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# The Synthesis of Perloline, 6-(3,4-Dimethoxyphenyl)-5-hydroxy-5,6-dihydrobenzo[*c*][2,7]naphthyridin-4(3*H*)-one

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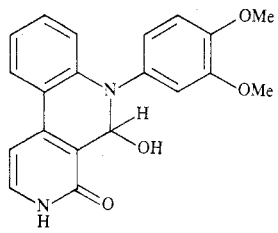
*Abstract*

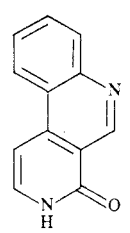
Dehydroperloline is obtained in high overall yield by an intramolecular cyclization of the benzyne generated from 4-(2-bromophenyl)-*N*-(3,4-dimethoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (21), by use of lithium hexamethyldisilazide. A benzyne intermediate has not been established. The pyridinone (21) was prepared in three steps from 2-[1-(2-bromophenyl)ethylidene]malononitrile. Dehydroperloline was smoothly reduced by sodium bis(methoxyethoxy)aluminium hydride to perloline, isolated as its hydrochloride.

## Introduction

Perloline (1) is an alkaloid of a novel type which occurs in several pasture grasses throughout the world, principally perennial rye grass, *Lolium perenne*[1] and tall fescue, *Festuca arundinacea*.[2] The concentration of the alkaloid in the grasses shows considerable seasonal variation,[3] corresponding to the peaks in susceptibility of sheep and cattle, grazing on the grass, to a disabling but temporary disease of the central nervous system called rye grass staggers.[3] Two syntheses of the minor alkaloid present in *L. perenne*, perlolidine (2), have been reported,[4,5] but none of perloline.




(1)

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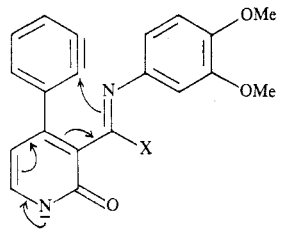



(3)

[1] Melville, J., and Grimmet, R. E. R., *Nature* (*London*), 1941, **148**, 782.
[2] White, E. P., and Reifer, I., *N.Z. J. Sci. Technol., Sect. B*, 1945, **27**, 38, 242.
[3] Aasen, A. J., Culvenor, C. C. J., Finnie, E. P., Kellock, A. W., and Smith, L. W., *Aust. J. Agric. Res.*, 1969, **20**, 71.
[4] Akhtar, M. A., Brouwer, W. G., Jeffreys, J. A. D., Gemenden, C. W., Taylor, W. I., Seelye, R. N., and Stanton, D. W., *J. Chem. Soc. C*, 1967, 859.
[5] Powers, J. C., and Ponticello, I., *J. Am. Chem. Soc.*, 1968, **90**, 7102.

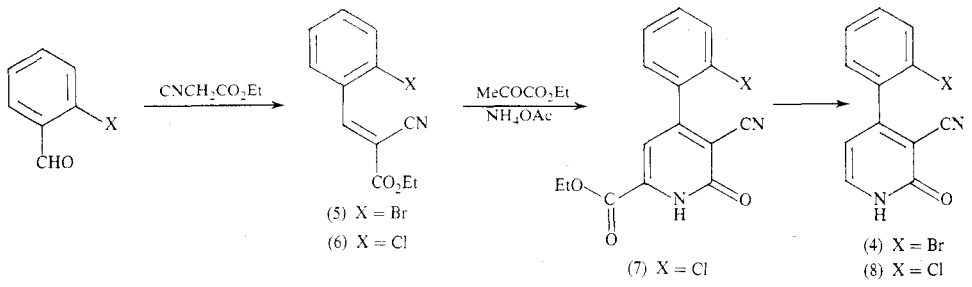
0004-9425/83/071441$02.00

In the accompanying paper[6] we report the first synthesis of dehydroperloline, which is capable of reduction to perloline. In this communication we report a synthesis of perloline in which the main strategy is the intramolecular capture of a benzyne intermediate by a delocalized pyridinone anion, (3).

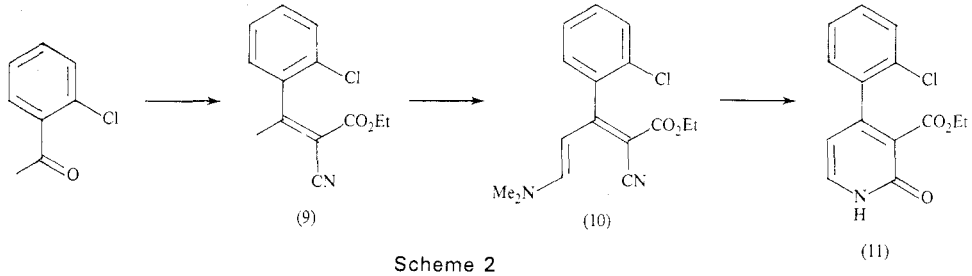
Accordingly, our first synthetic goal became the cyanopyridinone (4).

## Discussion

The Knoevenagel condensation of 2-bromobenzaldehyde with ethyl cyanoacetate followed literature procedures,[7,8] and the formation of the required pyridinone ring (Scheme 1) was then examined first by the method of Saito.[9,10] This procedure works well to produce 6-substituted pyridin-2-(1*H*)-ones, but its adaptation to pyridinones unsubstituted at C6 has not been reported. Reaction of the ester (5) with ethyl pyruvate proceeded only in very low yields, and use of the less bulky chloro derivative (6) gave a small improvement. This pathway to (8) was abandoned when it was found that decarboxylation of the acid derived from (7) proceeded only poorly. An alternative method for forming pyridin-2(1*H*)-ones of the required type was therefore sought, and is outlined in Scheme 2.




Scheme 1



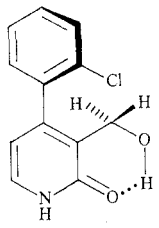

Scheme 2

The Knoevenagel condensation of 2-chloroacetophenone with ethyl cyanoacetate proceeded best in the presence of pentylammonium acetate.[11] Separation of the isomers of (9) was not necessary, as the mixture reacted smoothly with dimethyl-

[6] Duong, T., Prager, R. H., and Were, S. T., *Aust. J. Chem.*, 1983, **36**, 1431.
[7] Mariella, R. P., and Conway, T., *Can. J. Chem.*, 1965, **43**, 2426.
[8] Popp, F. D., *J. Org. Chem.*, 1960, **25**, 646.
[9] Sakurai, A., and Midorikawa, H., *Bull. Chem. Soc. Jpn*, 1967, **40**, 1680.
[10] Kambe, S., Saito, K., Sakurai, A., and Hayashi, T., *Synthesis*, 1977, 841.
[11] Hein, R. W., Astle, M. J., and Shelton, J. R., *J. Org. Chem.*, 1961, **26**, 4874.

formamide dimethyl acetal[12] to give the enamine (10), which was quite inert to nucleophilic attack under basic conditions, by e.g. ammonia. On the other hand, the action of refluxing 80% acetic acid converted (10) into (11) in 85% yield. Since the conditions used are considerably milder than those usually required to hydrolyse a nitrile to an amide, it may be presumed that the hydrolysis is induced by the intramolecular attack of the nitrile on the enamine carbon. Support for this hypothesis comes from the observation that a similar reaction of (14) and (16) resulted in the hydrolysis of only one of the two nitrile groups present.

