N-Amino-2-pyridones from Acetohydrazide Derivatives

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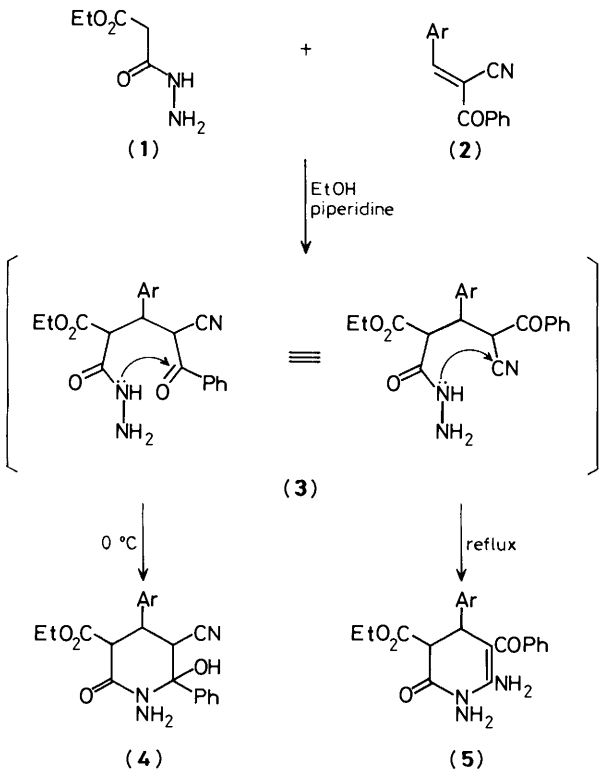
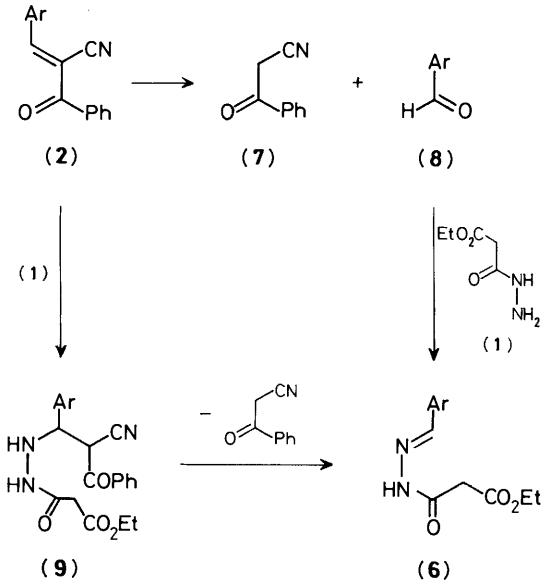
The synthesis of a variety of *N*-amino-2-pyridones from ethoxycarbonyl acetohydrazide (**1**) is described. α-Benzoylcinnamonitriles (**2**) react with (**1**), in two different ways, giving rise to two kinds of *N*-aminopyridones (**4**) and (**5**) depending upon the cyclization taking place at the carbonyl or cyano group. Reaction of (**1**) with ethyl α-cyanocinnamates (**10**) involves cyclization at the cyano group affording the diaminopyridones (**11**). In contrast, ethyl malonamate (**18**) reacts with (**10**) at the ester group, leading to piperidinediones (**20**). Aromatic rings obtained by oxidation of some of the above compounds are also reported.

A modification of the Guareschi synthesis involving conjugate addition by malonamide or malonamide derivatives to unsaturated carbonyl compounds was earlier reported in this journal and a general synthesis of pyridones resulted.[1] Further, we reported[2-4] the preparation of *N*-aminopyridone derivatives from cyanoacetohydrazide, prompted by the usefulness of these heterocycles as reagents for the interconversion of functional groups, as a result of the ability of the heterocyclic ring to act as a good leaving group from its *N*-derivatives.[5]

However, the above synthesis of *N*-aminopyridones involves a cyclization taking place at a cyano group, which undergoes nucleophilic attack by the hydrazide. Thus, position 6 of the resulting heterocycles necessarily bears a second, undesirable, amino group. If the attack could take place at a carbonyl group, the cyclization would yield an unfunctionalized position 6. Such a reaction would be that of an acetohydrazide derivative with unsaturated carbonyl compounds.



Scheme 1. Ar = **a**, C_6H_5; **b**, *p*-$MeOC_6H_4$; **c**, *p*-ClC_6H_4; **d**, *p*-MeC_6H_4; **e**, *m*-$NO_2C_6H_4$



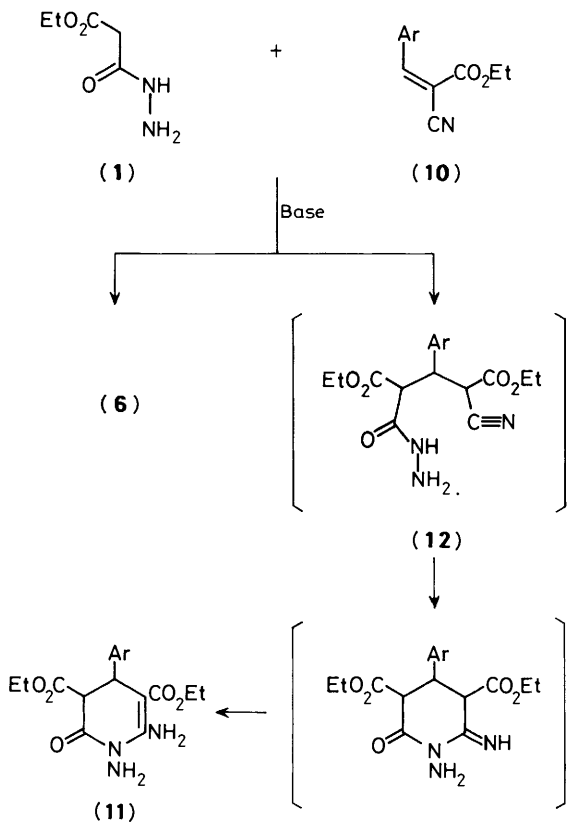
Scheme 2. Ar = C_6H_4R

Thus, ethoxycarbonylacetohydrazide (**1**) was treated with α-benzoylcinnamonitriles (**2**) (Scheme 1). Unlike the previous syntheses, the reaction presents now two possible cyclizations, either at the carbonyl group or at the cyano group, as shown in the two conformations of the cyclization intermediate depicted in Scheme 1. We found that both cyclizations are real possibilities. In fact, either of the alternative cyclization routes can be selected depending upon the reaction conditions.

