Reaction of 4-Phenylbut-3-en-2-one with Cyanoacetamide in 2:1 Ratio

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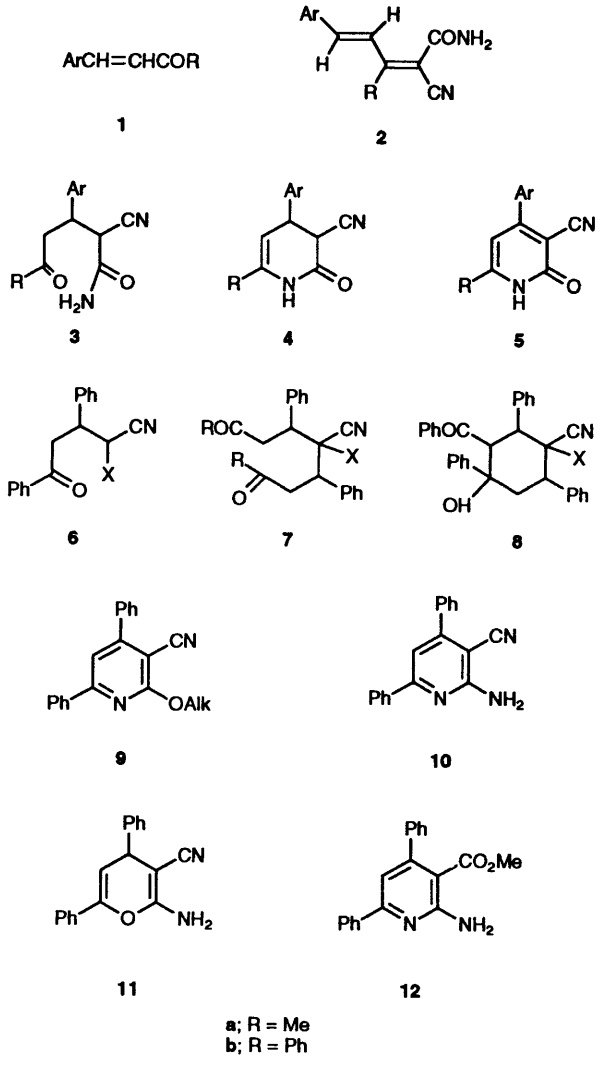
The reaction of 4-phenylbut-3-en-2-one with cyanoacetamide is not confined to a 1:1 reaction [which results in formation of 3-cyano-6-methyl-4-phenylpyridin-2(1*H*)-one]. The reaction of 2 mole equivalents of 4-phenylbut-3-en-2-one with one of cyanoacetamide also takes place, the products being 1-cyano-6-hydroxy-6-methyl-4-methylene-8,9-diphenyl-3-azabicyclo[3.3.1]nonan-2-one and 3-cyano-6-methyl-3-(3-oxo-1-phenylbutyl)-4-phenyl-3,4-dihydropyridin-2(1*H*)-one. The latter compound cyclises in acid medium to form 6-acetyl-4-cyano-1-methyl-5,8-diphenyl-2-azabicyclo-[2.2.2]octan-3-one. X-Ray crystal structures of the 3-azabicyclo[3.3.1]nonan-2-one and the 3-azabicyclo[2.2.2]octan-2-one derivatives are described.

Pyridin-2(1*H*)-one derivatives display important biological activity in a number of areas. Probably the best known compounds are the cardiotonics amrinone and milrinone,[1] but related pyridin-2(1*H*)-ones are also active as oral hypoglycaemic agents.[2] Very recently, research in AIDS chemotherapy has identified pyridin-2(1*H*)-ones as important HIV-1-specific reverse transcriptase inhibitors.[3–5]

Many pyridin-2(1*H*)-ones of type **5** have been synthesized (although in poor yield) by the reaction of α,β-unsaturated ketones of type **1** with cyanoacetamide (or, alternatively, with an alkyl cyanoacetate and ammonium acetate), or by very similar methods. An exception to this behaviour, resulting in the alternative formation of the butadiene derivatives **2a**, has recently been reported.[6] Apart from this, however, reaction of the ketones **1** with cyanoacetamide normally affords pyridin-2(1*H*)-ones, both when benzalacetone **1a** and chalcone **1b** derivatives are used. From the base-catalysed reaction of chalcone with cyanoacetamide (or with an alkyl cyanoacetate and ammonium acetate) it is possible to isolate the uncyclised product **3b**,[7,8] the dihydropyridin-2(1*H*)-one **4b** (which may be obtained directly from the reactants or from the uncyclised product **3b**)[7–11] or the fully oxidised pyridin-2(1*H*)-one **5b**.[7–12] From benzalacetone, however, no authenticated intermediate products, *e.g.*, **4a**, have been isolated, only the fully oxidised pyridin-2(1*H*)-one **5a** having been recorded.[9–11]

Only 1:1 reactions of α,β-unsaturated ketones **1** with cyanoacetamide have been described. This contrasts sharply with the behaviour of the ketones **1** when they react with other compounds containing an active methylene group. Thus, chalcone **1b** with benzyl cyanide affords not only a 1:1 adduct **6** (X = Ph),[13,14] but also a 2:1 adduct which is a cyclohexanol derivative **8** (X = Ph);[15] the open-chain formulation **7b** (X = Ph) originally proposed[13] was incorrect. Similarly, the reaction of chalcone with malononitrile may afford the simple 1:1 adduct **6** (X = CN)[7,16] or the 2:1 adduct which, again, is correctly formulated as the cyclohexanol **8** (X = CN)[16] rather than the open-chain structure **7b** (X = CN) originally formulated.[7] [In the presence of sodium alkoxide, the 1:1 adduct **6** (X = CN) may undergo cyclisation to form a 2-alkoxypyridine **9**,[17–19] while a 2-aminopyridine **10** may be formed in the presence of ammonium acetate;[20,21] a 2-aminopyran derivative **11** has also been reported.[18]]

To some extent, alkyl cyanoacetates behave in an analogous manner. Thus, an uncyclised 1:1 adduct **6** (X = CO_2Me) (and a 1:1 product having an aminopyridine structure **12**)[12] have been described, as well as a 2:1 product originally formulated as an open-chain structure **7b** (X = CO_2Me)[22] but now known



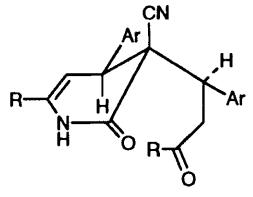
to be the cyclohexanol **8** (X = CO_2Me).[23] However, alkyl cyanoacetates and ammonium acetate may also react in the same way as cyanoacetamide, the reactions of which have already been described.

Clearly, the most significant difference between the reported reactions of α,β-unsaturated ketones with cyanoacetamide, and related reactions with other compounds containing an active

methylene group, has been the failure of cyanoacetamides to form 2:1 adducts. [This failure may be attributed to the readiness with which 1:1 adducts undergo ring closure involving the amide group to form pyridin-2(1*H*)-ones.] However, we now report the isolation of products which represent the reaction of 2 mole equivalents of the ketones **1a** with one of cyanoacetamide. The structures of these products differ significantly from those of the known 2:1 adducts **8**.

Results and Discussion

The 2:1 adducts obtained directly from the unsaturated ketones **1a** are the monocyclic 3,4-dihydropyridin-2(1*H*)-ones **13a** and the related bicyclic 3-azabicyclo[3.3.1]nonan-2-ones **14a**. These 2:1 products are obtained by varying the experimental conditions, the most favourable reaction conditions tending to be considerably milder than those described in the literature for the preparation of the pyridin-2(1*H*)-ones **5**. Any simple pyridin-2(1*H*)-ones **5** which may be formed as a result of 1:1 reaction tend to crystallise first from solution, the more soluble 2:1 products crystallising more slowly when the solution is stored for some time.



