 H, m, CH_2 piperidinium), 1.62 (4 H, m, 2 × CH_2 piperidinium), 2.35 (3 H, s, Me), 2.95 (4 H, m, 2 × CH_2 piperidinium), 4.05 (2 H, s, CH_2), 7.05–7.30 (9 H, m, ArH) and 8.17 (2 H, br s, NH_2); δ_C 20.91 (Me), 21.60 (C-γ, piperidinium), 22.22 (C-β, piperidinium), 34.43 (CH_2), 43.78 (C-α, piperidinium), 77.09, 82.77 (C-6, -8), 117.08 (CN), 118.47 (CN), 126.29 (2 C), 126.50, 128.34 (2 C), 128.50 (2 C), 128.82 (2 C), 133.09, 138.10, 138.89 (Ar), 153.24, 154.71, 156.35 (C-7, -8a, -2) and 164.42 (CO).

Piperidinium 2-benzyl-6,8-dicyano-3,5-dihydro-7-(p-methoxyphenyl)-5-oxo[1,2,4]triazolo[1,5-a]pyridin-3-ide **13c** was obtained in 85% yield, m.p. 194–196 °C (from EtOH) (Found: C, 69.45; H, 5.75; N, 17.9. $C_{27}H_{26}N_6O_2$ requires C, 69.55; H, 5.6; N, 18.0%); ν_{max}/cm^{-1} 3100–2400, 2200, 1640, 1610, 1550, 1510, 1410, 1390, 1250, 770, 710 and 690; δ_H 1.53 (2 H, m, CH_2 piperidinium), 1.62 (4 H, m, 2 × CH_2 piperidinium), 3.01 (4 H, m, 2 × CH_2 piperidinium), 3.84 (3 H, s, MeO), 4.10 (2 H, s, CH_2), 7.08 (2 H, d, ArH), 7.2–7.35 (5 H, m, ArH) and 7.44 (2 H, d, ArH); δ_C 21.60 (C-γ, piperidinium), 22.22 (C-β, piperidinium), 34.42 (CH_2), 43.80 (C-α, piperidinium), 55.21 (MeO), 77.06, 82.81 (C-6, -8), 113.61 (2 C, Ar), 117.20 (CN), 118.59 (CN), 126.00, 128.00 (2 C), 128.31 (2 C), 128.80, 130.00, 138.10 (2 C and Ar), 153.00, 154.44, 156.35 (C-7, -8a, -3), 159.98 (Ar) and 164.36 (CO).

Piperidinium 2-benzyl-7-(p-chlorophenyl)-6,8-dicyano-3,5-dihydro-5-oxo[1,2,4]triazolo[1,5-a]pyridin-3-ide **13d** was obtained in 60% yield, m.p. 195–197 °C (from EtOH) (Found: C, 66.15; H, 5.0; N, 17.7. $C_{26}H_{23}ClN_6O$ requires C, 66.3; H, 4.9; N, 17.85%); ν_{max}/cm^{-1} 3100–2400, 2200, 1640, 1600, 1550, 1520, 1420, 1390, 1250, 770, 700 and 690; δ_H 1.54 (2 H, m, CH_2 piperidinium), 1.62 (4 H, m, 2 × CH_2 piperidinium), 3.01 (4 H, m, 2 × CH_2 piperidinium), 4.05 (2 H, s, CH_2), 7.2–7.4 (5 H, m, ArH), 7.6 (4 H, dd, ArH) and 8.2 (2 H, br s, NH_2); δ_C 21.59 (C-γ, piperidinium), 22.20 (C-β, piperidinium), 34.42 (CH_2), 43.78 (C-α, piperidinium), 77.17, 82.72 (C-6, -8), 116.83 (CN), 118.27 (CN), 126.31, 128.34 (2 C), 128.47 (2 C), 128.82 (2 C), 130.51 (2 C), 134.18, 134.84, 138.03 (Ar), 153.07, 153.37, 156.16 (C-7, -8a, -2) and 164.51 (CO).