At low temperature (0 °C) in ethanol, the cyclization of the open-chain intermediate (**3**) follows the first route and involves regioselective attack at the carbonyl group, leading to a saturated 6-hydroxy-1-aminopyridone ring (**4**). In contrast, at reflux temperature cyclization is directed, with the same total regioselectivity, at the cyano group. Diamino derivatives (**5**) are thus generated. Hydroxypiperidones (**4**) are formed together with a variable amount of the hydrazone (**6**) as a by-product. This hydrazone is formally derived from the hydrazide (**1**) and the aromatic aldehyde (**8**) formed by retro-Knoevenagel cleavage of the substrate (**2**) (Scheme 2).

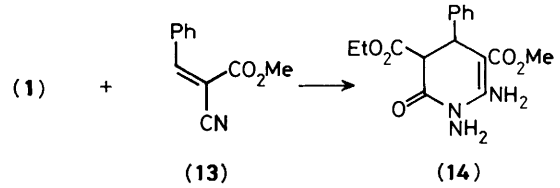
However, the fact that this side-reaction also takes place in dry ethanol suggests an alternative route to (**6**). It involves a 1,4-attack by the primary amino group of the hydrazide (**1**) to (**2**), leading to an intermediate addition compound (**9**). A retro-Michael *elimination* of ω-cyanoacetophenone (**7**) yields the hydrazone (**6**).

Formation of hydrazones (**6**) as by-products can also take place when the reaction of (**1**) and (**2**) is carried out at reflux temperature to give diaminopyridones (**5**). In fact, chromatographic examination of the reaction mixture shows that immediately after mixing of the reactants, the hydrazone (**6**) and the benzoylacetonitrile (**7**) are formed as the only compounds. Therefore, the diaminopyridones (**5**) seem to result from the evolution of (**6**) and (**7**), suggesting the reversibility of their formation. The same hydrazones (**6**) are also observed as by-products in the reaction depicted in Scheme 3, which allowed the preparation of diethoxycarbonyl substituted *N*-aminopyridones (**11**). Thus, when ethoxycarbonylacetohydrazide (**1**) is treated with ethyl α-cyanocinnamates (**10**), the initial Michael addition is followed again by nucleophilic attack by the NH group to give the six-membered ring (Scheme 3). Although this attack could take place at either the cyano or at the ester group in the open-chain intermediate (**12**), only attack at the cyano group was observed. 1,6-Diaminopyridones (**11**) formed through an imino-enamino tautomerization, are thus obtained as the reaction product, and are isolated as 3,4-dihydro derivatives.



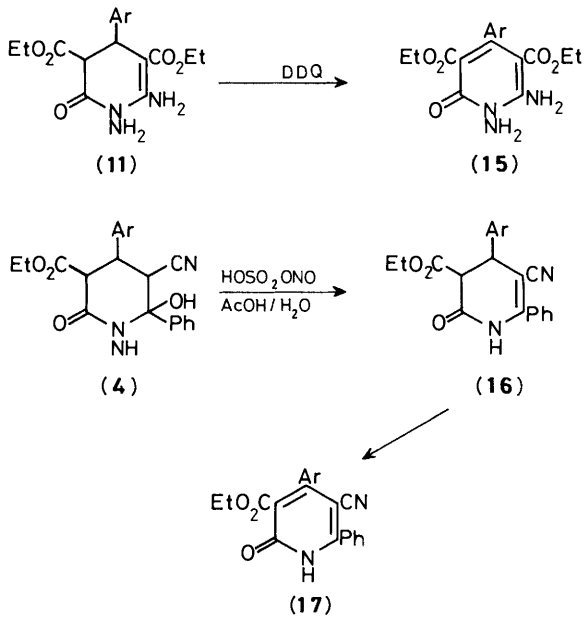
Scheme 3. Ar = **a**, C_6H_5; **b**, *p*-$MeOC_6H_4$; **c**, *p*-ClC_6H_4; **d**, *p*-MeC_6H_4; **e**, *m*-$NO_2C_6H_4$; **f**, *p*-$NO_2C_6H_4$; **g**, 2,6-$Cl_2C_6H_4$

Identification of the two amino groups in compounds (**11**) in the ^1H n.m.r. spectra results from their different chemical shifts, around δ 5.1 ($N-NH_2$, disappears with TFA) and δ 7.7 ($C-NH_2$) in agreement with the behaviour and chemical shifts of related *N*-amino heterocycles.[4] On the other hand, distinction of the two ester groups located at positions 3 and 5 in (**11**), required the preparation of *N*-aminopyridone (**14**) (Scheme 4). In it, a methoxycarbonyl group has been substituted for the ethoxycarbonyl group by using methyl benzylidenecyanoacetate (**13**) as the starting material. The ^1H n.m.r. spectrum of this compound (**14**) indicates that the ethoxycarbonyl group located at position 3 in compounds (**11**) is the one with the higher chemical shift for the methyl and methylene group (see Experimental section).



Scheme 4.