To set up the situation depicted in (3), the most obvious approach appeared to involve the imine (3; X = H), as this would lead directly to perloline. The reduction of the ester functionality in (11) to the aldehyde appeared trivial, but could not be achieved efficiently by a variety of reagents or strategies. It appeared that chelation of the metal in most reducing agents necessitated forcing conditions under which only the alcohol was formed. Thus, although the ester group in (7) was smoothly reduced to the corresponding aldehyde with diisobutylaluminium hydride, reduction of (11) under similar conditions failed totally, and more forcing conditions, such as several equivalents of the reducing agents in refluxing tetrahydrofuran or toluene, gave the primary alcohol (12). The $^1$H n.m.r. spectrum of this alcohol showed the hydroxymethyl group as an AB quartet, presumably due to a combination of strong intramolecular hydrogen bonding, and the lack of co-planarity of the diphenyl, as shown in the structure (12).



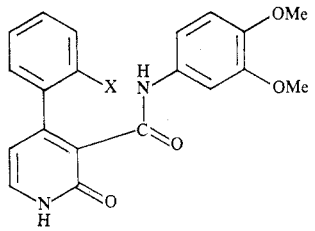

(12)

Attempts to oxidize (12) to the aldehyde were likewise unsuccessful; even when transition metal oxidants were replaced by activated dimethyl sulfoxide.[13] Similarly, a number of attempts to reduce the corresponding nitrile e.g. (15) and (17) to the aldehyde were unsuccessful. Accordingly, the ester (11) was converted into the amide (13), the most satisfactory method being by dicyclohexylcarbodiimide-induced[14,15] coupling of the acid and dimethoxyaniline.

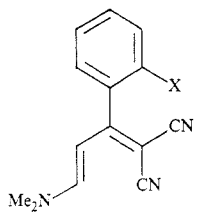
The parallel to Scheme 2, with bromine replacing chlorine, was also investigated, as it was felt the benzyne reaction would proceed more easily with bromine as leaving group. In contrast to the chloroacetophenone, 2-bromoacetophenone was very sluggish in its reaction with ethyl cyanoacetate, and accordingly the more electron-deficient malononitrile was used, the reaction now occurring in 87% yield. The product reacted very readily with dimethylformamide dimethyl acetal to give (16)

[12] Abdulla, R. F., and Brinkmeyer, R. S., *Tetrahedron*, 1979, **35**, 1675.
[13] Mancuso, A. J., and Swern, D., *Synthesis*, 1981, 165.
[14] Buehler, C. A., and Pearson, D. E., 'Survey of Organic Synthesis' Vols 1 and 2 (Wiley–Interscience: New York 1970 and 1977).
[15] Albertson, N. F., *Org. React.*, 1962, **12**, 157.

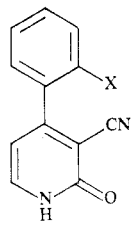
(95%). The dinitrile (14) was cyclized to the corresponding pyridinone (15) considerably more slowly than the cyano-ester (10), and the use of 5 M hydrochloric acid was necessary. The bromo analogue (16) under similar conditions gave a mixture of the pyridinone (17) and the chloropyridine (18), the latter compound being reminiscent of the formation of 2-bromopyridines in similar syntheses, as noted by Bryson.[16]



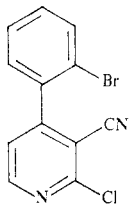
(13) X = Cl
(21) X = Br



(14) X = Cl
(16) X = Br



(15) X = Cl
(17) X = Br



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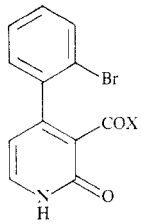


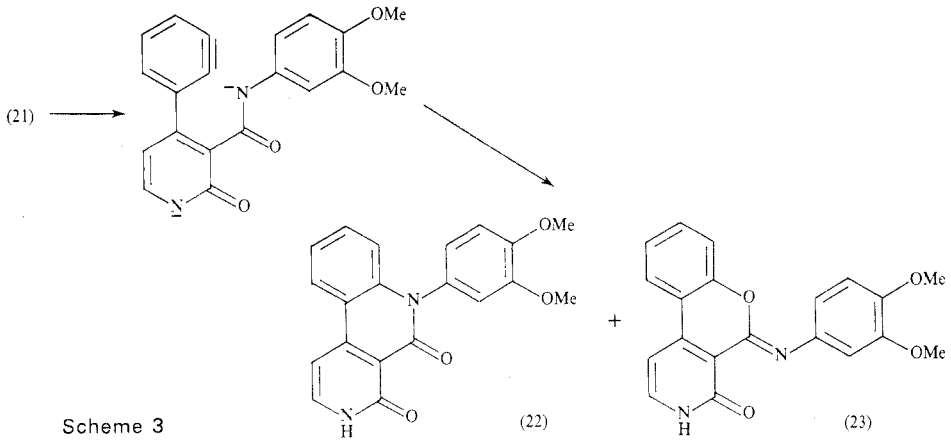
(19) X = $NH_2$
(20) X = OH

Other cyclization conditions were investigated, with varying success. Thus the use of acetic acid led to a very slow reaction and the formation of the cyanopyridinone (17), together with the corresponding carboxamide (19), but sulfuric acid/acetic acid/water (2 : 10 : 3) gave (17) in 87% yield. This nitrile was inert to alkaline hydrolysis but readily gave carboxamide (19) on refluxing with 70% sulfuric acid. The carboxamide was itself very resistant to hydrolysis under either acidic or alkaline conditions and eventually it was found that hydrolysis to the carboxylic acid (20) could best be achieved with nitrous acid.[17,18] Since the sequence (16) → (17) → (19) → (20) required acidic conditions for each step, attempts were made to combine them. Thus the enamine (16) could be converted into the amide (19) in 92% overall yield in one step, and the three steps were achieved in one pot in 91% overall yield. The dimethoxyanilide (21) was then prepared by the same procedure that had been used for (13).

Both (13) and (21) have been converted into dehydroperloline (22) and thence to perloline. Considerable experimentation with choice of a suitable base was necessary because of the very slow nature of the aryne reactions presumably due to the formation of a dianion prior to aryne formation. The reaction of (21) with butyllithium gave a mixture of products in which dehydroperloline was absent, and which

[16] Bryson, T. A., Donelson, D. M., Dunlap, R. B., Fisher, R. R., and Ellis, P. D., *J. Org. Chem.*, 1976, **41**, 2066.
[17] Sarel, S., and Newman, M. S., *J. Am. Chem. Soc.*, 1956, **78**, 5416.
[18] Ladenheim, H., and Bender, M. L., *J. Am. Chem. Soc.*, 1960, **82**, 1895.

contained butylated compounds. Although the chloroamide (13) gave no dehydroperloline with lithium diisopropylamide ($LiNPr^i_2$), the bromo amide (21) gave a mixture of products which contained dehydroperloline (18%) and 3,4-dimethoxyaniline under the same conditions. It is suggested the aryne intermediate is captured equally well by the ambident anion of the amide acting through the nitrogen or oxygen atoms,[19] the product (23) from the latter pathway subsequently hydrolysing on workup (Scheme 3). The use of lithium hexamethyldisilazide in tetrahydrofuran[20,21] proved very efficient, (21) being converted into dehydroperloline (22) in 86% yield. We believe the reagent is acting not only as a base, but then as a source of hexamethyldisilazane which is a powerful silylating agent,[22,23] and could thus reasonably be expected to produce a species like (24), which would react intramolecularly exclusively through the nitrogen atom.