7-Aryl-2-benzyl-3,5-dihydro-5-oxo[1,2,4]triazolo-[1,5-a]pyridine-6,8-dicarbonitriles **14**: *General Procedure.*—To a solution of the appropriate piperidinium salt **13** (0.2 mmol) in ethanol (~10–20 cm^3) was added 10% aq. HCl (15–20 cm^3). The reaction mixture was stirred for 10 min and then left at room temperature overnight. The neutral compound **14** had precipitated out, and was collected by filtration and washed with plenty of water (neutral pH). Further purification was accomplished by recrystallization from the appropriate mixture of solvents.

2-Benzyl-3,5-dihydro-5-oxo-7-phenyl[1,2,4]triazolo[1,5-a]pyridine-6,8-dicarbonitrile **14a** was obtained in 70% yield, m.p. 282–284 °C (from aq. MeCN) (Found: C, 71.6; H, 3.6; N, 19.85. $C_{21}H_{13}N_5O$ requires C, 71.8; H, 3.7; N, 19.95%); ν_{max}/cm^{-1} 3100–2300, 2220, 1660, 1570, 1500, 1390, 1220, 750, 730 and 700; δ_H 4.19 (2 H, s, CH_2) and 7.2–7.6 (10 H, m, ArH); δ_C 33.37 (CH_2), 75.75, 85.74 (C-6, -8), 116.25, 117.76 (2 × CN), 126.97 (Ar), 128.72 (2 C), 128.75 (2 C), 129.15 (4 C), 130.02, 135.54, 136.91 (Ar), 151.25, 155.54, 156.39 (C-7, -8a, -2) and 160.85 (CO).

2-Benzyl-3,5-dihydro-7-(p-methylphenyl)-5-oxo[1,2,4]triazolo[1,5-a]pyridine-6,8-dicarbonitrile **14b** was obtained in 80% yield, m.p. 316–318 °C (from aq. MeCN) (Found: C, 72.25; H, 4.1; N, 19.3. $C_{22}H_{15}N_5O$ requires C, 72.35; H, 4.1; N, 19.2%); ν_{max}/cm^{-1} 3100–2500, 2220, 1650, 1570, 1500, 1440, 1380, 1270, 1220, 770, 730 and 690; δ_H 2.40 (3 H, s, Me), 4.18 (2 H, s, CH_2) and 7.2–7.45 (9 H, m, ArH).

2-Benzyl-3,5-dihydro-7-(p-methoxyphenyl)-5-oxo[1,2,4]triazolo[1,5-a]pyridine-6,8-dicarbonitrile **14c** was obtained in 65% yield, m.p. 248–250 °C (from aq. MeCN) (Found: C, 69.15; H, 4.00; N, 18.05. $C_{22}H_{15}N_5O_2$ requires C, 69.3; H, 3.95; N, 18.35%); ν_{max}/cm^{-1} 3100–2400, 2220, 1660, 1610, 1520, 1450, 1390, 1260, 770 and 730; δ_H 3.84 (3 H, s, MeO), 4.17 (2 H, s, CH_2) and 7.0–7.5 (9 H, m, ArH).

2-Benzyl-7-(p-chlorophenyl)-3,5-dihydro-5-oxo[1,2,4]triazolo[1,5-a]pyridine-6,8-dicarbonitrile **14d** was obtained in 70% yield, m.p. 258–260 °C (from aq. MeCN) (Found: C, 65.15; H, 3.25; N, 17.9. $C_{21}H_{12}ClN_5O$ requires C, 65.35; H, 3.1; N, 18.15%); ν_{max}/cm^{-1} 3100–2500, 2220, 1680, 1650, 1610, 1570, 1500, 1390, 1270, 770, 730 and 700; δ_H 4.15 (2 H, s, CH_2), 7.2–7.35 (5 H, m, ArH), 7.54 (2 H, d, ArH) and 7.63 (2 H, d, ArH).

Piperidinium Salt of Alkyl 3-(5-Amino-2,3-dihydro-3-oxo-1-phenylacetylpyrazol-4-yl)-2-cyano-3-phenylpropionates **15**. *General Procedure.*—These compounds were prepared by following the same experimental procedure as described for compounds **9** (see above), but by carrying out the reaction at room temperature.