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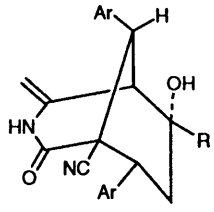

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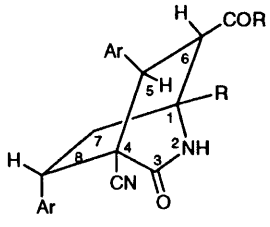


15

a; R = Me
b; R = Ph

4-Phenylbut-3-en-2-one and cyanoacetamide, when heated together for several hours in ethanol containing catalytic piperidine, afford only the pyridin-2(1*H*)-one **5a** (Ar = Ph). When the same reaction mixture is heated under reflux for 15 min and then set aside at room temperature, the bicyclic product **14a** (Ar = Ph) is obtained. A similar reaction mixture, warmed very gently for 40 min, affords the monocyclic dihydropyridin-2(1*H*)-one product **13a** (Ar = Ph). [This crystallises to a slight extent as a separate compound, but mainly as an intimate mixture with the pyridin-2(1*H*)-one **5a** (Ar = Ph); an unsuccessful attempt to form a hydrazone of the dihydropyridin-2(1*H*)-one derivative **13a** (Ar = Ph) led to the finding that heating of this mixture in ethanol with a little hydrazine hydrate has the effect of causing the two components to crystallise separately.]

When the monocyclic dihydropyridin-2(1*H*)-one **13a** (Ar = Ph) is heated in acid solution, the active methylene group in the side-chain reacts with the pyridin-2-one ring at the 6-position, affording the bicyclic 6-acetyl-2-azabicyclo[2.2.2]-octan-3-one **15a** (Ar = Ph) in excellent yield.

A tetraphenyl-substituted dihydropyridin-2(1*H*)-one **13b** (Ar = Ph) has also been prepared, in a two-step synthesis. When the reaction of chalcone with cyanoacetamide is carried out in aq. ethanol, the main product is found to be the known, uncyclised adduct **3b** (Ar = Ph). However, when the known dihydropyridin-2(1*H*)-one derivative **4b** (Ar = Ph)[7–11] is first prepared and then treated with a second mole equivalent of chalcone, the 2:1 product **13b** (Ar = Ph) is obtained. This suggests that, while the 2:1 products **13** and **14** may well be formed *via* an uncyclised 2:1 intermediate **7** (X = $CONH_2$), it is also possible that an unstable, cyclised tetrahydropyridine intermediate of type **4** may be involved.

The two possible pathways by which 4-phenylbut-3-en-2-one may react with cyanoacetamide are outlined in Scheme 1. Formation of the 2:1 compounds **13** and **14** is not confined to phenyl derivatives (Ar = Ph). The *o*-methoxyphenyl derivative **13a** (Ar = C_6H_4OMe-*o*) is obtained in small yield when the *o*-methoxyphenyl-substituted ketone **1a** (Ar = C_6H_4OMe-*o*) is heated at 40 °C in ethanol containing catalytic piperidine with cyanoacetamide, but when acetone is used as reaction solvent the bicyclic product **14a** (Ar = C_6H_4OMe-*o*) is obtained. (Minor products formed from the reaction of acetone with cyanoacetamide include the piperidine salt of the 4,4-dimethyl-3,4-dihydropyridin-2(1*H*)-one derivative **19**, and 2,4-dicyano-3,3-dimethylpentane-1,5-diamide **20**, which is present as a mixture of *meso*- and (±)-forms). A further variation of the reaction conditions, using aq. ethanol, results unexpectedly in the formation of the carbamoyl-substituted 1:1 reaction product **16** (Ar = C_6H_4OMe-*o*).

Reaction of cyanoacetamide with the 3,4-dimethoxyphenyl-substituted ketone **1a** [Ar = $C_6H_3(OMe)_2$-3,4]in ethanol affords only the pyridin-2(*H*)-one **4a** [Ar = $C_6H_3(OMe)_2$-3,4], but in acetone both the pyridin-2(1*H*)-one and the 3-azabicyclo[3.3.1]nonan-2-one derivative **14a** [Ar = C_6H_3-$(OMe)_2$-3,4] are obtained

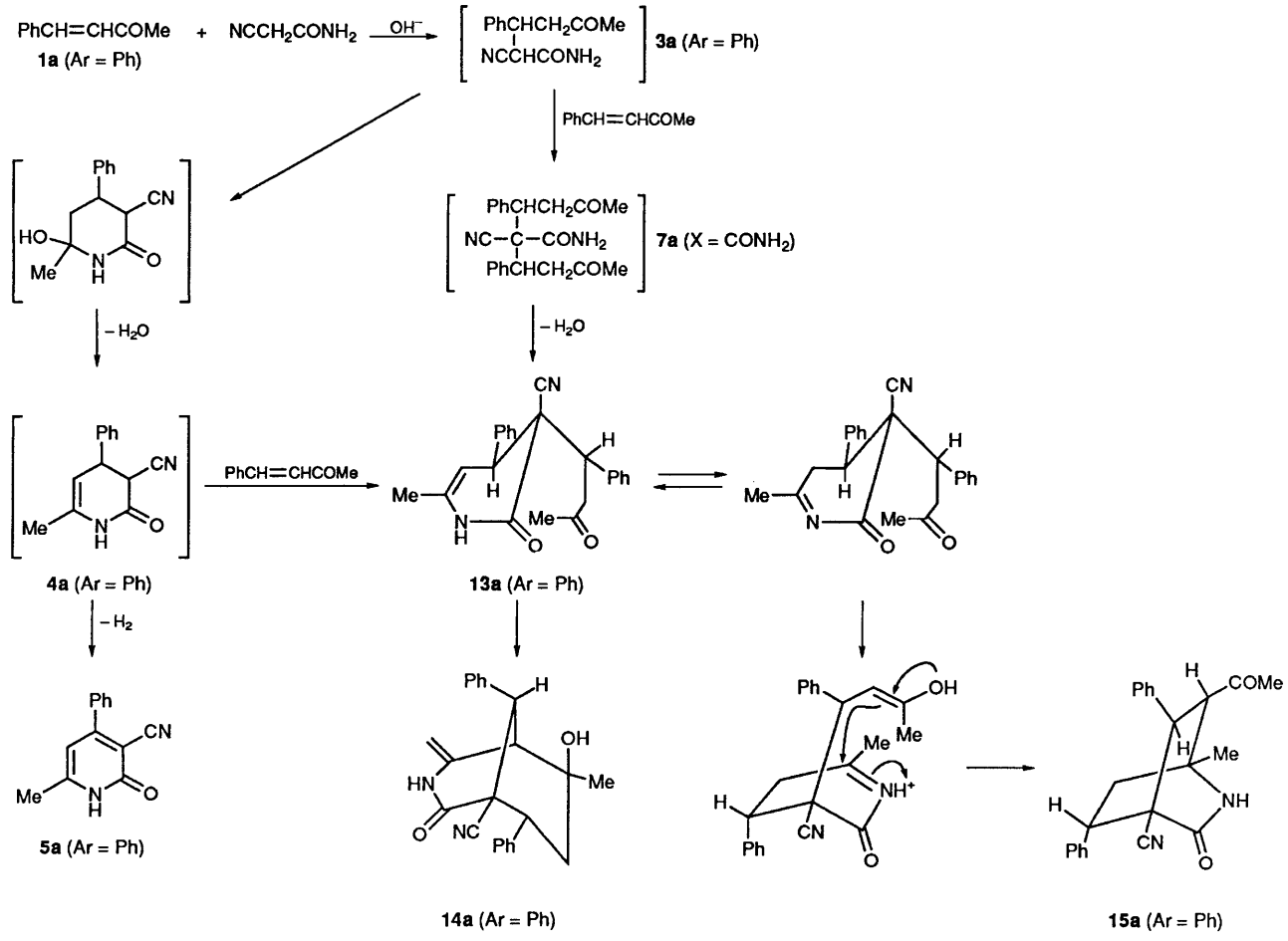
The catalytic effect of alkoxide ions on the reaction of cyanoacetamide with the unsaturated ketones **1** differs from that of piperidine. When a trace of sodium alkoxide is used as catalyst with chalcone, the product is the 3-carbamoyl-3,4-dihydropyridin-2(1*H*)-one **17b** (Ar = Ph) which has previously been obtained using malonamide.[11] In the case of the methyl ketones **1a** (Ar = Ph) and **1a** (Ar = C_6H_4OMe-*o*), the products are the related 3-carbamoyl-4,5-dihydropyridin-2-(3*H*)-ones **18a** (Ar = Ph) and **18a** (Ar = C_6H_4OMe-*o*). (The existence of isomeric forms of 3-carbamoyltetrahydro-2-oxopyridines has previously been demonstrated.[11,24,25])