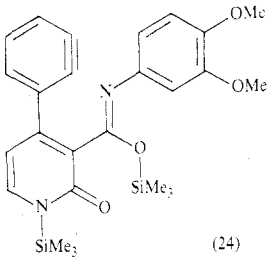

Scheme 3

In an attempt to obtain further evidence for the benzyne intermediate (24), the isomeric bromo amide (25) was synthesized by means of essentially identical chemistry to that used for the synthesis of (21). Reaction of (25) with lithium hexamethyldisilazide in tetrahydrofuran was extremely slow, and even after four days some starting material remained. Careful chromatography failed to find any dehydroperloline and thus the question of a benzyne intermediate must remain open.

The synthesis of perloline was completed by the reduction of dehydroperloline with sodium bis(2-methoxyethoxy)aluminium hydride ('Redal'), the product being identical with an authentic specimen extracted from *L. perenne*. In an endeavour to utilize our experience with the model compound (26), which was easily oxidized to the perloline analogue,[24] attempts were made to reduce the amide (13) to (27), which we felt would probably undergo facile aryne capture. Reduction was attempted using lithium aluminium hydride, 'Redal', and borane–dimethyl sulfide, but no clean reaction could be observed.

[19] El-Sheikh, M. I., Marks, A., and Biehl, E. R., *J. Org. Chem.*, 1981, **46**, 3256.
[20] Kende, A. S., and Fludzinski, P., *Tetrahedron Lett.*, 1982, **23**, 2369.
[21] Stork, G., Takahashi, T., Kawamoto, I., and Suzuki, T., *J. Am. Chem. Soc.*, 1978, **100**, 8272.
[22] Birkofer, L., and Ritter, A., *Angew. Chem., Int. Ed. Engl.*, 1965, **4**, 417 (peptide synthesis).
[23] Fieser, L. F., and Fieser, M., 'Reagents for Organic Synthesis' Vols. 1, 2, 5–7 and 9 (John Wiley: New York).
[24] Clarke, S. I., and Prager, R. H., *Aust. J. Chem.*, 1982, **35**, 1645.

Finally, we were curious to learn if an intramolecular Ullmann reaction on the amide (13) and (21) would provide an alternative pathway to dehydroperloline. Ullmann reactions with amides are not very common but isolated instances[25,26] have been reported. The chloro amide (13) did not give dehydroperloline on treatment with copper bronze/copper(I) iodide in pentan-1-ol, but the bromo amide (21) reacted quite smoothly, giving dehydroperloline in 73% yield.

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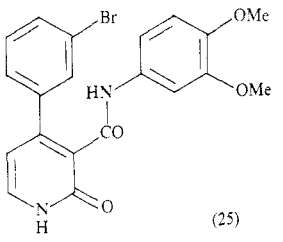


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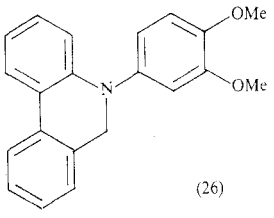


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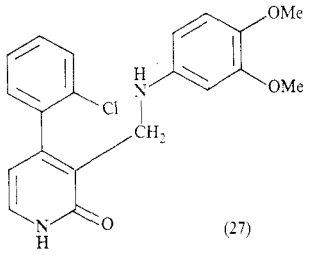


(27)

## Experimental

*Ethyl 4-(2-Chlorophenyl)-5-cyano-6-oxo-1,6-dihydropyridine-2-carboxylate* (7)

Ethyl 3-(2-chlorophenyl)-2-cyanoprop-2-enoate[7,8] (2·3 g, 10 mmol), ethyl pyruvate (1·09 ml, 10 mmol) and ammonium acetate (1 g) were dissolved in ethanol at 70–80° and kept at that temperature for 24 h. The solution was concentrated and the solid was collected, yielding the *pyridinone* (0·62 g, 20%). Recrystallization from dichloromethane/light petroleum gave almost white crystals, m.p. 234–235·5° (Found: C, 59·5; H, 3·7; N, 9·3. $C_{15}H_{11}ClN_2O_3$ requires C, 59·5; H, 3·7; N, 9·3%). $\nu_{max}$ 2225, 1730, 1645 $cm^{-1}$. N.m.r. $\delta$ 1·37, t, $J$ 7 Hz, 3H; 2·48, q, $J$ 7 Hz, 2H; 7·12, s, 1H, 7·5–7·9, m, 4H.

*4-(2-Chlorophenyl)-5-cyano-6-oxo-1,6-dihydropyridine-2-carboxylic Acid*

The ester (7) (100 mg, 0·33 mmol) was refluxed in methanol (20 ml) containing water (5 ml) and sodium hydroxide (0·1 g) for 2 h. The resulting solution was cooled and acidified, giving a white *powder* (82 mg, 90%), m.p. 282–287° (dec.) (Found: C, 56·7; H, 2·6; N, 9·9. $C_{13}H_7ClN_2O_3$ requires C, 56·9; H, 2·6; N, 10·2%). $\nu_{max}$ 3300–3200, 3125, 2230, 1900, 1705, 1620 $cm^{-1}$. N.m.r. $\delta$ 6·95, s, 1H; 7·3–7·5, m, 4H.

*4-(2-Chlorophenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile* (8)

(i) The acid above (443 mg, 1·61 mmol) was mixed with copper bronze (2·6 g) in a sublimator and then heated to 320–340° under vacuum (0·01 mm Hg). After heating for 30 min the pressure returned to 0·01 mm, and heating was then terminated. The material which had sublimed was

[25] Weston, P. E., and Adkins, H., *J. Am. Chem. Soc.*, 1928, **50**, 859.
[26] Schulenberg, J. W., and Archer, S., *Org. React.*, 1965, **14**, 1.

dissolved in dichloromethane (20 ml) and combined with an extract of the residue. The solution was chromatographed on silica using dichloromethane/methanol (95 : 5). The nitrile (8) was recrystallized from dichloromethane/light petroleum and was recovered in 41% yield (152 mg, 0·66 mmol), m.p. 214–218°, and was identical in all respects with that obtained below.

(ii) The enamine (14) (223 mg, 0·87 mmol) was dissolved in a solution of acetic acid and 11 M hydrochloric acid (1 : 1) (10 ml) at reflux, forming a green solution. After 2 h at reflux the colourless solution was neutralized with solid sodium hydrogen carbonate and water. The aqueous solution was then extracted with dichloromethane (3 × 20 ml), the combined organic extracts dried, and the solvent was removed.

The residue was purified by preparative t.l.c. on silica by using dichloromethane/methanol (95 : 5). The band at $R_F$ 0·25–0·40 was isolated and afforded the *nitrile* (8) in 80% yield (160 mg, 0·69 mmol). Recrystallization from dichloromethane/light petroleum gave colourless prisms, m.p. 218–222° (Found: C, 62·4; H, 3·3; N, 12·0. $C_{12}H_7ClN_2O$ requires C, 62·5; H, 3·1; N, 12·1%). $\nu_{max}$ 2240, 1600, 1605, 770 $cm^{-1}$. N.m.r. ($CD_3SOCD_3$) (80 MHz) $\delta$ 6·33, d, $J$ 6·6 Hz, H 5; 7·4–7·7, m, 4H; 7·84, d, $J$ 6·6 Hz, H 6.