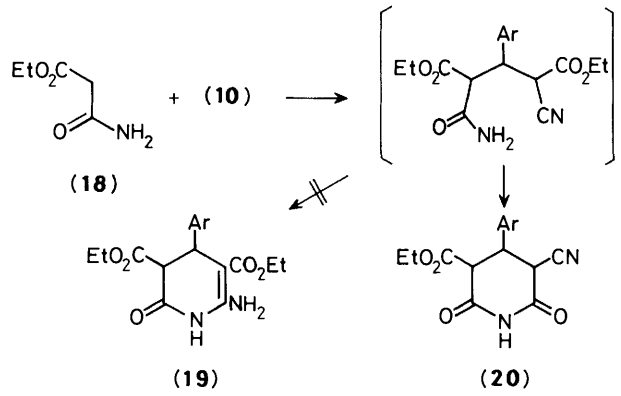
Finally, the partially unsaturated rings described above were oxidized to the aromatic systems. Thus, diethoxycarbonyl derivatives (**11**) (Scheme 5) are transformed into aromatic *N*-aminopyridones (**15**) by oxidation with DDQ.



Scheme 5.

As for hydroxy substituted pyridones (**4**), formation of the aromatic ring involves dehydration and aromatization. This could be achieved using nitrosylsulphuric acid which gives an acid and oxidative character to the reaction medium. Depending upon the reaction time, nitrosulphuric acid in acetic acid solution affords either dihydropyridone (**16**) or aromatic pyridones (**17**). In both cases, the *N*-amino group has been lost because of the nitrosating ability of the nitrosylsulphuric acid. Other examples of this kind of *N*-deamination are known.[6] The difficulties of aromatization of some of these compounds are increased in compounds (**5**). Attempts at aromatization resulted in extensive decomposition.

An *N*-deaminated pyridone ring (**19**) should be obtained by reaction of ethyl malonamate (**18**) with ethyl α-cyanocinnamate (**10**). We found, however, that the cyclization following Michael addition takes place through attack by the amide at the ethoxycarbonyl group. Piperidinedione (**20**) is the resulting ring (Scheme 6).



Scheme 6. Ar = p-MeC_6H_4

Experimental

M.p.s were determined in capillary tubes in a Büchi 510 apparatus and are uncorrected. The ^1H n.m.r. spectra were recorded at 60 MHz, unless otherwise stated, on a Varian T-60A instrument and chemical shifts are given in δ values against $SiMe_4$ as the internal standard. A Brucker WM 400 machine was used for the recording of ^{13}C n.m.r. spectra. All n.m.r. spectra were recorded in $(CD_3)_2SO$ solution. I.r. spectra were measured with a Perkin-Elmer 257 instrument as KBr pellets. Mass spectra were obtained in a Varian MAT 711 machine. Microanalyses were performed by C.S.I.C. of Madrid and Barcelona and the University of Tübingen. The reactions and purity of compounds were monitored by t.l.c., performed on silica gel plates (Merck 60-F) and using toluene–ethyl acetate as the eluant.

Cyanoacetohydrazide, ethyl malonate, and aromatic aldehydes were obtained from commercial sources and were used without further purification. Benzoylacetonitrile,[7] ethoxycarbonylacetohydrazide,[8] α-benzoylcinnamonitriles,[9] and ethyl benzyldenecyanoacetates[10] were prepared according to previously reported procedures. Ethyl malonamate was prepared following the method reported by Rising[11] from imidomalonic ester hydrochloride.

Ethyl 1-Amino-4,6-diaryl-5-cyano-6-hydroxy-2-oxopiperidine-3-carboxylates (**4**): *General Procedure.*—Ethoxycarbonylacetohydrazide (**1**) (6 mmol) and the appropriate α-benzoylcinnamonitrile (**2**) (12 mmol) were dissolved in 96% ethanol (*ca.* 40 ml)* in an ice-bath and a few drops of piperidine were added. The solution was stirred at 0 °C for 8—10 h. The solid that precipitated, (**4**), was collected by filtration. From the mother liquors, kept at low temperature, further crops of product were obtained. However, in some instances, these crops also contained a second compound identified as the hydrazones (**6**). Both compounds were purified by crystallization in ethanol.

Ethyl 1-amino-5-cyano-6-hydroxy-2-oxo-4,6-diphenylpiperidine-3-carboxylate (**4a**). This compound was obtained in 36% yield by following the above general procedure; m.p. 154—156 °C (from ethanol) (Found: C, 66.45; H, 5.35; N, 11.10. $C_{21}H_{21}N_3O_4$ requires C, 66.48; H, 5.58; N, 11.07%); $\nu_{max.}$ 3 400, 3 320, 3 280, 2 980, 2 250, 1 735, 1 645, 1 600, 1 500, and 1 450 cm^{-1}; δ_H 0.93 (t, 3 H, CH_3), 3.93—4.17 (m, 5 H, CH_2, 3-CH), 4.33 (br s, 2 H, NH_2), and 7.3—7.5 (m, 11 H, ArH, OH); *m/z* (relative intensities) 379 (M^+, 30), 306 (9), 279 (3), 233 (34), 105 (100), 101 (10), 100 (13), and 77 (55).