The formulations **13**–**18** are confirmed by their IR, ^1H NMR and ^{13}C NMR spectra. The molecular structures of 1-cyano-6-hydroxy-6-methyl-4-methylene-8,9-diphenyl-3-azabicyclo-[3.3.1]nonan-2-one **14a** (Ar = Ph) and 6-acetyl-4-cyano-1-methyl-5,8-diphenyl-2-azabicyclo[2.2.2]octan-3-one **15a** (Ar = Ph), as determined by X-ray diffraction, are presented in Figs. 1 and 2, respectively. The intermolecular hydrogen-bonding scheme in compound **15a** (Ar = Ph) is shown as the two thick bonds in Fig. 3.

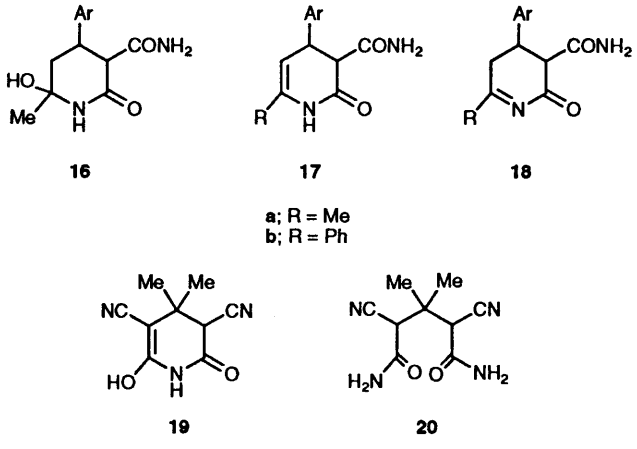
Experimental

All m.p.s were determined on a Gallenkamp melting point apparatus and are uncorrected; NMR spectra were recorded in ppm from TMS, in the solvent stated, on a Bruker WP80 or MSL 300 spectrometer. *J* Values are measured in Hz. ^{13}C NMR spectra were recorded on the MSL 300 instrument. IR spectra were recorded on a Perkin–Elmer 298 or 883 instrument.

Reaction of 4-*Phenylbut*-3-*en*-2-*one* **1a** (Ar = Ph) *with Cyanoacetamide.*—(*a*) A mixture of 4-phenylbut-3-en-2-one **1a** (Ar = Ph) (1.46 g, 10 mmol) and cyanoacetamide (0.84 g, 10 mmol) in ethanol (40 cm^3) containing piperidine (0.2 cm^3), heated under reflux for 7 h and then cooled to 20 °C, afforded 6-



Scheme 1



methyl-2-oxo-4-phenyl-1,2-dihydropyridine-3-carbonitrile **5a** (Ar = Ph)[8] (0.53 g, 25%).

(*b*) A solution of 4-phenylbut-3-en-2-one **1a** (Ar = Ph) (7.30 g, 50 mol) in ethanol (10 cm^3) containing piperidine (0.4 cm^3) was added to a solution of cyanoacetamide (4.20 g, 50 mmol) in ethanol (50 cm^3) which had been warmed to 35 °C. The temperature of the reaction mixture was maintained at 35 °C for 40 min before the mixture was cooled to room temperature. Unchanged cyanoacetamide (1.9 g, 45%) which separated was removed by filtration, and the filtered solution was evaporated slowly, to afford a thick, syrupy gum. This was dissolved in methanol, and the solution was set aside until, after several days, crystallisation began. A crop of crystals was harvested daily for 14 days. The product collected on the fifth and sixth days was 6-*methyl*-2-*oxo*-3-(3′-*oxo*-1′-*phenylbutyl*)-4-*phenyl*-1,2,3,4-*tetrahydropyridine*-3-*carbonitrile* **13a** (Ar = Ph) (0.26 g), m.p. 227–229 °C (from MeOH) (Found: C, 76.9; H, 6.2; N, 7.8. $C_{23}H_{22}N_2O_2$ requires C, 77.1; H, 6.2; N, 7.8%); M^+, 358; ν_{max}(Nujol)/cm^{-1} 3249 (NH), 2252 (C≡N), 1704 (CO) and 1680 (CONH); δ_H[300 MHz; $(CD_3)_2SO$; Me_4Si] 9.78 (1 H, br s, NH), 7.37–7.20 (10 H, m, ArH), 5.01 (1 H, d, *J* 6.3, 5-H), 3.92 (1 H, d, *J* 6.3, 4-H), 3.83 (1 H, dd, *J* 3.7 amd 9.8, 1′-H), 3.34 (2 H, ddd, *J* 3.7, 9.8 and 17.8, 2′-H_2), 2.07 (3 H, s, Me) and 1.91 (3 H, s, Me); δ_C 205.3 (C=O), 162.8 (amide C=O), 138.6 (Ar C-1), 138.3 (Ar C-1), 133.7 (C-6), 128.6 (two Ar C), 128. 4 (two Ar C), 128.3 (two Ar C), 127.8 (two Ar C), 127.6 (Ar C), 127.3 (Ar C), 117.4 (C≡N), 100.8 (C-5), 56.8 (C-3), 44.8 (C-4 and C-2′), 42.0 (C-1′), 30.3 (Me) and 18.0 (Me).

All of the other crystallisation crops proved to be a 1:1 mixture of the tetrahydropyridin-2-one product **13a** (Ar = Ph) and 6-methyl-2-oxo-4-phenyl-1,2-dihydropyridine-3-carbonitrile **5a** (Ar = Ph) (1.97 g). This mixture, in ethanol (100 cm^3) containing hydrazine hydrate (1.0 cm^3), was heated on a water-bath for 45 min and was then stored at room temperature overnight. The pyridin-2(1*H*)-one **5a** (Ar = Ph) crystallised overnight and was removed by filtration. The filtered solution was then concentrated under reduced pressure, when the tetrahydropyridin-2-one product **13a** (Ar = Ph) crystallised; separation of the components of the mixture took place to the extent of ~90%. The total yield of the tetrahydropyridin-2-one product **13a** (Ar = Ph) was 1.35 g (15%).