*Ethyl 3-(2-Chlorophenyl)-2-cyanobut-2-enoate (9)*

A solution of 2-chloroacetophenone (3·93 g, 25·4 mmol), ethyl cyanoacetate (2·97 ml, 28 mmol), pentylamine (0·32 ml, 2·8 mmol) and acetic acid (0·16 ml, 2·8 mmol) in benzene (20 ml) was refluxed, and the water formed was collected in a Dean–Stark water separator until the theoretical amount of water (0·5 ml) had been collected. The solvent was removed under reduced pressure and the residue distilled. The *ester* (9) (5·3 g, 84%) boiled at 118°/0·01 mm (Found: C, 62·2; H, 5·1; N, 5·8. $C_{13}H_{12}ClNO_2$ requires C, 62·5; H, 4·8; N, 5·6%). $\nu_{max}$ (liquid film) 2230 (CN), 1730, 1615 $cm^{-1}$. N.m.r. $\delta$ 1·12, t, $J$ 7 Hz, 1·35, t, $J$ 7 Hz, 3H; 2·43, s, 2·57, s, 3H; 3·97, q, $J$ 7 Hz, 4·30, q, $J$ 7 Hz, 2H; 6·7–7·4, m, 4H. *m/e* 251, 249 (M), 214 (M−Cl).

*Ethyl 3-(2-Chlorophenyl)-2-cyano-5-dimethylaminopenta-2,4-dienoate (10)*

Dimethylformamide dimethyl acetal (1·0 ml, 1·2 equiv.) was added to ethyl 3-(2-chlorophenyl)-2-cyanobut-2-enoate (9) (2·5 g, 10 mmol) under nitrogen. The mixture rapidly coloured and solidified after 30 min. The residue was dried under vacuum and then chromatographed on alumina with dichloromethane: the product (3·0 g, 98%) was eluted rapidly. Recrystallization from dichloromethane/light petroleum gave yellow prisms of the *enamine* (10), m.p. 193·5–194·5° (Found: C, 63·1; H, 5·6; N, 9·1. $C_{16}H_{17}ClN_2O_3$ requires C, 63·1; H, 5·6; N, 9·2%). $\nu_{max}$ 2200, 1680, 1610 $cm^{-1}$. N.m.r. $\delta$ 1·12, t, $J$ 7 Hz, 1·32, t, $J$ 7 Hz, 3H; 2·97, s, 6H; 3·78, q, $J$ 7 Hz, 4·20, q, $J$ 7 Hz, 2H; 5·78, d, $J$ 12 Hz, 6·27, d, $J$ 12 Hz, 1H; 6·8–7·4, m, 5 Hz. *m/e* 306, 304 (M).

*Ethyl 4-(2-Chlorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (11)*

The enamine (10) (615 mg, 2·0 mmol) was dissolved in refluxing 80% acetic acid (50 ml) under nitrogen with stirring. The heating was stopped after the solution changed colour from green-yellow to tan. After removal of most of the solvent the solution was neutralized with sodium hydrogen carbonate and extracted with dichloromethane (4 × 20 ml). The combined organic extracts were dried and the solvent removed. Chromatography on silica, with 30% ethyl acetate in dichloromethane, gave 470 mg (85%) of a solid which was recrystallized from dichloromethane/light petroleum to give (11) as white *crystals*, m.p. 202·5–203° (Found: C, 60·4; H, 4·3; N, 4·9. $C_{14}H_{12}ClNO_3$ requires C, 60·6; H, 4·3; N, 5·0%). $\nu_{max}$ 1735, 1685, 1640 $cm^{-1}$. N.m.r. $\delta$ 0·87, t, $J$ 7 Hz, 3H; 3·98, q, $J$ 7 Hz, 2H; 6·18, d, $J$ 6 Hz, 1H; 7·0–7·7 m, 5H (including 7·68, d, $J$ 6 Hz). Mass spectrum *m/e* 242 (M−Cl), 234, 232 (M−$OC_2H_5$).

*4-(2-Chlorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic Acid*

The pyridinone ester (11) (194 mg, 0·70 mmol) was dissolved in methanol (30 ml) and aqueous sodium hydroxide (10 ml, 2 M) and the solution was refluxed for 1 h. The solution was acidified (3 M HCl), the methanol was removed under reduced pressure and the *acid* (157 mg, 0·63 mmol; 90%) was collected. Recrystallization of the product from acetone afforded tan feathery crystals, m.p. 250–255° (Found: C, 57·8; H, 3·3; N, 5·5. $C_{12}H_8ClNO_3$ requires C, 57·7; H, 3·2; N, 5·6%). $\nu_{max}$ 3200, 1720, 1620, 1595 $cm^{-1}$. N.m.r. ($CD_3SOCD_3$) $\delta$ 6·48, d, $J$ 6 Hz, H 5; 7·1–7·7 m, 4H; 7·94, d, $J$ 6 Hz, H 6. Mass spectrum *m/e* 234, 232 (M−OH); 214 (M−Cl).

*4-(2-Chlorophenyl)-N-(3,4-dimethoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (13)*

4-(2-Chlorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (390 mg, 1·6 mmol) and 3,4-dimethoxyaniline (303 mg, 1·98 mmol, 1·2 equiv.) were dissolved in dry tetrahydrofuran (20 ml), and the solution cooled in ice. Dicyclohexylcarbodiimide (0·4 g, 1·2 equiv.) was added and the solution was stirred under nitrogen at 15° for 14 h. The solid dicyclohexylurea was removed and the solvent was evaporated. The residue was recrystallized from dichloromethane/light petroleum which gave the *amide* (13) as green needles, m.p. 248–250° (510 mg, 1·33 mmol, 83%).

Flash chromatography in dichloromethane/methanol (95 : 5) followed by recrystallization from dichloromethane/light petroleum afforded yellow *amide* (13), m.p. 250–252° (Found: C, 62·6; H, 4·2; N, 7·4. $C_{20}H_{17}ClN_2O_4$ requires C, 62·4; H, 4·5; N, 7·3%). $\nu_{max}$ 3200 br, NH; 1675, 1615, 1590, 1240, 1215; 760 $cm^{-1}$. $^1H$ n.m.r. ($CD_3SOCD_3$, 80 MHz) $\delta$ 3·58, s, OMe; 3·66, s, OMe; 6·16, d, $J$ 6·0 Hz, H5; 6·6–7·8 m, 8H (including 7·62, d, $J$ 6·0 Hz, H6). $^{13}C$ n.m.r. ($CD_3SOCD_3$) $\delta$ 55·8, 56·0, 105·2, 109·3, 112·1, 112·5, 124·6, 127·2, 129·5, 129·9, 130·8, 132·8, 136·5, 138·7, 140·8, 145·5, 149·1, 152·5, 161·9, 162·4. Mass spectrum *m/e* 386, 384 (M).