Ethyl 1-amino-5-cyano-6-hydroxy-4-(p-methoxyphenyl)-2-oxo-6-phenylpiperidine-3-carboxylate (**4b**). Obtained in 40% yield, m.p. 147—149 °C (from ethanol) (Found: C, 64.35; H, 5.85; N, 10.3. $C_{22}H_{23}N_3O_5$ requires C, 64.55; H, 5.62; N, 10.27%); $\nu_{max.}$ 3 410, 3 320, 3 280, 2 990, 2 810, 2 240, 1 730, 1 640, 1 600, 1 510, and 1 380 cm^{-1}; δ_H 0.93 (t, 3 H, CH_3), 3.66 (s, 3 H, OCH_3), 3.8—4.2 (m, 5 H, CH_2, 3-CH), 4.3 (br s, 2 H, NH_2), and 6.7—7.5 (m, 10 H, ArH, OH). From the mother liquors,† the hydrazone (**6b**) was isolated in 31% yield; m.p. 118—120 °C (from ethanol) (Found: C, 59.05; H, 6.3; N, 10.7. $C_{13}H_{16}N_2O_4$ requires C, 59.09; H, 6.06; N, 10.60); $\nu_{max.}$ 3 200, 3 080, 2 980, 1 740, 1 680, 1 610, 1 580, 1 500, 1 430, and 1 420 cm^{-1}; δ_H 1.26 (t, 3 H, CH_3), 3.6 (s, 2 H, CH_2), 3.76 (s, 3 H, OCH_3), 4.1 (q, 2 H, CH_2), 6.86—7.80 (dd, 4 H, ArH), 7.9 (s, 1 H, =CH), and 11.40 (s, 1 H, NH).

Ethyl 1-amino-5-cyano-4-(p-chlorophenyl)-6-hydroxy-2-oxo-6-phenylpiperidine-3-carboxylate (**4c**). Obtained in 16% yield, m.p. 184—186 °C (from ethanol) (Found: C, 60.75; H, 5.35; N, 10.05; Cl, 8.3. $C_{21}H_{20}ClN_3O_4$ requires C, 60.94; H, 4.83; N, 10.16; Cl, 8.58); $\nu_{max.}$ 3 420, 3 340, 3 280, 2 980, 2 900, 2 250, 1 740, 1 650, 1 600, 1 500, 1 460, and 1 400 cm^{-1}; δ_H 1.03 (t, 3 H, CH_3), 3.86—4.20 (m, 5 H, CH_2, 3-CH), 4.3 (br s, 2 H, NH_2), and 7.2—7.6 (m, 10 H, ArH, OH).

From the mother liquors,† the hydrazone (**6c**) was isolated in 13% yield, m.p. 164—166 °C (from ethanol) (Found: C, 53.8; H, 4.75; Cl, 13.5; N, 10.45. $C_{12}H_{13}N_2O_3Cl$ requires C, 53.63; H, 4.84; Cl, 13.22; N, 10.43%); $\nu_{max.}$ 3 180, 3 160, 2 980, 2 940, 1 730, 1 670, 1 610, and 1 490 cm^{-1}; δ_H 1.06 (t, 3 H, CH_3), 3.46 (s, 2 H, CH_2), 3.93 (q, 2 H, CH_2), 7.06—7.60 (m, 4 H, ArH), 7.7 (s, 1 H, =CH), and 11.3 (s, 1 H, NH).

Ethyl 1-amino-5-cyano-6-hydroxy-4-(p-tolyl)-2-oxo-6-phenylpiperidine-3-carboxylate (**4d**). Obtained in 20% yield, m.p. 154—156 °C (from ethanol or acetonitrile) (Found: C, 67.3; H, 5.8; N, 10.8. $C_{22}H_{23}N_3O_4$ requires C, 67.17; H, 5.85; N, 10.69%); $\nu_{max.}$ 3 400, 3 320, 3 280, 2 985, 2 240, 1 735, 1 645, 1 600, 1 515, and 1 450 cm^{-1}; δ_H 0.96 (t, 3 H, CH_3), 2.26 (s, 3 H, CH_3), 3.86—4.16 (m, 5 H, CH_2, 3-CH), 4.36 (br s, 2 H, NH_2), and 7.26—7.66 (m, 10 H, ArH, OH). From the mother liquors,† the hydrazone (**6d**) was isolated in 10% yield, m.p. 144—146 °C (from ethanol) (Found: C, 62.8; H, 6.2; N, 19.15. $C_{13}H_{16}N_2O_3$ requires C, 62.90; H, 6.45; N, 19.35); $\nu_{max.}$ 3 180, 3 080, 2 980, 1 740, 1 680, 1 610, 1 500, 1 470, 1 450, 1 400, and 1 390 cm^{-1}; δ_H 1.16 (t, 3 H, CH_3), 2.33 (s, 3 H, CH_3), 3.63 (s, 2 H, CH_2), 4.1 (q, 2 H, CH_2), 7.13—7.6 (dd, 4 H, ArH), 7.93 (s, 1 H, =CH), and 11.36 (s, 1 H, NH).

Ethyl 1-amino-5-cyano-6-hydroxy-4-(m-tolyl)-2-oxo-6-phenylpiperidine-3-carboxylate (**4e**). Obtained in 30% yield, m.p. 142—144 °C (from ethanol) (Found: C, 59.8; H, 5.05; N, 13.55. $C_{21}H_{20}N_4O_6$ requires C, 59.43; H, 4.71; N, 13.20%); $\nu_{max.}$ 3 400, 3 350, 3 290, 3 080, 2 980, 2 250, 1 730, 1 650, 1 600, 1 540, 1 450, and 1 400 cm^{-1}; δ_H 1.1 (t, 3 H, CH_3), 3.96—4.30 (m, 5 H, CH_2, 3-CH), 5.26 (br s, 2 H, NH_2), and 6.86—8.20 (m, 10 H, ArH, OH).

Ethyl 1,6-diamino-4-aryl-5-benzoyl-1,2,3,4-tetrahydro-2-oxopyridine-3-carboxylate (**5**): *General Procedure.*—To a solution of ethoxycarbonylacetohydrazide (**1**) (10 mmol) and the appropriate α-benzoylcinnamonitrile (**2**) (10 mmol) in ethanol (50 ml), a few drops of piperidine were added. The solution was refluxed for 40—70 h. The solid that precipitated from the cooled reaction mixture‡ was recrystallized and identified as (**5**). In some instances, it was contaminated with the

* Dry ethanol can also be used but, probably because of solubility reasons, the yield is lower.