(*c*) A mixture of 4-phenylbut-3-en-2-one **1a** (Ar = Ph) (1.46 g, 10 mmol) and cyanoacetamide (0.84 g, 10 mmol) in ethanol (25 cm^3) containing piperidine (0.2 cm^3) was heated under reflux for 15 min, and was then cooled to 20 °C. After 1 h

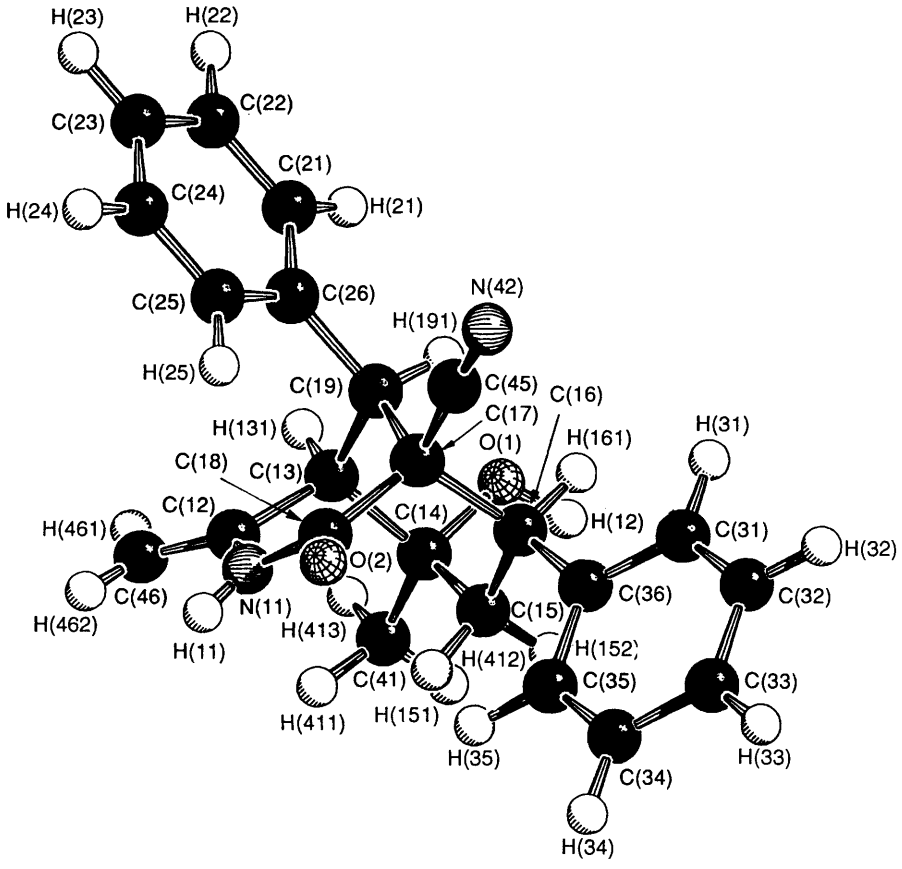


Fig. 1 X-Ray molecular structure of compound **14a** (Ar = Ph)

unchanged cyanoacetamide (0.26 g, 31%), which had crystallised from solution, was removed by filtration. The filtered solution was set aside in an open beaker; gradual evaporation of the solvent afforded a viscous gum. After 14 days, addition of a little methanol and scratching effected crystallisation of a solid which was a mixture of two products. These were readily separated by crystallisation, when they were identified as 6-methyl-2-oxo-4-phenyl-1,2-dihydropyridine-3-carbonitrile **5a** (Ar = Ph) (0.05 g, 5%) and 6-*hydroxy*-6-*methyl*-4-*methylene*-2-*oxo*-8,9-*diphenyl*-3-*azabicyclo*[3.3.1]*nonane*-1-*carbonitrile* **14a** (Ar = Ph) (0.22 g, 12%), m.p. 235–237 °C (Found: C, 76.9; H, 6.1; N, 7.9. $C_{23}H_{22}N_2O_2$ requires C, 77.1; H, 6.2; N, 7.8%); M^+, 358; ν_{max}(Nujol)/cm^{-1} 3443 (OH), 3222 (NH), 2257 (C≡N) and 1674 (C=O); δ_H[300 MHz $(CD_3)_2SO$; Me_4Si] 10.63 (1 H, s, NH), 7.38–7.20 (10 H, m, ArH), 5.25 (1 H, s, OH), 4.55 (1 H, s, H^a of =CH_2), 4.29 (1 H, d, *J* 1.6, H^b of =CH_2), 4.10 (1 H, s, 9-H), 3.75 (1 H, dd, *J* 3.3 and 13.5, 8-H), 2.58 (1 H, s, 5-H), 2.03 (1 H, t, *J* 13.5, H^a of CH_2), 1.72 (1 H, dd, *J* 3.3 and 13.5, H^b of CH_2) and 1.30 (3 H, s, Me); δ_C 162.5 (C=O), 140.1 (Ar C-1), 139.5 (Ar C-1), 138.4 (C-4), 129.3 (two Ar C), 128.6 (two Ar C), 127.7 (four Ar C), 127.3 (two Ar C), 118.3 (C≡N), 96.7 (=CH_2), 69.5 (C-5), 51.7 (C-9), 51.3 (C-1), 47.1 (C-8), 44.6 (C-5), 39.2 (C-7) and 28.4 (Me).

(*d*) A suspension of cyanoacetamide (1.26 g, 15 mmol) in dry ethanol (50 cm^3) was heated to dissolution, and the solution was then cooled to room temperature. A solution of sodium ethoxide from sodium (0.34 g) in dry ethanol (20 cm^3) was added to this, followed by 4-phenylbut-3-en-2-one **1a** (Ar = Ph) (2.19 g, 15 mmol), and the mixture was set aside at room temperature for 3 days. It was then saturated with carbon dioxide, when a solid separated. This product, when collected by filtration and recrystallised (methanol), was identified as 6-methyl-2-oxo-4-phenyl-2,3,4,5-tetrahydropyridine-3-carboxamide **18a** (Ar = Ph)[24] (1.82 g, 79%), δ_H[300 MHz; $(CD_3)_2SO$; Me_4Si] 8.94 (1 H, br s, NH), 8.83 (1 H, br s, NH), 7.27 (5 H, m, ArH), 3.55 (1 H, ddd, *J* 2.3, 5.3 and 10.1, 4-H), 2.97 (1 H, dd, *J* 2.3 and 1.6 (smaller coupling disappears on exchange with D_2O), 3-H], 2.44 (1 H, dd, *J* 10.1 and 12.5, H^a of CH_2), 1.98 (1 H, dd, *J* 5.3 and 12.5, H^b of CH_2) and 1.51 (3 H, s, Me).