*4-(2-Chlorophenyl)-3-hydroxymethylpyridin-2(1H)-one (12)*

The ester (11) (1·06 g, 3·8 mmol) was suspended in tetrahydrofuran (20 ml) and sodium bis-(methoxyethoxy)aluminium hydride (2·04 M, 4 ml, *c.* 2 equiv.) was added. The solution was refluxed and the reaction followed by t.l.c. When no further ester remained (1·5 h) the reaction mixture was cooled to 20° and hydrochloric acid (3 M, 20 ml) was added. Brine (20 ml) was added to the solution, the layers separated, and the aqueous phase extracted with dichloromethane (3 × 20 ml). The combined organic extracts were dried and the solvent removed.

The residue was recrystallized from dichloromethane/light petroleum which gave the *alcohol* (840 mg, 94%). The analytical sample was prepared by flash chromatography in dichloromethane/methanol (95 : 5), followed by recrystallization from dichloromethane/light petroleum, and had m.p. 203–205° (Found: C, 61·0; H, 4·4; N, 6·2. $C_{12}H_{10}ClNO_2$ requires C, 61·2; H, 4·3; N, 5·9%). $\nu_{max}$ 3250, 3100, 1660, 1590 $cm^{-1}$. $^1H$ n.m.r. $\delta$ 2·7–3·1, s(br), 1H, OH; 4·21, 4·52, ABq, $J$ 12 Hz, $CH_2O$; 6·18, d, $J$ 7 Hz, H5; 7·1–7·6, m, 5H. $^{13}C$ n.m.r. ($CD_3SOCD_3$) $\delta$ 56·63, 107·64, 127·20, 128·90, 129·50, 130·11, 131·20, 133·51, 137·03, 149·06, 163·15. Mass spectrum *m/e* 237, 235 (M), 198, 182.

*Attempted Reduction of Ethyl 4-(2-Chlorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (11) to 4-(2-Chlorophenyl)-2-oxo-1,2-dihydropyridine-3-carbaldehyde*

The ester (11) was partly dissolved in the solvent (20 ml) and diisobutylaluminium hydride was added under nitrogen. The reaction was worked up by pouring into 3 M hydrochloric acid (10 ml) followed by brine (10 ml). The layers were separated and the aqueous phase was extracted with dichloromethane (4 × 20 ml). The combined organic extracts were dried and the solvent was removed under reduced pressure. The residue was examined by t.l.c. and by infrared and $^1H$ n.m.r. spectroscopy.

*Attempted Oxidation of 4-(2-Chlorophenyl)-3-hydroxymethylpyridin-2(1H)-one (12) to 4-(2-Chlorophenyl)-2-oxo-1,2-dihydropyridine-3-carbaldehyde*

(i) The alcohol (12) (412 mg, 1·7 mmol) was dissolved in dichloromethane (40 ml), then pyridinium chlorochromate[27] (0·4 g, 1·1 equiv.) was added. After 3 h the mixture was passed through a short column of Florisil which was then washed with dichloromethane and ethyl acetate. The solvents were removed under vacuum but no products were eluted.

(ii) The alcohol (31·6 mg, 0·13 mmol) was dissolved in dichloromethane (15 ml) (12) and manganese dioxide[28] (0·2 g) was added. The mixture was stirred for 3 days, then filtered through Celite and Florisil and washed with ethyl acetate and acetone; this gave a white solid (3 mg) which was identified by $^1H$ n.m.r. spectroscopy as the alcohol (12).

[27] Corey, E. J., and Suggs, J. W., *Tetrahedron Lett.*, 1975, 2647.
[28] Ball, S., Goodwin, T. W., and Morton, R. A., *Biochem. J.*, 1948, **42**, 516.

(iii) To a solution of oxalyl chloride (0·20 ml, 2·3 mmol) in dichloromethane (5 ml) at −60° was added dimethyl sulfoxide (0·4 ml, 5·6 mmol) in dichloromethane (5 ml). The alcohol (496 mg, 2·10 mmol) in dichloromethane (20 ml) was added and the mixture stirred at −60°, followed by the addition of triethylamine (1 ml). The reaction was warmed to 20° and water (15 ml) was added. The layers were separated and the aqueous phase was extracted with dichloromethane (3 × 10 ml). The combined organic layers were dried and evaporated to dryness. $^1$H n.m.r. spectroscopy showed an aldehyde resonance at $\delta$ 10·13 which accounted for 5% of the pyridinone-containing material.

*2-[1-(2-Bromophenyl)ethylidene]malononitrile*

A solution of 2-bromoacetophenone (5·0 g, 25 mmol), malononitrile (2·49 g, 37·7 mmol, 1·5 equiv.), pentylamine (0·28 ml, 2·5 mmol, 0·1 equiv.) and acetic acid (0·14 mmol, 2·5 mmol, 0·1 equiv.) in benzene (30 ml) was refluxed for 24 h with a water separator. The reaction mixture was then cooled and the solvent was removed. The residual *oil* (5·3 g, 87%) distilled at 102–104°/0·02 mm (Found: C, 53·3; H, 3·1; N, 11·6. $C_{11}H_7BrN_2$ requires C, 53·5; H, 2·9; N, 11·3%). $\nu_{max}$ (liquid film) 2230 (CN), 1600, 1580, 1465, 1420, 1025, 760 cm$^{-1}$. $^1$H n.m.r. $\delta$ 2·53, s, $CH_3$; 7·1–7·8, m, 4H. $^{13}$C n.m.r. $\delta$ 24·2, 89·1, 111·1, 118·8, 127·5, 127·8, 131·4, 133·1, 137·4, 176·7. Mass spectrum *m/e* 248, 246 (M), 167, 140.

*2-[1-(2-Chlorophenyl)ethylidene]malononitrile*

A solution of 2-chloroacetophenone (15·3 g, 99 mmol), malononitrile (6·6 g, 100 mmol), pentylamine (1·2 ml, 10 mmol) and acetic acid (0·57 ml, 10 mmol) in benzene (35 ml) was refluxed for 24 h under nitrogen. The water produced was removed in a Dean–Stark apparatus. After the theoretical amount of water (1·8 ml) was collected the reaction mixture was cooled, the solvent was removed and *2-[1-(2-chlorophenyl)ethylidene]malononitrile* (19 g, 95%) was distilled at 102°/0·05 mm (Found: C, 65·4; H, 3·8; N, 13·9. $C_{11}H_7ClN_2$ requires C, 65·2; H, 3·5; N, 13·8%). $\nu_{max}$ (liquid film) 2240 (CN), 1600, 1585, 765. $^1$H n.m.r. $\delta$ 2·53, s, $CH_3$; 7·0–7·5, m, 4H. $^{13}$C n.m.r. $\delta$ 24·4, 111·6, 127·7, 128·1, 130·6, 131·9, 135·8. Mass spectrum *m/e* 204, 202 (M).