† Sometimes, the hydrazones (**6**) precipitate together with a second crop of the piperidine (**4**) and they must be separated by fractional crystallization. Depending upon the selective solubility, hydrazones can sometimes precipitate first.

‡ Precipitation is slow and can take several days in the refrigerator. In some instances, several crops can be collected.

corresponding hydrazone (**6**), but could be purified by fractional crystallization in ethanol.

Ethyl 1,6-*diamino*-5-*benzoyl*-1,2,3,4-*tetrahydro*-2-*oxo*-4-*phenylpyridine*-3-*carboxylate* (**5a**). Obtained in 25% yield, m.p. 166—168 °C (from ethanol) (Found: C, 66.65; H, 5.7; N, 11.45. $C_{21}H_{21}N_3O_4$ requires C, 66.48; H, 5.58; N, 11.07%); $\nu_{max.}$ 3 360, 3 330, 3 280, 3 040, 2 940, 1 730, 1 700, 1 620, 1 580, 1 470, and 1 390 cm^{-1}; δ_H 1.15 (t, 3 H, CH_3), 3.9 (d, 1 H, CH), 4.15 (q, 2 H, CH_2), 4.26 (d, 1 H, CH), 5.26 (br s, 2 H, N-NH_2), and 6.93—7.30 (m, 12 H, ArH, C-NH_2); *m/z* (relative intensities) 379 (M^+, 20), 306 (100), 289 (13), 274 (31), 233 (14), and 105 (83).

Ethyl 1,6-*diamino*-5-*benzoyl*-1,2,3,4-*tetrahydro*-4-(p-*methoxyphenyl*)-2-*oxopyridine*-3-*carboxylate* (**5b**). In this case, the first crop of precipitate was the hydrazone (**6b**) in 14% yield. The pyridone (**5b**) was obtained from the mother liquors in 27% yield, m.p. 195—197 °C (from ethanol) (Found: C, 64.25; H, 5.3; N, 10.2. $C_{22}H_{23}N_3O_5$ requires C, 64.55; H, 5.62; N, 10.27%); $\nu_{max.}$ 3 400, 3 340, 3 280, 2 980, 1 730, 1 690, 1 610, 1 580, 1 500, and 1 470 cm^{-1}; δ_H 1.15 (t, 3 H, CH_3), 3.70 (s, 3 H, OCH_3), 3.86 (d, 1 H, CH), 4.16 (q, 2 H, CH_2), 4.23 (d, 1 H, CH), 5.35 (br s, 2 H, N-NH_2), and 6.8—7.3 (m, 11 H, ArH, C-NH_2); *m/z* (relative intensities) 409 (M^+, 18), 337 (16), 336 (71), 304 (14), 263 (22), 105 (91), and 77 (51).

Ethyl 1,6-*diamino*-5-*benzoyl*-4-(p-*chlorophenyl*)-1,2,3,4-*tetrahydro*-2-*oxopyridine*-3-*carboxylate* (**5c**). The hydrazone (**6c**) was precipitated initially (6% yield) followed by the pyridone (**5c**) (25% yield), m.p. 184—186 °C (from toluene) (Found: C, 61.05; H, 5.15; Cl, 9.2; N, 9.85. $C_{21}H_{20}ClN_3O_4$ requires C, 60.94; H, 4.83; Cl, 8.58; N, 10.16%); $\nu_{max.}$ 3 400, 3 320, 3 280, 2 980, 1 730, 1 710, 1 630, 1 610, 1 490, 1 470, and 1 380 cm^{-1}; δ_H 1.26 (t, 3 H, CH_3), 3.83 (d, 1 H, CH), 4.16 (q, 2 H, CH_2), 4.23 (d, 1 H, CH), 5.20 (br s, 2 H, N-NH_2), and 6.70—7.30 (m, 11 H, ArH, C-NH_2).

Ethyl 1,6-*diamino*-5-*benzoyl*-1,2,3,4-*tetrahydro*-2-*oxo*-4-(p-*tolyl*)*pyridine*-3-*carboxylate* [**5d**). The hydrazone (**6d**) was precipitated initially (15% yield) followed by the pyridone (**5d**) (20% yield), m.p. 196—198 °C (from ethanol) (Found: C, 67.25; H, 6.15; N, 10.55. $C_{22}H_{23}N_3O_4$ requires C, 67.17; H, 5.85; N, 10.69%); $\nu_{max.}$ 3 400, 3 340, 3 280, 1 730, 1 700, 1 620, 1 580, 1 520, 1 470, and 1 380 cm^{-1}; δ_H 1.10 (t, 3 H, CH_3), 2.23 (s, 3 H, CH_3), 3.76 (d, 1 H, CH), 4.05 (q, 2 H, CH_2), 4.13 (d, 1 H, CH), 5.10 (br s, 2 H, N-NH_2), and 6.80—7.10 (m, 11 H, ArH, C-NH_2); *m/z* (relative intensities) 393 (M^+, 33), 321 (24), 320 (100), 303 (13), 288 (30), 216 (8), 147 (7), and 105 (58).

Ethyl 1,6-*diamino*-5-*benzoyl*-1,2,3,4-*tetrahydro*-4-(m-*nitrophenyl*)-2-*oxopyridine*-3-*carboxylate* (**5e**). Obtained in 17% yield, m.p. 178—180 °C (from ethanol) (Found: C, 59.55; H, 5.05; N, 12.9. $C_{21}H_{20}N_4O_6$ requires C, 59.43; H, 4.71; N, 13.20%); $\nu_{max.}$ 3 420, 3 320, 3 280, 3 040, 2 960, 1 740, 1 700, 1 610, 1 580, 1 530, and 1 480 cm^{-1}; δ_H 1.26 (t, 3 H, CH_3), 4.13 (d, 1 H, CH), 4.20 (q, 2 H, CH_2), 4.40 (d, 1 H, CH), 5.30 (br s, 2 H, N-NH_2), and 6.83—-8.00 (m, 11 H, ArH, C-NH_2).