Synthesis of 6-*Acetyl*-1-*methyl*-3-*oxo*-5,8-*diphenyl*-2-*azabicyclo*[2.2.2]*octane*-4-*carbonitrile* **15a** (Ar = Ph).—A solution of 6-methyl-3-(3-oxo-1-phenylbutyl)-2-oxo-4-phenyl-1,2,3,4-tetrahydropyridine-3-carbonitrile **13a** (Ar = Ph) (358 mg, 1 mmol) in ethanol (50 cm^3) and dil. hydrochloric acid (10%; 25 cm^3) was heated under reflux for 6 h. The solution was then concentrated under reduced pressure to 10 cm^3, and at room temperature a solid separated. This was collected by filtration, and was then extracted into methanol (80 cm^3) and set aside; after several days, as slow evaporation took place, 6-*acetyl*-1-*methyl*-3-*oxo*-5,8-*diphenyl*-2-*azabicyclo*[2.2.2]*octane*-4-*carbonitrile* **15a** (Ar = Ph) crystallised (255 mg, 71%), m.p. 294–296 °C (Found: C, 76.9; H, 6.15; N, 7.8. $C_{23}H_{22}N_2O_2$ requires C, 77.1; H, 6.2; N, 7.8%); ν_{max}(Nujol)/cm^{-1} 3280 (NH), 2252 (C≡N), 1710 (C=O) and 1687 (CONH); δ_H[300 MHz; $(CD_3)_2SO$; Me_4Si] 8.93 (1 H, s, NH), 7.58–7.05 (10 H, m, ArH), 3.62 (1 H, d, *J* 7.5, 5-H), 3.55 (1 H, d, *J* 7.5, 6-H), 3.51 (1 H, dd, *J* 10.6 and 5.7, 8-H), 2.75 (1 H, dd, *J* 10.6 and 13.3, H^a of CH_2), 2.10 (3 H, s, Me), 1.80 (1 H, dd, *J* 5.7 and 13.3, H^b of CH_2) and 1.37 (3 H, s, Me); δ_C 207.9 (C=O), 167.0 (amide C=O), 141.0 and 135.8 (two Ar C-1), 129.8 (Ar C), 128.6 (two Ar C), 128.4 (two Ar C), 128.3 (two Ar C), 128.2 (two Ar C), 127.4 (Ar C), 116.6 (CN), 58.0 (C-5), 54.3 and 53.9 (C-4 and -1), 48.3 (C-8), 44.5 (C-7), 39.7 (C-6), 31.8 (Me) and 21.8 (Me).

Reaction of 4-(2-*Methoxyphenyl*)*but*-3-*en*-2-*one* **1a** (Ar = C_6H_4OMe-*o*) *with Cyanoacetamide*.—(*a*) A mixture of 4-(2-methoxyphenyl)but-3-en-2-one (**1a**; Ar = C_6H_4OMe-*o*)[26]

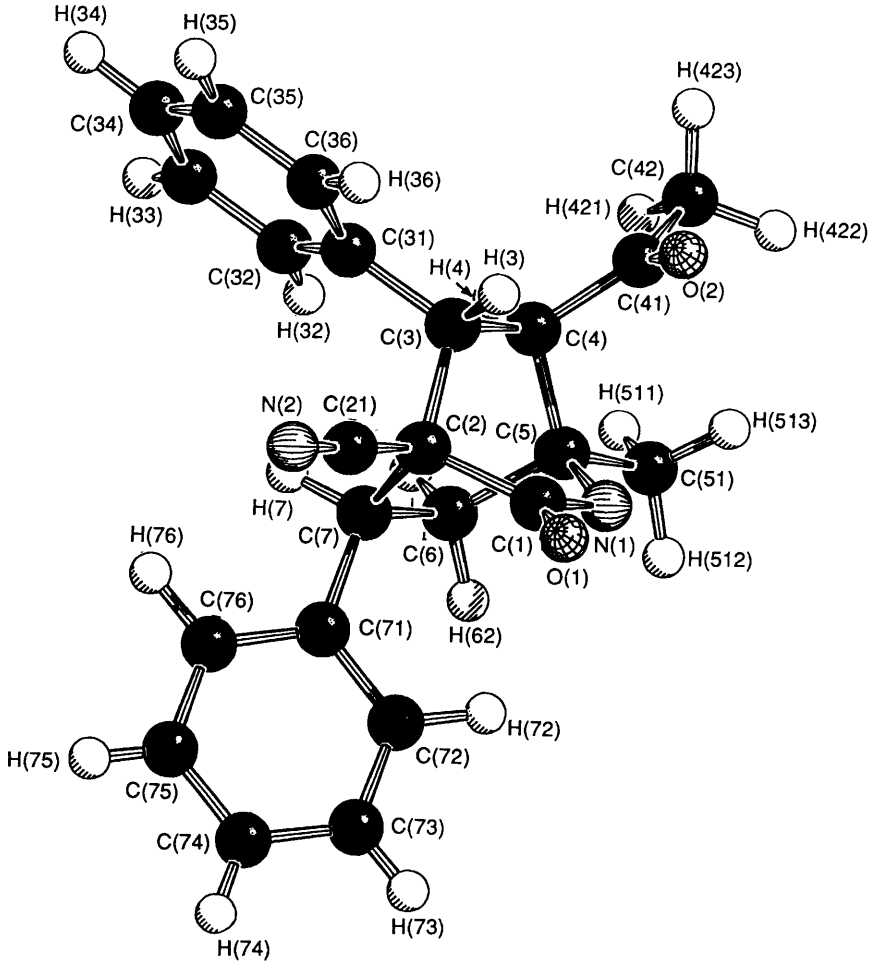


Fig. 2 X-Ray molecular structure of compound **15a** (Ar = Ph)

(1.76 g, 10 mmol) and cyanoacetamide (0.84 g, 10 mmol) in ethanol (30 cm^3) containing piperidine (0.2 cm^3) was heated under reflux for 7 h. The mixture was set aside at room temperture, and the solvent gradually evaporated. The only solid product, which crystallised slowly, was 4-(2-*methoxyphenyl*)-6-*methyl*-2-*oxo*-1,2-*dihydropyridine*-3-*carbonitrile* **5a** (Ar = C_6H_4OMe-*o*) (0.27 g, 14%), m.p. 300–302 °C (Found: C, 69.8; H, 5.0; N, 11.4. $C_{14}H_{12}N_2O_2$ requires C, 70.0; H, 5.0; N, 11.7%); ν_{max}(Nujol)/cm^{-1} 3303w (NH), 2231 (C≡N) and 1651 (C=O); δ_H[300 MHz; $(CD_3)_2SO$; Me_4Si] 12.62 (1 H, br s, NH), 7.59–6.97 (4 H, m, ArH), 6.20 (1 H, s, 5-H), 3.81 (3 H, s, OMe) and 2.30 (3 H, s, Me).

(*b*) A solution of 4-(2-methoxyphenyl)but-3-en-2-one (1.76 g, 10 mmol) and cyanoacetamide (0.84 g, 10 mmol) in acetone (30 cm^3) containing piperidine (0.4 cm^3) was warmed at 35 °C for 6 h. The mixture was then set aside in an open beaker for 4 days, when the solvent slowly evaporated, leaving a viscous gum. Addition of methanol (4 cm^3) and scratching caused immediate crystallisation of small quantities of products formed by the reaction of acetone with cyanoacetamide, *i.e.* the piperidine salt of 6-hydroxy-4,4-dimethyl-2-oxo-1,2,3,4-tetrahydropyridine-3,5-dicarbonitrile **19**[27] (0.04 g) and 2,4-*dicyano*-3,3-*dimethylpentane*-1,5-*diamide* **20** (0.03 g), m.p. 155–157 °C (Found: C, 51.9; H, 6.0; N, 26.9. $C_9H_{12}N_4O_2$ requires C, 51.9; H, 5.8; N, 26.9%); ν_{max}(Nujol)/cm^{-1} 3406 (NH), 3360 (NH), 3190 (NH), 2261 (C≡N), 1689 (C=O) and 1651 (C=O). The presence of a mixture of *meso* and (±) forms of the compound (in the ratio 2:3) was shown by the NMR spectra [300 MHz; $(CD_3)_2SO$; Me_4Si]. *meso*-Form: δ_H 7.99 (2 H, br s, exchangeable, NH_2), 7.67 (2 H, br s, exchangeable, NH_2), 3.75 (2 H, s, 2 × CH), 1.33 (3 H, s, Me), 1.25 (3 H, s, Me); δ_C 164.59 (2 × C=O), 116.8 (2 × C≡N), 45.32 (2 × CH), 45.30 (C-3), 23.9 (Me) and 21.9 (Me).