*2-[1-(2-Chlorophenyl)-3-dimethylaminoprop-2-enylidene]malononitrile (14)*

Dimethylformamide dimethyl acetal (3·3 ml, 24·8 mmol, 1·2 equiv.) was added to 2-[1-(2-chlorophenyl)ethylidene]malononitrile (4·27 g, 21·1 mmol) under nitrogen with stirring at 20°. After the solid had formed (1 h) the volatile materials were removed under vacuum at 50°. The residue was dissolved in dichloromethane and chromatographed on alumina with dichloromethane. *2-[1-(2-Chlorophenyl)-3-dimethylaminoprop-2-enylidene]malononitrile* (14) (4·73 g, 18·3 mmol, 89%) was obtained pure after recrystallization from dichloromethane/light petroleum as yellow prisms, and had m.p. 185–186° (Found: C, 65·2; H, 4·6; N, 16·0. $C_{14}H_{12}ClN_3$ requires C, 65·3; H, 4·7; N, 16·3%). $\nu_{max}$ 2200, 1620, 1460, 1380 cm$^{-1}$. N.m.r. (80 MHz) $\delta$ 3·02, s, 2 × OMe; 5·86, d, *J* 12·8 Hz, 1H, NCH=C**H**; 6·49, d, *J* 12·8 Hz, 1H, NC**H**=CH; 7·1–7·7, m, 4H. Mass spectrum *m/e* 259, 257 (M), 222 (M − Cl).

*2-[1-(2-Bromophenyl)-3-dimethylaminoprop-2-enylidene]malononitrile (16)*

To 2-[1-(2-bromophenyl)ethylidene]malononitrile (3·11 g, 12·6 mmol) was added, with stirring under nitrogen at 20°, dimethylformamide dimethyl acetal (2·5 ml, 1·5 equiv.). The reaction mixture immediately turned yellow, then darkened to red and eventually purple. After about 1 h the reaction mixture became solid. The reaction mixture was heated (50°) under vacuum to remove volatile material. The residue was dissolved in dichloromethane and chromatographed on alumina. The *enamine* (16) (3·60 g, 95%) was recrystallized from dichloromethane/light petroleum as yellow needles, m.p. 177–178° (Found: C, 55·4; H, 4·1; N, 13·8. $C_{14}H_{12}BrN_3$ requires C, 55·7; H, 4·0; N, 13·9%). $\nu_{max}$ 2200 (CN), 1610, 1265, 770 cm$^{-1}$. $^1$H n.m.r. (80 MHz) $\delta$ 3·03, s, 2 × NMe; 5·84, 6·54, ABq, *J* 12·5 Hz, HC=CH; 7·1–7·9, m, 4H. $^{13}$C n.m.r. $\delta$ 37·9, 46·0 (2 × NMe), 97·5, 116·2, 122·1, 128·0, 130·5, 131·3, 132·0, 133·7, 136·3, 155·8, 170·2. Mass spectrum *m/e* 303, 301 (M), 222.

*4-(2-Bromophenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (17)*

(i) The enamine (16) (244 mg, 0·81 mmol) was dissolved in acetic acid (10·5 ml) containing 11 M hydrochloric acid (3 ml) and water (1·5 ml) and the solution was refluxed for 2 h. On cooling, the solution was basified with 2 M sodium hydroxide and extracted with dichloromethane (4 × 20 ml). The combined organic extracts were dried and the solvent was removed leaving the *2-chloropyridine* (18) (57 mg, 19 mmol, 24%), m.p. 135° (Found: $M^{+\bullet}$, 291·9411. $C_{12}H_6{}^{79}Br^{35}ClN_2$ requires $M^{+\bullet}$, 291·9403). $\nu_{max}$ 2215 (CN), 1565, 1360, 750 $cm^{-1}$. $^1H$ n.m.r. $\delta$ 7·0–7·9, m, 5H; 8·53, d, $J$ 5 Hz, H 6. Mass spectrum *m/e* 296, 294, 292 (M), 215, 213 (M − Br), 178 (M − Br − Cl), 177.

The aqueous solution was acidified with 3 M hydrochloric acid and then neutralized to pH 7 with sodium hydrogen carbonate. The aqueous solution was extracted with dichloromethane (4 × 20 ml). The combined organic extracts were dried and the solvent removed under vacuum. The residue (95 mg, 43%) was shown by $^1H$ n.m.r. spectroscopy and t.l.c. comparison to be the *nitrile* (17) (see below).

(ii) The enamine (16) (966 mg, 3·2 mmol) was dissolved in acetic acid (10 ml) containing 98% sulfuric acid (2 ml) and water (3 ml). The solution was refluxed for 2 h after which time the reaction was complete. The solution was then neutralized with sodium hydrogen carbonate and extracted with dichloromethane (4 × 15 ml). The combined organic extracts were dried and the solvent removed. The residue was recrystallized from dichloromethane/light petroleum giving the nitrile (17) as off-white crystals (723 mg, 87%).

The analytical sample was prepared by flash chromatography with dichloromethane/methanol (95 : 5). The *nitrile* (17) was then recrystallized from dichloromethane/light petroleum, and had m.p. 228–229° (Found: C, 52·2; H, 2·5; N, 9·7. $C_{12}H_7BrN_2O$ requires C, 52·4; H, 2·6; N, 10·2%). $\nu_{max}$ 3240, 3110, 2230 (CN), 1700, 1628, 1603, 1210, 755 $cm^{-1}$. N.m.r. $\delta$ 6·14, d, $J$ 7 Hz, H 5; 7·1–7·7 m, 5H. Mass spectrum *m/e* 276, 274 (M), 195 (M − Br).

*4-(2-Bromophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (19)*

(i) The nitrile (17) (237 mg, 0·86 mmol) was dissolved in hot 75% sulfuric acid (10 ml) at 100–120°. The solution was stirred at that temperature for 3 h, then cooled and diluted with water (40 ml). The solution was then neutralized with sodium hydrogen carbonate and extracted with dichloromethane (4 × 20 ml). The combined organic extracts were dried and the solvent removed. Recrystallization from dichloromethane/light petroleum afforded the *amide* (19) (234 mg, 0·80 mmol, 93%) m.p. 230–232°. The analytical sample was purified by flash chromatography in dichloromethane/methanol (92 : 8) and had m.p. 233–234° (Found: C, 48·8; H, 2·9; N, 9·6. $C_{12}H_9BrN_2O_2$ requires C, 49·2; H, 3·1; N, 9·6%). $\nu_{max}$ 3540, 3420 (NH), 3150 (OH); 1670 $cm^{-1}$. $^1H$ n.m.r. (80 MHz) $\delta$ 6·46, d, $J$ 6·9 Hz, H 5; 7·0–8·0, m, 7H (including 7·75, d, $J$ 6·9 Hz, H 6); 12·95, br s, 1H, NH. $^{13}C$ n.m.r. ($CD_3SOCD_3$) $\delta$ 109·1, 120·6, 123·7, 127·4, 129·1, 129·5, 132·2, 136·2, 141·3, 153·9, 161·9, 165·8. Mass spectrum *m/e* 293, 291 (M), 213.

(ii) The enamine (16) (711 mg, 2·35 mmol) was dissolved in 75% sulfuric acid (20 ml) at 80–100° and the solution was stirred for 4 h. The resulting solution was poured into water (20 ml) and then neutralized with sodium carbonate until the amide (19) precipitated. The amide (648 mg, 92%) was collected and was identical with that obtained above.

*4-(2-Bromophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic Acid (20)*

(i) The amide (19) (212 mg, 0·72 mmol) was dissolved in 70% sulfuric acid (10 ml) at 80–100° with stirring. Then sodium nitrite (950 mg, *c.* 20 equiv.) was added portionwise over 2 h. The reaction mixture was cooled and poured into water (50 ml). Sodium hydroxide solution (2 M) was added until the acid (20) precipitated (pH 2) and the solid (166 mg, 0·56 mmol, 78%) was collected.