Diethyl 1,6-*diamino*-4-*aryl*-1,2,3,4-*tetrahydro*-2-*oxopyridine*-3,5-*dicarboxylates* (**11**): *General Procedure*.—The appropriate ethyl benzylidenecyanoacetate (**10**) (10 mmol) was dissolved in ethanol (30—70 ml) (depending upon solubility of the starting material). An equimolar amount of ethoxycarbonylacetohydrazide (**1**) and a few drops of piperidine was added. The reaction mixture was refluxed for a variable time (2—16 h) until t.l.c. showed the absence of starting material. With time the pyridones (**11**) were precipitated at room temperature and were filtered off and purified by recrystallization. In some instances, the precipitate was a mixture of the pyridone (**11**) and the hydrazone (**6**), but they could be easily separated by fractional crystallization in ethanol because of the higher solubility of the hydrazones. A second crop of product was recovered from the mother liquors.

Diethyl 1,6-*diamino*-1,2,3,4-*tetrahydro*-2-*oxo*-4-*phenylpyridine*-3,5-*dicarboxylate* (**11a**). Obtained in 32% yield, m.p. 121—122 °C (from ethanol) (Found: C, 59.0; H, 6.3; N, 12.4. $C_{17}H_{21}N_3O_5$ requires C, 58.78; H, 6.09; N, 12.10%); $\nu_{max.}$ 3 350, 3 320, 3 310, 2 980, 1 730, 1 700, 1 645, 1 580, 1 495, and 1 315 cm^{-1}; δ_H 1.05 (t, 3 H, 5-CH_3), 1.15 (t, 3 H, 3-CH_3), 3.80 (d, 1 H, CH), 3.99 (q, 2 H, 5-CH_2), 4.16 (q, 2 H, 3-CH_2), 4.48 (d, 1 H, CH), 5.18 (br s, 2 H, N-NH_2), 7.25 (br s, 5 H, ArH), and 7.75 (br s, 2 H, C-NH_2); δ_C(SFORD multiplicities) 13.8, 14.4 (q, 2 × CH_3), 37.6 (d, 4-C), 55.5 (d, 3-C), 58.3, 61.3 (t, 2 × CH_2), 75.2 (s, 5-C), 126.7, 127.7, 128.5 (d, 5-Ar), 127.9 (s, 6-C), 142.4 (s, *ipso*-Ar), 154.9 (s, 2-C), and 164.9, 168.1 (s, 2-CO).

Diethyl 1,6-*diamino*-1,2,3,4-*tetrahydro*-4-(p-*methoxyphenyl*)-2-*oxopyridine*-3,5-*dicarboxylate* (**11b**). Obtained in 41% yield, m.p. 139—141 °C (from ethanol) (Found: C, 57.0; H, 6.25; N, 11.45. $C_{18}H_{23}N_3O_6$ requires C, 57.28; H, 6.14; N, 11.14%); $\nu_{max.}$ 3 420, 3 340, 3 290, 2 980, 2 960, 1 730, 1 690, 1 645, 1 580, and 1 505 cm^{-1}; δ_H 1.06 (t, 3 H, CH_3), 1.15 (t, 3 H, CH_3), 3.76 (d, 1 H, CH), 3.99 (q, 2 H, CH_2), 4.16 (q, 2 H, CH_2), 4.43 (d, 1 H, CH), 5.16 (br s, 2 H, N-NH_2), 6.80—7.10 (m, 4 H, ArH), and 7.73 (br s, 2 H, C-NH_2).

Diethyl 1,6-*diamino*-4-(p-*chlorophenyl*)-1,2,3,4-*tetrahydro*-2-*oxopyridine*-3,5-*dicarboxylate* (**11c**). Obtained in 32% yield, m.p. 141—142 °C (from ethanol) (Found: C, 53.75; H, 5.4; Cl, 9.25; N, 11.25. $C_{17}H_{20}ClN_3O_5$ requires C, 53.46; H, 5.28; N, 11.01; Cl, 9.29%); $\nu_{max.}$ 3 430, 3 350, 3 300, 2 980, 1 725, 1 715, 1 645, 1 600, 1 505, and 1 485 cm^{-1}; δ_H 1.06 (t, 3 H, CH_3), 1.15 (t, 3 H, CH_3), 3.84 (d, 1 H, CH), 3.99 (q, 2 H, CH_2), 4.16 (q, 2 H, CH_2), 4.45 (d, 1 H, CH), 5.18 (br s, 2 H, N-NH_2), and 7.76 (br s, 2 H, C-NH_2).

Diethyl 1,6-*diamino*-1,2,3,4-*tetrahydro*-2-*oxo*-4-(p-*tolyl*)*pyridine*-3,5-*dicarboxylate* (**11d**). Obtained in 37% yield, m.p. 143—145 °C (from ethanol) (Found: C, 60.0; H, 6.25; N, 12.0. $C_{18}H_{23}N_3O_5$ requires C, 59.82; H, 6.41; N, 11.63%); $\nu_{max.}$ 3 445, 3 300, 3 310, 2 980, 2 945, 1 720, 1 685, 1 650, 1 620, 1 590, and 1 500 cm^{-1}; δ_H 1.06 (t, 3 H, CH_3), 1.15 (t, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 3.78 (d, 1 H, CH), 3.98 (q, 2 H, CH_2), 4.16 (q, 2 H, CH_2), 4.45 (d, 1 H, CH), 5.16 (br s, 2 H, N-NH_2), 7.06 (s, 4 H, ArH), and 7.73 (br s, 2 H, C-NH_2).