(±)-Form: δ_H 8.04 (2 H, br s, exchangeable, NH_2), 7.67 (2 H, br s, exchangeable, NH_2), 3.84 (2 H, s, 2 × CH) and 1.26 (6 H, s, 2 × Me); δ_C 164.62 (2 × C=O), 116.6 (2 × C≡N), 45.17 (C-3), 45.15 (2 × CH) and 22.2 (2 × Me).

Following removal of the two products **19** and **20** by filtration, another product crystallised quickly from the filtered solution. This, collected by filtration and purified by recrystallisation from methanol, was 4-(2-*methoxyphenyl*)-3-[1′-(2-*methoxyphenyl*)-3′-*oxobutyl*]-6-*methyl*-2-*oxo*-1,2,3,4-*tetrahydropyridine*-3-*carbonitrile* **13a** (Ar = C_6H_4OMe-2) (0.06 g, 3%) m.p. 220–222 °C (Found: C, 71.5; H, 6.1; N, 6.5. $C_{25}H_{26}N_2O_4$ requires C, 71.8; H, 6.2; N, 6.7%); ν_{max}(Nujol)/cm^{-1} 3228 (NH), 2247w (C≡N), 1712 (C=O) and 1674 (CONH); δ_H[300 MHz; $(CD_3)_2SO$; Me_4Si] 9.55 (1 H, br s, NH), 7.38–6.77 (8 H, m, ArH), 4.79 (1 H, d, *J* 6.4, 5-H), 4.53 (1 H, t, *J* 6.8, 1′-H), 4.27 (1 H, d, *J* 6.4, 4-H), 3.82 (3 H, s, OMe), 3.76 (3 H, s, OMe), 3.21 (2 H, d, *J* 6.8, 2′-H_2), 2.03 (3 H, s, Me) and 1.82 (3 H, s, Me).

The filtered solution was set aside at room temperature for a further 14 days, when another product began to crystallise slowly. This, collected by filtration and purified by recrystallisation from methanol, was 6-*hydroxy*-8,9-*bis*(2-*methoxyphenyl*)-6-*methyl*-4-*methylene*-2-*oxo*-3-*azabicyclo*[3.3.1]*nonane*-1-*carbonitrile* **14a** (Ar = C_6H_4OMe-2) (0.41 g, 23%), m.p. 232–235 °C (Found: C, 68.9; H, 6.6; N, 6.4. $C_{25}H_{26}N_2O_4 \cdot H_2O$ requires C, 68.8; H, 6.4; N, 6.4%); ν_{max}(Nujol)/cm^{-1} 3480 (H_2O), 3380 (OH), 3200 (NH), 2256 (C≡N) and 1674 (C=O);

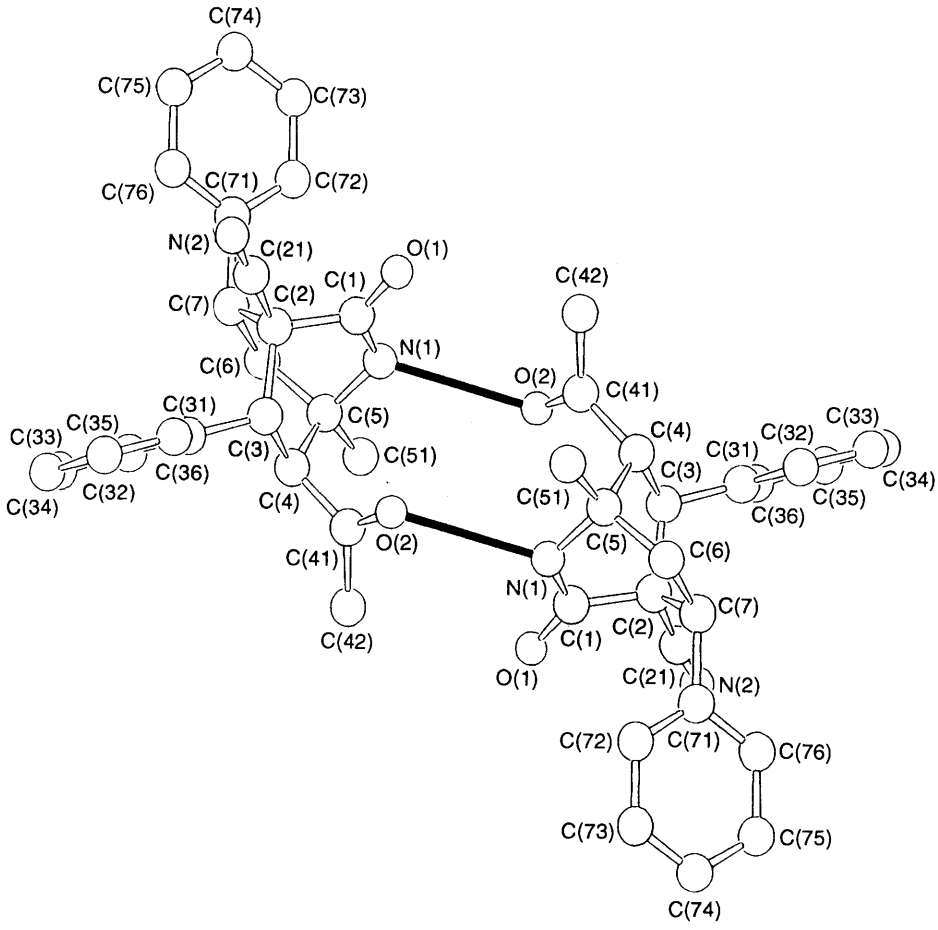


Fig. 3 X-Ray diagram of H-bonding scheme in compound **15a** (Ar = Ph)

δ_H[300 MHz; $(CD_3)_2SO$; Me_4Si] 10.50 (1 H, br s, NH), 7.25–6.87 (8 H, m, ArH), 5.04 (1 H, s, OH), 4.74 (1 H, s, H^a of $=CH_2$), 4.55 (1 H, s, H^b of $=CH_2$), 4.47 (1 H, dd partly concealed, *J* 3.2 and 13.5, 8-H), 3.99 (1 H, s, 9-H), 3.86 (3 H, s, OMe), 3.76 (3 H, s, OMe), 2.50 (1 H, s, 5-H), 1.98 (1 H, t, *J* 13.5, H^a of 7-H_2), 1.55 (1 H, dd, *J* 3.2 and 13.5, H^b of 7-H_2) and 1.27 (3 H, s, Me); δ_C 163.3 (C=O), 156.7 (two Ar C-2), 140.6 (C-4), 128.5 (Ar C-3), 128.4 (Ar C-3 and Ar C-6), 127.3 (Ar C-1), 126.7 (Ar C-1), 126.4 (Ar C-6), 120.0 (Ar C-4), 119.6 (Ar C-4), 118.3 (C≡N), 111.1 (Ar C-5), 111.0 (Ar C-5), 96.0 ($=CH_2$), 69.6 (C-6), 55.6 (2 × Me), 49.9 (C-9), 49.7 (C-1), 48.6 (C-8), 39.1 (C-7), 37.8 (C-5) and 28.5 (Me).