Piperidinium salt of methyl 3-(5-amino-2,3-dihydro-3-oxo-1-phenylacetylpyrazol-4-yl)-2-cyano-3-phenylpropionate **15a** was obtained in 62% yield, m.p. 158–160 °C (from EtOH) (Found: C, 66.2; H, 6.3; N, 14.15. $C_{27}H_{31}N_5O_4$ requires C, 66.25; H, 6.35; N, 14.3%); ν_{max}/cm^{-1} 3460, 3260, 3000–2300, 2160, 1690, 1660, 1610, 1570, 1490, 1370 and 1280; δ_H 1.49 (6 H, m, 3 × CH_2 piperidine), 2.79 (4 H, m, 2 × CH_2 piperidine), 3.42 (3 H, s, MeO), 3.62 (2 H, s, CH_2), 4.19 (1 H, s, CH), 6.0 (2 H, br s, NH_2) and 7.0–7.4 (11 H, ArH, NH); δ_C 22.33 (C-γ, piperidinium), 23.02 (C-β, piperidinium), 40.75 (*C*H_2Ph), 44.31 (C-α, piperidinium), 49.84 (*C*CN), 51.02 (OMe), 75.93 (*C*HPh), 125.96, 126.63 (2 C), 127.06, 127.61 (2 C), 128.04 (2 C), 128.71, 129.51 (2 C), 135.38 (Ar), 148.51, 155.13 (C-4, -5) and 160.78, 166.57, 171.16 (C × CO).

Piperidinium salt of ethyl 3-(5-*amino*-2,3-*dihydro*-3-*oxo*-1-*phenylacetylpyrazol*-4-*yl*)-2-*cyano*-3-*phenylpropionate* **15b** was obtained in 63% yield, m.p. 151–153 °C (from EtOH) (Found: C, 66.45; H, 6.4; N, 13.8. $C_{28}H_{33}N_5O_4$ requires C, 66.8; H, 6.55; N, 13.9%); ν_{max}/cm^{-1} 3460, 3260, 3000–2300, 2160, 1690, 1660, 1610, 1570, 1490 and 1450; δ_H 1.03 (3 H, t, Me), 1.48 (6 H, m, 3 × CH_2 piperidine), 2.79 (4 H, m, 2 × CH_2 piperidine), 3.62 (2 H, s, CH_2), 3.87 (2 H, q, CH_2O), 4.19 (1 H, s, CH), 6.5 (2 H, br s, NH_2) and 7.0–7.4 (11 H, m, ArH, NH); δ_C 14.61 (Me), 22.51 (C-γ, piperidinium), 23.19 (C-β, piperidinium), 40.53 (*C*H_2Ph), 44.64 (C-α, piperidinium), 51.60 (*C*CN), 58.01 (CH_2O), 76.05 (*C*HPh), 125.42, 126.55, 127.65, 128.25 (4 C), 129.73 (4 C), 135.64 (Ar), 149.0, 155.1 (C-4, -5) and 160.96, 168.48, 171.41 (3 × CO).

Methyl 3-(5-*amino*-2,3-*dihydro*-3-*oxo*-1-*phenylacetylpyrazol*-4-*yl*)-2-*cyano*-3-*phenylpropionate* **16** was obtained, in 75% yield, by following the general procedure for the liberation from the corresponding salt **15a**; m.p. 214–215 °C (from aq. MeOH) (Found: C, 65.4; H, 5.1; N, 13.75. $C_{22}H_{20}N_4O_4$ requires C, 65.35; H, 4.95; N, 13.85%); ν_{max}/cm^{-1} 3400, 3340, 3280, 2260, 1740, 1720, 1690, 1630, 1530, 1450 and 1370; δ_H (major isomer of the diastereoisomeric mixture) 3.50 (3 H, s, MeO), 3.69 (2 H, s, *C*H_2Ph), 4.33 (1 H, m, CH), 5.29 (1 H, m, CH), 7.2–7.6 (10 H, m, ArH), 8.0 (2 H, br s, NH_2) and 10.72 (1 H, s, NH); δ_C (major isomer) 41.49 (*C*H_2Ph), 50.60 (MeO), 76.60, 77.19 (*C*HPh, *C*HCN), 115.22 (CN), 126.60, 127.54, 128.21 (4 C), 128.55, 129.36 (2 C), 129.45 (2 C, 134.76 (Ar), 139.86, 153.32 (C-4, -5) and 160.93, 167.93, 170.92 (3 × CO).

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