Diethyl 1,6-*diamino*-1,2,3,4-*tetrahydro*-4-(m-*nitrophenyl*)-2-*oxopyridine*-3,5-dicarboxylate (**11e**). Obtained in 46% yield, m.p. 169—170 °C (from ethanol) (Found: C, 51.7; H, 5.4; N, 14.55. $C_{17}H_{20}N_4O_7$ requires C, 52.04; H, 5.14; N, 14.28%); $\nu_{max.}$ 3 440, 3 330, 3 290, 3 090, 3 080, 2 990, 1 725, 1 690, 1 650, 1 590, 1 520, and 1 345 cm^{-1}; δ_H 1.05 (t, 3 H, CH_3), 1.15 (t, 3 H, CH_3), 3.73 (d, 1 H, CH), 4.04 (q, 2 H, CH_2), 4.21 (q, 2 H, CH_2), 4.58 (d, 1 H, CH), 5.18 (br s, 2 H, N-NH_2), and 7.46—8.20 (m, 6 H, ArH, C-NH_2).

Diethyl 1,6-*diamino*-1,2,3,4-*tetrahydro*-4-(p-*nitrophenyl*)-2-*oxopyridine*-3,5-*dicarboxylate* (**11f**). Obtained in 68% yield, m.p. 204—206 °C (from ethanol) (Found: C, 52.2; H, 5.3; N, 14.45. $C_{17}H_{20}N_4O_7$ requires C, 52.04; H, 5.14; N, 14.28%); $\nu_{max.}$ 3 445, 3 345, 3 295, 2 990, 2 950, 2 910, 1 730, 1 725, 1 690, 1 650, 1 585, 1 510, and 1 490 cm^{-1}; δ_H 1.05 (t, 3 H, CH_3), 1.16 (t, 3 H, CH_3), 3.93 (d, 1 H, CH), 4.09 (q, 2 H, CH_2), 4.16 (q, 2 H, CH_2), 4.56 (d, 1 H, CH), 5.18 (br s, 2 H, N-NH_2), 7.60 (br s, 2 H, C-NH_2), and 7.71 (q, 4 H, ArH).

Diethyl 1,6-*diamino*-4-(2,6-*dichlorophenyl*)-1,2,3,4-*tetrahydro*-2-*oxopyridine*-3,5-*dicarboxylate* (**11g**). Obtained in 18% yield, m.p. 153—154 °C (from ethanol) (Found: C, 48.95; H, 4.75; N, 10.0; Cl, 17.05. $C_{17}H_{19}Cl_2N_3O_5$ requires C, 49.05; H, 4.60; Cl, 17.03; N, 10.10%); $\nu_{max.}$ 3 450, 3 340, 3 280, 3 200, 3 070, 2 995, 2 950, 1 720, 1 650, 1 585, and 1 490 cm^{-1}; δ_H 0.82 (t, 3 H, CH_3), 1.15 (t, 3 H, CH_3), 3.63 (d, 1 H, CH), 3.77 (q, 2 H, CH_2), 4.12 (q, 2 H, CH_2), 5.21 (br s, 2 H, N-NH_2), 5.25 (d, 1 H, CH), 7.0—7.5 (m, 3 H, ArH), and 7.86 (br s, 2 H, C-NH_2).

3-*Ethyl* 5-*Methyl* 1,6-*Diamino*-1,2,3,4-*tetrahydro*-2-*oxo*-4-*phenylpyridine*-3,5-*dicarboxylate* (**14**).—This compound was

obtained in 34% yield by following the general procedure for compounds (**11**), starting from ethoxycarbonylacetohydrazide (**1**) and methyl benzylidenecyanoacetate (**13**), with a few drops of piperidine in ethanol (30 ml), m.p. 116—118 °C (from ethanol) (Found: C, 57.9; H, 5.8; N, 12.9. $C_{16}H_{19}N_3O_5$ requires C, 57.65; H, 5.74; N, 12.90%); $\nu_{max.}$ 3 420, 3 350, 3 305, 2 840, 1 735, 1 710, 1 660, 1 590, 1 500, and 1 440 cm^{-1}; δ_H 1.15 (t, 3 H, CH_3), 3.48 (s, 3 H, CH_3), 3.78 (d, 1 H, CH), 4.13 (q, 2 H, CH_2), 4.46 (d, 1 H, CH), 5.18 (s, 2 H, N-NH_2), 7.20 (s, 5 H, ArH), and 7.76 (s, 2 H, C-NH_2).

Diethyl 1,6-*diamino*-1,2,3,4-*tetrahydro*-2-*oxo*-4-*phenylpyridine* (**15a**).—A solution of the dihydropyridone (**11a**) (1.3 mmol) and dichlorodicyanoquinone (DDQ) (1.3 mmol) in ethanol (25 ml) was refluxed for 40 min after which it was allowed to cool and left at room temperature. The solid that separated* was filtered off and recrystallized from methanol; 27% yield, m.p. 206—208 °C (Found: C, 59.25; H, 5.45; N, 12.55. $C_{17}H_{19}N_3O_5$ requires C, 59.12; H, 5.54; N, 12.17%); $\nu_{max.}$ 3 430, 3 320, 2 980, 1 715, 1 675, 1 655, 1 585, 1 560, and 1 490 cm^{-1}; δ_H 0.60—1.10 (m, 6 H, 2-CH_3), 3.76 (q, 2 H, CH_2), 3.89 (q, 2 H, CH_2), 4.72 (br s, 2 H, N-NH_2), 7.0—7.4 (m, 5 H, ArH), and 7.91 (br s, 2 H, C-NH_2).