(*c*) Aq. cyanoacetamide (1.68 g, 20 mmol in 10 cm^3) was added to a solution of 4-(2-methoxyphenyl)but-3-en-2-one (3.52 g, 20 mmol) in ethanol (10 cm^3) containing piperidine (0.5 cm^3), and the temperature of the mixture was maintained at 40 °C for several hours. The reaction mixture was then set aside at room temperature for 5 days, when a heavy, viscous layer settled at the bottom. The upper layer was removed by decantation, and the lower layer was then dried, and triturated with a little methanol. The solid which crystallised (and which was essentially homogeneous), was *6-hydroxy-4-(2-methoxyphenyl)-6-methyl-2-oxohexahydropyridine-3-carboxamide* **16** (Ar = C_6H_4OMe-2) (1.57 g, 30%), m.p. 196–198 °C (from MeOH; the molecule retains water tenaciously) (Found: C, 56.7; H, 6.8; N, 9.4. $C_{14}H_{18}N_2O_3{\cdot}H_2O$ requires C, 56.7; H, 6.8; N, 9.5%); ν_{max}(Nujol)/cm^{-1} 3456 (OH), 3411 (NH), 3212 (NH), 1674 (C=O) and 1650 (C=O); δ_H[300 MHz; $(CD_3)_2SO$; Me_4Si] 8.03 (1 H, s, NH), 7.24–6.7 (6 H, m, 4 × ArH and 2 × NH), 5.47 (1 H, s, OH), 4.05 (1 H, dt, *J* 3.9 and 11.9, 4-H), 3.76 (3 H, s, OMe), 3.48 (1 H, d, *J* 11.8, 3-H), 1.85 (1 H, t, *J* 12.6, H^a of 5-H_2), 1.76 (1 H, dd, *J* 3.9 and 13.1, H^b of 5-H_2) and 1.34 (3 H, s, Me); δ_C 170.8 (C=O), 168.7 (C=O), 157.1 (Ar C-2), 130.6 (Ar C-1), 127.9 (Ar C-3), 127.4 (Ar C-6), 120.2 (Ar C-4), 111.2 (Ar C-5), 79.2 (C-6), 55.4 (OMe) 53.1 (C-4), 42.3 (C-5), 32.2 (C-3) and 29.8 (Me).

(*d*) A suspension of cyanoacetamide (1.26 g, 15 mmol) in dry ethanol (50 cm^3) was heated to dissolution, and the solution was then cooled to room temperature. A solution of sodium ethoxide from sodium (0.34 g) in dry ethanol (20 cm^3) was added, followed by 4-(2-methoxyphenyl)but-3-en-2-one (2.64 g, 15 mmol), and the mixture was set aside at room temperature for 14 days. It was then acidified with acetic acid and stored overnight, when a solid separated. This, collected by filtration and recrystallised, was *4-(2-methoxyphenyl)-6-methyl-2-oxo-2,3,4,5-tetrahydropyridine-3-carboxamide* **18a** (Ar = C_6H_4O-Me-*o*) (1.89 g, 73%), m.p. 269–271 °C (Found: C, 64.5; H, 6.2; N, 10.7. $C_{14}H_{16}N_2O_3$ requires C, 64.6; H, 6.2; N, 10.8%); ν_{max}(Nujol)/cm^{-1} 3380w (NH), 3210 (br, unresolved, NH), 1705br (C=O) and 1668 (C=O); δ_H[300 MHz; $(CD_3)_2SO$; Me_4Si] 8.88 (1 H, s, NH), 8.81 (1 H, s, NH) 7.24–6.88 (4 H, m, ArH), 3.81 (3 H, s, OMe), 3.80 (1 H, ddd, partly concealed, *J* 2.3, 5.0 and 10.1, 4-H), 2.92 [1 H, dd, *J* 0.6 and 2.3 (the smaller coupling disappeared on D_2O exchange), 3-H], 2.44 (1 H, dd, *J* 10.2 and 12.7, H^a of CH_2), 1.98 (1 H, dd, *J* 5.5 and 12.7, H^b of CH_2) and 1.50 (s, 3 H, Me).

Reaction of 4-(3-*Dimethoxyphenyl*)*but*-3-*en*-2-*one with Cyanoacetamide.*—(*a*) A solution of 4-(3,4-dimethoxyphenyl)but-3-en-2-one **1a** [Ar = $C_6H_3(OMe)_2$-3,4][28] (2.06 g, 10 mmol) and cyanoacetamide (0.84 g, 10 mmol) in ethanol (30 cm^3) containing piperidine (0.2 cm^3) was heated under reflux for 1 h.

This was cooled to room temperature and stored overnight, when a crystalline product separated. This, collected by filtration and recrystallised from methanol, was 4-(3,4-*dimethoxyphenyl*)-6-*methyl*-2-*oxo*-1,2-*dihydropyridine*-3-*carbonitrile* **5a** [Ar = $C_6H_3(OMe)_2$-3,4] (0.48 g, 18%), m.p. 304 °C (hygroscopic) (Found: C, 64.6; H, 5.2; N, 9.8. $C_{15}H_{14}NO_3 \cdot \frac{1}{2}H_2O$ requires C, 64.5; H, 5.4; N, 10.0%); ν_{max}(Nujol)/cm^{-1} 2217 (NH), 1669 (C=O) and 1628w; δ_H[80 MHz; $(CD_3)_2SO$; Me_4Si] 12.85 (1 H, br s, NH), 7.29–7.04 (3 H, m, ArH), 6.37 (1 H, d, *J* 0.6, 5-H), 3.83 (6 H, s, 2 × OMe) and 2.30 (3 H, s, Me).

(*b*) A solution of 4-(3,4-dimethoxyphenyl)but-3-en-2-one **1a** [Ar = $C_6H_3(OMe)_2$-3,4] (3.09 g, 15 mmol) and cyanoacetamide (0.84 g, 10 mmol) in acetone (60 cm^3) containing piperidine (0.4 cm^3) was warmed at 40 °C for 7 h. Evaporation of the solvent at room temperature afforded a gum, which was redissolved in methanol. The methanolic solution was set aside at room temperature for several days, until crystallisation commenced, and the crystalline product was then harvested daily. The first three crops collected were 8,9-*bis*(3,4-*dimethoxyphenyl*)-6-*hydroxy*-6-*methyl*-4-*methylene*-2-*oxo*-3-*azabicyclo*[3.3.1]*nonane*-1-*carbonitrile* **14a** [Ar = $C_6H_3(OMe)_2$-3,4], m.p. 255–257 °C (from MeOH) (Found: C, 67.5; H, 6.2; N, 5.8. $C_{27}H_{30}N_2O_6$ requires C, 67.8; H, 6.3; N, 5.9%); ν_{max}(Nujol)/cm^{-1} 3516 (OH), 3189 (NH) and 1669 (C=O); δ_H[300 MHz; $(CD_3)_2SO$; Me_4Si] 10.5 (1 H, br s, NH), 6.87–6.66 (6 H, m, ArH), 5.1 (1 H, s, OH), 4.50 (1 H, s, H^a of =CH_2), 4.11 (1 H, s, H^b of =CH_2), 4.01 (1 H, s, 9-H), 3.70 (1 H, dd partly concealed, *J* 3 and 13, 8-H), 3.68 (6 H, s, 2 × OMe), 3.65 (6 H, s, 2 × Me), 2.42 (1 H, s, 5-H), 1.90 (1 H, t, *J* 13, H^a of 7-H_2), 1.63 (1 H, dd, *J* 3 and 13, H^b of 7-H_2) and 1.23 (3 H, s, Me); δ_C 162.8 (C=O), 149.4, 149.3, 147.9 and 147.7 (two Ar C-4 and two Ar C-3), 140.6 (C-4), 131.7 (Ar C-1), 130.9 (Ar C-1), 121.4 (Ar C-2), 119.4 (Ar C-2), 118.5 (C≡N), 113.2, 112.2, 111.7 and 110.9 (two Ar C-5 and two Ar C-6), 96.4 (=CH_2), 69.5 (C-6), 55.4 (4 × OMe), 52.2 (C-9), 51.3 (C-1), 46.9 (C-8), 44.1 (C-5), 38.9 (C-7) and 28.4 (Me).