The analytical sample was prepared by flash chromatography in ethyl acetate/methanol (1 : 1). The *acid* (24) was recrystallized from ethanol/water and then from acetone/water and had m.p, 248–250° (Found: C, 48·9; H, 2·9; N, 4·9. $C_{12}H_8BrNO_3$ requires C, 49·0; H, 2·7; N, 4·8%). $\nu_{max}$ 3220, 3140, (NH, OH), 2700 (br) (OH), 1725, 1590, 1210 $cm^{-1}$. $^1H$ n.m.r. ($CD_3SOCD_3$, 80 MHz) $\delta$ 6·34, d, $J$ 6·5 Hz, H 5; 7·1–7·7, m, 4H; 7·86, d, $J$ 6·5 Hz, H 6. $^{13}C$ n.m.r. ($CD_3SOCD_3$) $\delta$ 111·2, 120·0, 127·5, 128·4, 129·7, 132·1, 132·6, 140·3, 157·6, 164·2. Mass spectrum *m/e* 293, 291 (M − 2), 251, 249.

(ii) The nitrile (17) (323 mg, 1·17 mmol) was dissolved in 75% sulfuric acid (10 ml) at 80–100° and stirred for 2 h. Then sodium nitrite (*c.* 0·5 g) was added portionwise over 2 h. The reaction

mixture was worked up as above to give (20) (262 mg, 76%) m.p. 246–248°. The infrared spectrum matched that of the acid (20).

(iii) The enamine (16) (789 mg, 2·61 mmol) was dissolved in 75% sulfuric (25 ml) at 100°. The solution was sitrred for 4 h. Sodium nitrite (768 mg, 2·6 equiv.) was added as before and the reaction mixture worked up as described above. The yield of (20) was 698 mg (91%), m.p. 246–248°.

*4-(2-Bromophenyl)-N-(3,4-dimethoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (21)*

The acid (20) (276 mg, 0·94 mmol) was dissolved in dry tetrahydrofuran (30 ml) and 3,4-dimethoxyaniline (176 mg, 1·15 mmol, 1·2 equiv.) was added. The solution was cooled in ice and dicyclohexylcarbodiimide (255 mg, 1·25 mmol, 1·3 equiv.) was added. The solution was stirred under nitrogen at 15–20° for 14 h, additional dicyclohexylcarbodiimide (100 mg) being added after 11 h, and stirring was then continued for 14 h. The reaction mixture was then cooled in ice. The dicyclohexylurea was removed by filtration and the solvent evaporated. The residue was recrystallized from dichloromethane/light petroleum to give the *amide* (21) as yellow needles (351 mg, 87%), m.p. 242–245°.

The analytical sample was prepared by flash chromatography in dichloromethane/methanol (94 : 6), then recrystallized from dichloromethane/light petroleum and had m.p. 247–249° (Found: C, 55·6; H, 4·2; N, 6·5. $C_{20}H_{17}BrN_2O_4$ requires C, 56·0; H, 4·0; N, 6·5%). $\nu_{max}$ 3350 (NH), 3150 (br) (OH), 1735, 1680, 1540, 1515 $cm^{-1}$. $^1H$ n.m.r. (80 MHz) $\delta$ 3·86, s, 2×OMe; 6·34, d, $J$ 6·9 Hz, H5; 6·7–7·8, m, 8H (including 7·54, d, $J$ 6·9 Hz, H6); 11·15, br s, NH; 11·83, br s, NH. $^{13}C$ n.m.r. ($CD_3SOCD_3$) $\delta$ 55·5, 55·8, 104·9, 109·0, 111·6, 112·2, 120·4, 123·8, 127·4, 128·9, 129·5, 132·3, 136·2, 139·6, 140·6, 145·2, 148·7, 153·6, 161·7, 168·1. Mass spectrum $m/e$ 430, 420 (M), 349 (M−Br).

*Dehydroperloline (6-(3,4-Dimethoxyphenyl)benzo[c][2,7]naphthyridine-4,5(3H,6H)-dione) (22)*

(i) The amide (21) (223 mg, 0·52 mmol) was partly dissolved in dry tetrahydrofuran (20 ml) at −70° under nitrogen and lithium diisopropylamide in tetrahydrofuran (10 ml) at −70° [prepared from diisopropylamine (0·4 ml, 2·9 mmol, 5·5 equiv.) and butyllithium (2·5 ml, 1 M, 2·5 mmol, 4·8 equiv.) in tetrahydrofuran (10 ml)] was added dropwise over 10 min. The reaction mixture was allowed to warm slowly to 20° and became homogeneous during warming. The solution changed colour from orange to dark burgundy over 2 h. After 4 h the solution was poured into 3 M hydrochloric acid (10 ml) followed by brine (20 ml). The layers were separated and the aqueous phase was extracted with dichloromethane (5 × 15 ml). The combined organic extracts were dried and the solvent was removed under vacuum.

The residue was purified by preparative t.l.c. on silica with dichloromethane/ethanol (90 : 10), the plate being run twice. The components which fluoresced intensely under 360-nm light were collected and further purified by chromatography on a commercial alumina t.l.c. plate, with dichloromethane/ethanol (85 : 15). The band which fluoresced under 360-nm light was collected and recrystallized from dichloromethane/light petroleum to give colourless needles of dehydroperloline, m.p. 276–283° (lit. 284°) (21 mg, 12%).

The aqueous solution was neutralized with sodium carbonate, which caused a colour change from yellow to red. The neutral solution was extracted with dichloromethane (3 × 20 ml). The combined organic extracts were dried and the solvent was removed under vacuum. The residue was purified by preparative t.l.c. on silica with dichloromethane/methanol (95 : 5). The component at $R_F$ 0·65 was identified by t.l.c. and $^1H$ n.m.r. spectroscopy as 3,4-dimethoxyaniline (12 mg, 15%).

(ii) The amide (21) (453 mg, 1·06 mmol) was partly dissolved in dry tetrahydrofuran (20 ml) at −60°, then lithium hexamethyldisilazide (4·1 equiv.) [prepared from butyllithium (4·3 ml, 1 M, 4·1 equiv.) and hexamethyldisilazane (0·95 ml, 730 mg, 4·5 mmol, 4·3 equiv.) in tetrahydrofuran (10 ml) at −60°] was added slowly over 10 min. The reaction mixture became homogeneous on warming and was then refluxed. The progress of the reaction was followed by t.l.c.; after 4 days no starting amide (21) remained. The solution was poured into 3 M hydrochloric acid (10 ml), then brine (10 ml) was added, the layers were separated and the aqueous phase was extracted with dichloromethane (4 × 15 ml). The combined organic extracts were dried and evaporated to dryness. Flash chromatography of the residue with dichloromethane/ethanol (80 : 20) gave dehydroperloline (317 mg, 86%) m.p. 283–287°. The sample was recrystallized from ethanol, which gave dehydroperloline as white crystals, m.p. 284–287° (Found: $M^{+\cdot}$ 348·1103. Calc. for $C_{20}H_{16}N_2O_4$: $M^{+\cdot}$

348·1110). $\nu_{max}$ 3340, 1695, 1630, 1585 $cm^{-1}$. N.m.r. ($CD_3SOCD_3$, 80 MHz) $\delta$ 3·72, s, 3H, OMe; 3·85, s, 3H, OMe; 6·62, d, *J* 7 Hz, 1H, H5; 6·8–8·2, m, 7H; 8·40, d, *J* 7 Hz, 1H, H6. Mass spectrum *m/e* 348 (M).