Diethyl 1,6-*Diamino*-4-(p-*nitrophenyl*)-2-*oxopyridine*-3,5-*dicarboxylate* (**15f**).—The dihydropyridone (**11f**) (3 mmol) was dissolved in methanol (30 ml) and DDQ (3 mmol) was added. The solution was refluxed for 30 min and then allowed to stand at room temperature. The solid that precipitated was filtered off and a second crop was recovered from the mother liquors; 33% yield, m.p. 225—226 °C (from ethanol) (Found: C, 52.3; H, 4.75; N, 14.6. $C_{17}H_{18}N_4O_7$ requires C, 52.30; H, 4.64; N, 14.62%); $\nu_{max.}$ 3 445, 3 320, 2 990, 1 718, 1 675, 1 630, 1 540, and 1 485 cm^{-1}; δ_H 1.05 (t, 3 H, CH_3), 1.25 (t, 3 H, CH_3), 4.02 (q, 2 H, CH_2), 4.19 (q, 2 H, CH_2), 4.82 (br s, 2 H, N-NH_2), 7.68—8.08 (dd, 4 H, ArH), and 7.7 (br s, 2 H, C-NH_2).

Ethyl 5-*Cyano*-1,2,3,4-*tetrahydro*-4-(p-*methoxyphenyl*)-6-*phenylpyridine*-3-*carboxylate* (**16**).—A solution of nitrosylsulphuric acid[12] was prepared from sodium nitrite (111 mg) and 50% sulphuric acid (32 ml) at 0 °C. This solution was added dropwise at 0 °C to a suspension of (**4b**) (0.4 g, 9 mmol). The reaction mixture was kept at 0 °C for 8 h and then allowed to warm to room temperature. The solid that precipitated was filtered off and washed with plenty of water. The mother liquors were poured over crushed ice and the resulting solid was treated as the first crop. The combined fractions were recrystallized from ethanol; 96% yield, m.p. 161—163 °C (decomp.) (Found: C, 70.25; H, 5.15; N, 7.5. $C_{22}H_{20}N_2O_4$ requires C, 70.21; H, 5.32; N, 7.45%); $\nu_{max.}$ 3 280, 3 200, 3 100, 2 960, 2 920, 2 820, 2 200, 1 730, 1 690, 1 610, 1 520, 1 500, 1 480, 1 460, 1 440, and 1 420 cm^{-1}; δ_H† 1.06 (t, 3 H, CH_3), 3.74 (s, 3 H, OCH_3), 4.06 (q, 2 H, CH_2), 4.07 (d, 1 H, *J* 10 Hz, CH), 4.32 (d, 1 H, *J* 10 Hz, CH), 6.94, 7.30 (dd, 4 H, ArH), 7.59—7.48 (s, 5 H, ArH), and 10.88 (s, 1 H, NH); δ_C 13.82 (CH_3), 41.75 (C-4), 53.72, 55.00 (C-3, OCH_3), 61.01 (CH_2), 88.19 (C-5), 114.13 (C-6), 118.38 (CN), 128.31, 128.43, 129.32, 130.68, 131.99, 151.11, 158.76 (Ar), 165.78, and 167.43 (COO, CONH); *m*/*z* (relative intensities) 376 (M^+, 2), 304 (24), 303 (100), 288 (4), 261 (5), 151 (5), and 127 (2).

* Precipitation is slow and can take several days.

† Clear identification of the signals due to the ring protons (δ 4.07 and 4.32), which appear together with the methylene quartet of the ester group, required a 400 MHz spectrum.

5-*Cyano*-1,2-*dihydro*-2-*oxo*-4,6-*diphenylpyridine*-3-*carboxylate* (**17**).—The hydroxypiperidone (**4a**) (0.2 g, 5 mmol) was suspended in acetic acid (2 ml). To this suspension, a solution of nitrosylsulphuric acid,[12] obtained from sodium nitrite (60 ml) and 50% sulphuric acid (17.5 ml), was added dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 8 h and then kept at room temperature for 3 days. A solid was precipitated and this was collected by filtration on a sintered glass funnel and washed with plenty of water to eliminate the acid. The mother liquors were poured over crushed ice, to obtain a second crop of solid, which was also washed with water and added to the first solid. The combined fractions were recrystallized from ethanol; 56% yield, m.p. 258—260 °C (Found: C, 73.65; H, 4.55; N, 8.3. $C_{21}H_{16}N_2O_3$ requires C, 73.26; H, 4.65; N, 8.14%); $\nu_{max.}$ 2 900br, 2 210, 1 730, 1 640, 1 600, 1 550, 1 500, 1 480, 1 450, and 1 400 cm^{-1}; δ_H 0.73 (t, 3 H, CH_3), 3.76 (q, 2 H, CH_2), 7.16—7.50 (m, 11 H, ArH, NH).

Ethyl 5-*Cyano*-3,4-*dihydro*-2,6-*dioxo*-4-(p-*tolyl*)*piperidine*-3-*carboxylate* (**20**).—Ethyl *p*-tolylidenecyanoacetate (**10b**) (10 mmol) and ethyl malonamate (10 mmol) were dissolved in ethanol (15 ml) and a few drops of piperidine added. The solution was stirred at room temperature for 4 h and then half the solvent was evaporated under reduced pressure. A small amount of starting material precipitated which was filtered off. From the mother liquors, compound (**20**) was precipitated and collected by filtration and recrystallized from ethanol; 15% yield, m.p. 214—216 °C (Found: C, 64.1; H, 5.65; N, 9.25. $C_{16}H_{16}N_2O_4$ requires C, 63.94; H, 5.37; N, 9.33%); $\nu_{max.}$ 3 210, 3 120, 2 900, 2 260, 1 735, 1 715, 1 685, 1 510, and 1 435 cm^{-1}; δ_H 0.93 (t, 3 H, CH_3), 2.3 (s, 3 H, CH_3), 3.94 (q, 2 H, CH_2), 4.13—4.95 (m, 3 H, 3-CH), and 7.23 (br s, 4 H, ArH).

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