Subsequent crystalline crops proved to be mixtures of the bicyclic product **14a** [Ar = $C_6H_3(OMe)_2$-3,4] and the pyridin-2(1*H*)-one **5a** [Ar = $C_6H_3(OMe)_2$-3,4], which were separated into their constituents by fractional crystallisation. The yield of the bicyclic product **14a** [Ar = $C_6H_3(OMe)_2$-3,4] was 0.33 g (9%) and that of the pyridinone **5a** [(Ar = $C_6H_3(OMe)_2$-3,4] was 0.12 g (5%).

Reaction of Chalcone **1b** *with Cyanoacetamide.*—(*a*) Aq. cyanoacetamide (1.78 g, 20 mmol in 15 cm^3) was added at room temperature to a stirred solution of chalcone (4.16 g, 20 mmol) in ethanol (50 cm^3) containing piperidine (0.5 cm^3). The mixture was stored overnight, when the product which had separated was collected by filtration, dried at 80 °C, and recrystallised from methanol; it was identified as 4-benzoyl-2-cyano-3-phenylbutyramide **6** (X = $CONH_2$)[7,8] (4.26 g, 73%).

(*b*) A suspension of cyanoacetamide (0.84 g, 10 mmol) in dry methanol (30 cm^3) was heated to dissolution, and cooled again to room temperature, and a solution of sodium methoxide from sodium (0.23 g) in dry methanol (10 cm^3) was added. A solution of chalcone **1b** (2.08 g, 10 mmol) in methanol (20 cm^3) was then added to the stirred mixture at room temperature. The mixture was stored for 48 h, then was diluted with water (60 cm^3) and acidified with acetic acid. The acidified solution was set aside for 7 days, when a semi-solid mass had separated. The upper (aqueous) layer was removed by decantation, and the residue was triturated with methanol, to give a small quantity of crystalline material identified as 2-oxo-4,6-diphenyl-1,2-dihydropyridine-3-carbonitrile **5b** (Ar = Ph)[5–10] (0.1 g, 4%). The filtered solution was set aside, when 2-oxo-4,6-diphenyl-1,2,3,4-tetrahydropyridine-3-carboxamide **17b** (Ar = Ph)[9] (1.16 g, 40%) crystallised.

Table 1 Crystallographic data for compounds **14a** (Ar = Ph) and **15a** (Ar = Ph)

Compound	**14a** (Ar = Ph)	**15a** (Ar = Ph)
Mol. formula	$C_{23}H_{22}N_2O_2$	$C_{23}H_{22}N_2O_2$
M_r	358.439	358.439
Crystal system	orthorhombic	monoclinic
a (Å)	6.5785(3)	8.946(2)
b (Å)	12.5587(2)	16.485(5)
c (Å)	23.8189(4)	13.522(2)
β(°)	90.000	101.737(8)
V (Å^3)	1967.8(2)	1952.7(8)
Space group	*P*2*nn*	$P2_1/c$
Z	4	4
D_c (g cm^{-3})	1.21	1.22
μ(Mo-K*α*) (cm^{-1})	0.44	0.44
F(000)	760	760
θ range (°)	$0 < \theta < 25$	$0 < \theta < 22$
Total data measured	2038	2628
Total data unique	1897	2393
Reflections observed $\|\|F\| \geqslant 4\sigma\|F\|\|$	1688	1911
R_{merg}	0.0000[a]	0.0080
R	0.0318	0.0419
R_w	0.0365	0.0480
No. of parameters	315	288
Max. final shift/esd	0.046	−0.036
Max. residual electron density (e Å^{-3})	0.1100	0.2324
Min. residual electron density (e Å^{-3})	0.1465	0.1558

[a] There were no equivalent reflections measured in this data set.

Synthesis of 3-(2′-*Benzoyl*-1′-*phenylethyl*)-2-*oxo*-4,6-*diphenyl*-1,2,3,4-*tetrahydropyridine*-3-*carbonitrile* **13b** (Ar = Ph).—A solution of 2-oxo-4,6-diphenyl-1,2,3,4-tetrahydropyridine-3-carbonitrile **4b** (Ar = Ph)[5–9] (0.55 g, 2 mmol) and chalcone **1b** (0.42 g, 2 mmol) in ethanol (70 cm^3) containing piperidine (0.1 cm^3) was heated under reflux for 90 min. The solution was cooled to room temperature and stored for 24 h, when a product crystallised; this, collected and recrystallised from methanol, was 3-(2′-*benzoyl*-1′-*phenylethyl*)-2-*oxo*-4,6-*diphenyl*-1,2,3,4-*tetrahydropyridine*-3-*carbonitrile* **13b** (Ar = Ph) (0.58 g, 60%), m.p. 226–228 °C (Found: C, 82.4; H, 5.4; N, 5.8. $C_{33}H_{26}N_2O_2$ requires C, 82.2; H, 5.4; N, 5.8%); ν_{max}(Nujol)/cm^{-1} 3227 (NH), 2248 (C≡N), 1688 (C=O) and 1662 (C=O); δ_H[300 MHz; $(CD_3)_2SO$; Me_4Si] 10.53 (1 H, s, NH), 7.98–6.94 (20 H, m, ArH), 5.78 (1 H, d, *J* 6.8, 5-H), 4.12 (1 H, dd, *J* 4.3 and 8.6, 1′-H), 3.77 (2 H, ddd, *J* 4.3, 8.6 and 17.7, 2′-H_2) and 3.26 (1 H, d, *J* 6.8, 4-H); δ_C 195.2 (C=O), 165.1 (CONH), 138.0 (Ar C-1), 137.5 (Ar C-1), 137.4 (Ar C-1), 136.8 (Ar C-1), 136.1 (C-6), 133.4 (Ar C), 133.1 (Ar C), 129.1 (Ar C), 128.7 (nine Ar C), 128.3 (two Ar C), 127.8 (two Ar C), 127.5 (Ar C), 125.9 (two Ar C), 125.6 (Ar C), 117.0 (C≡N), 102.3 (C-5), 56.5 (C-3), 44.6 (C-4), 42.5 (C-2′) and 39.7 (C-1′).

Crystal Structure Determinations.—The reflections were measured using a single crystal on an Enraf–Nonius CAD-4 diffractometer (Mo radiation, graphite monochromator, ω–2*θ* scans) at 20 °C. Crystal data and experimental parameters are summarised in Table 1. The cell parameters were determined using the Celdim routine. Decay and absorption were minimal and were ignored in the data processing.

The data were reduced to give the number of unique reflections and those with $\|F\| \geqslant 4\sigma|F\|$ were then used in structure solution and refinement. Each structure was solved using the direct methods of SHELXS. The hydrogen atoms were located from subsequent difference Fourier maps,

except for the Me and CH_2 groups of compound **15a** which were placed geometrically. We inferred the presence of the H-bond illustrated in Fig. 3 by the N(1)···O(2) distance of 2.948 Å.

The structures were refined by full-matrix least-squares analysis; the non-hydrogen atoms anisotropically, hydrogens in similar environments with common temperature factors to the final *R*-factors given in Table 1.*

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* *Supplementary data* (see 'Instructions for Authors,' issue 1). Tables of atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

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