(iii) The reaction was repeated using amide (13) (170 mg, 0·44 mmol) and lithium hexamethyldisilazide (4 equiv.), refluxed for 4 days. Dehydroperloline (22) was obtained in 50% yield (77 mg), m.p. 282–287°, and was identical by t.l.c. with that obtained above.

(iv) The amide (21) (175 mg, 0·41 mmol), potassium carbonate (225 mg, 4 equiv.), copper bronze (2 mg, 1%) and copper(I) iodide (2 mg, 1%) were mixed in butan-1-ol and the mixture was refluxed for 2 h. The solvent was removed and the residue was dissolved in 1 M hydrochloric acid and dichloromethane. The layers were separated and the aqueous phase was extracted with dichloromethane (4 × 15 ml). The combined organic extracts were dried and the solvent removed under vacuum, leaving dehydroperloline (103 mg, 73%) which was identical by t.l.c. analysis (silica, dichloromethane/ethanol (90 : 10)) with that obtained above.

*6-(3,4-Dimethoxyphenyl)-5-hydroxy-5,6-dihydrobenzo*[c][*2,7*]*naphthyridin-4*(3H)*-one* (*1*)

Dehydroperloline (156 mg, 0·45 mmol) was partly dissolved in dry tetrahydrofuran (10 ml) at 20°, then sodium bis(methoxyethoxy)aluminium hydride (1 ml, 2 M, 2 equiv.) was added. The mixture became homogeneous and after 2 min the solution was poured into 3 M hydrochloric acid (10 ml) followed by brine (10 ml). The layers were separated and the aqueous phase was extracted with dichloromethane (4 × 15 ml). The combined organic extracts were dried and evaporated to dryness. The residue was chromatographed on alumina with dichloromethane/ethanol (90 : 10) which gave perloline (111 mg, 0·32 mmol, 70%) identical by t.l.c. (alumina and silica) with an authentic sample of perloline hydrochloride. The mass spectrum and m.p. and mixed m.p., 220–225°, were identical with those of an authentic sample.

*Attempted Reduction of 4-(2-Chlorophenyl)-*N*-(3,4-dimethoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide* (*13*)

(i) The amide (13) (83 mg, 0·22 mmol) was dissolved in tetrahydrofuran (20 ml) and a solution of sodium bis(methoxyethoxy)aluminium hydride in benzene (2 M, 3 ml, excess) was added under nitrogen. The solution was stirred at reflux but after 2 h no evidence for reduction products could be obtained.

(ii) The amide (13) (285 mg, 0·76 mmol) was partly dissolved in tetrahydrofuran (40 ml) and lithium aluminium hydride (0·1 g) was added and the mixture was refluxed under nitrogen. After 4 h no change in the amide (13) was observed.

(iii) The amide (13) (293 mg, 0·76 mmol) was dissolved in tetrahydrofuran (20 ml) under nitrogen, then borane–dimethyl sulfide (10 M, 0·2 ml, 2 mmol, 3 equiv.) was added and the solution was stirred at reflux for 3 days. None of the starting amide (13) remained, and the reaction was quenched by pouring into 3 M hydrochloric acid (10 ml) and neutralized with sodium carbonate. The solution was then extracted with dichloromethane (5 × 20 ml). The combined organic extracts were dried and evaporated to dryness, which gave an intractable mixture. Under similar conditions the amide (21) also gave only intractable mixtures.

*Ethyl 3-(3-Bromophenyl)-2-cyanobut-2-enoate*

3-Bromoacetophenone (2 g) and ethyl cyanoacetate (1·35 ml) were made to react as in the synthesis of (9) above, and the crude product purified by chromatography on alumina, followed by distillation, to give 2·5 g (85%) of a colourless *liquid*, b.p. 125°/0·1 mm (Found: $M^{+\cdot}$ 293·0149. $C_{13}H_{12}BrNO_2$ requires $M^{+\cdot}$ 293·0144). $\nu_{max}$ 2165, 1705, 1665 $cm^{-1}$. N.m.r. $\delta$ 7·2–7·6, m, 4H; 4·34, q, *J* 7 Hz, 4·08, q, *J* 7·5 Hz, 2H; 2·65, s, 2·50, s, 3H; 1·42, t, *J* 7 Hz, 1·07, t, *J* 7·5 Hz, 3H.

*Ethyl 3-(3-Bromophenyl)-2-cyano-5-dimethylaminopenta-2,4-dienoate*

The ester above (1·0 g) was treated with dimethylformamide dimethyl acetal (1 ml) as for the synthesis of (10) above. Chromatography on alumina eluted the product as yellow needles (0·49 g), m.p. 123–125° after recrystallization from acetone/light petroleum (Found: $M^{+\cdot}$, 348·0479. $C_{16}H_{17}BrN_2O_2$ requires $M^{+\cdot}$, 348·0473). $\nu_{max}$ 2150, 1655, 1595 $cm^{-1}$. N.m.r. $\delta$ 7·1–7·6, m, 5H; 6·48, d, *J* 13 Hz, 5·90, d, *J* 13 Hz, 1H; 4·26, q, *J* 6·5 Hz, 4·15, q, *J* 7 Hz, 2H; 3·00, s, 6H; 1·33, t, *J* 6·5 Hz, 1·18, t, *J* 7 Hz, 3H.

*Ethyl 4-(3-Bromophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate*

The enamine above (0·4 g) was refluxed with 80% acetic acid for 1·5 h and worked up as for (11) above. The acidic fraction was recrystallized from dichloromethane/light petroleum as off-white needles, m.p. 134–136° (0·23 g, 62%) (Found: $M^{+\cdot}$, 321·0007. $C_{14}H_{12}BrNO_3$ requires $M^{+\cdot}$, 321·0001). $\nu_{max}$ 1730, 1650, 1620 $cm^{-1}$. N.m.r. $\delta$ 7·5, m, 5H; 6·32, d, $J$ 5 Hz, H4; 4·08, q, $J$ 7·5 Hz, 2H; 0·96, t, $J$ 7·5 Hz, 3H.

*4-(3-Bromophenyl)-N-(3,4-dimethoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (25)*

The *ester* (100 mg) was hydrolysed in the usual way with aqueous-methanolic sodium hydroxide. The crude acid (80 mg) was converted into the title compound in an identical fashion to that used in the preparation of (13) above. The crude product was chromatographed on silica, and dichloromethane/5% ethanol eluted the *amide* as colourless crystals (20 mg), m.p. 237–240° (Found: $M^{+\cdot}$, 428·0386. $C_{20}H_{17}BrN_2O_4$ requires $M^{+\cdot}$, 428·0372).

*Reaction of (25) with Lithium Hexamethyldisilazide*

The amide above (6 mg) was refluxed for 4 days with lithium hexamethyldisilazide (1 ml, 1 M), as with (13) above. The reaction progress was followed by t.l.c. comparison with an authentic sample of dehydroperloline. No dehydroperloline was observed, even after concentration of the corresponding $R_F$ material by thin-layer chromatography.

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