2-Azabicyclo[4.2.0]octane Derivatives: Stereoselective Photochemical Synthesis and Chemical Reactivity

Giorgio Adembri, Donato Donati, Stefania Fusi and Fabio Ponticelli*
Istituto di Chimica Organica, Pian dei Mantellini, 44, 53100 Siena, Italy

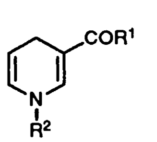
Photochemical addition of acrylonitrile to 1,4-dihydropyridines **1** and **2** followed by catalytic hydrogenation of the products gave *trans*-8- and *trans*-7-cyano-*cis*-2-azabicyclo[4.2.0]octane-6-carboxylates **6a, b** and **8a, b**; the corresponding *cis* **7b, 9** and *trans* **6b, 8b** stereoisomers were both obtained from 1,4,5,6-tetrahydropyridine **4**. Using the chiral 1,4-dihydropyridine **3**, azabicyclo[4.2.0]-octanes **6c, 7c** and **8c** were obtained with an enantiomeric excess in the range 45–15%. Thermal cycloaddition of *p*-chlorobenzonitrile oxide on the same substrates yielded compounds **10** and **11**, with site- and regio-selectivity but without stereoselectivity. Cyclobutane ring opening under basic or acid conditions was observed only for 8-cyano-2-azabicyclo[4.2.0]octane **6b** which gave the 1,4,5,6-tetrahydropyridylpropionitrile **15** or the piperidine-2-ol **17**.

Recently, during a study of the photoreactions of NADH model compounds under non-oxidizing conditions, we reported that site-selective acrylonitrile photoaddition to 1,4-dihydropyridines **1, 2** followed by catalytic hydrogenation of the product produces the 2-azabicyclo[4.2.0]octanes **6a, b** and **8a, b**.[1] This reaction occurs under high stereochemical control: only isomers with a *trans*-configuration between the CN and COR^1 groups are obtained.

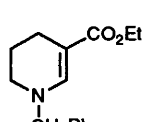
Since the photochemical [2 + 2] cross cycloadditions between differently substituted alkenes, followed by cyclobutane ring opening, can be valuable in stereoselective organic synthesis,[2] we focussed attention on factors affecting stereocontrol of acrylonitrile photoaddition to 1,4-dihydropyridines. We also investigated some aspects of the chemical reactivity of 2-azabicyclo[4.2.0]octanes resulting from the above process, with the aim of obtaining differently substituted systems and verifying their utility as synthons.

Results and Discussion

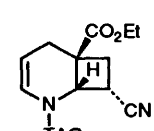
At a first sight, the 5,6-double bond of 1,4-dihydropyridines **1** and **2** is not involved in photoaddition, however it plays an important role in the stereochemistry of the reaction. In fact, when 1,4,5,6-tetrahydropyridine **4** was irradiated in the presence of acrylonitrile, both **6b, 8b** and **7b, 9** azabicyclooctanes were obtained.



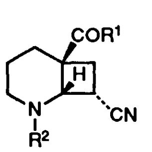
1 $R^1 = NH_2$, $R^2 = CH_2Ph$
2 $R^1 = OEt$, $R^2 = CH_2Ph$
3 $R^1 = OEt$, $R^2 = TAG$



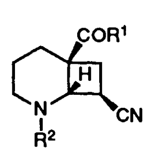
4



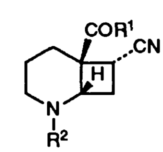
5



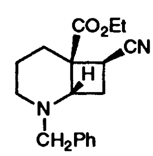
6



7



8



9

a $R^1 = NH_2$, $R^2 = CH_2Ph$
b $R^1 = OEt$, $R^2 = CH_2Ph$
c $R^1 = OEt$, $R^2 = H$
d $R^1 = OEt$, R^2 = α-methoxy-α-trifluoromethylphenylacetyl

The structure of the latter compounds was deduced by comparison of spectral data (see Experimental section) with the corresponding isomers **6b** and **8b**.[1] MS spectra are nearly identical, all showing a very weak molecular ion (*m*/*z* 298) and a strong ion at *m*/*z* 245, due to the easy retroaddition of acrylonitrile under electron impact, to give the tetrahydropyridine **4**. As a consequence of the different stereochemistry of the CN group, a paramagnetic shift for 1-H was observed in ^{1}H NMR spectra of isomers with a *cis* configuration between the CN and CO_2Et groups (**7b**, δ 4.04; **9**, δ 3.89) with respect to the corresponding *trans* isomers (**6b**, δ 3.73; **8b**, δ 3.53). In agreement with this effect,[1a] a diamagnetic shift was observed for the axial 3-H (**7b**, δ 2.30, **9**; δ < 2.50; **6b**, δ 3.15; **8b**, δ 2.51).

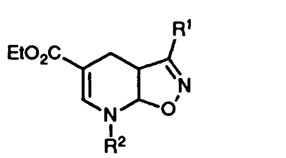
With the aim of evaluating chiral induction during the above photoaddition, we considered 1-TAG-1,4-dihydropyridine **3** [TAG = 1-(tetraacetyl-β-D-glucopyranosyl)], due to its easy preparation from tetracetylbromoglucose and ethyl nicotinate and the easy removal of the glucosidic moiety after photochemical reaction.

Irradiation of compound **3** in the presence of an excess of acrylonitrile gave a complex mixture of products. The ^{1}H NMR spectrum was complicated by overlapping of signals and it was impossible to evaluate directly the enantiomeric excess. Separation of the individual components was not achieved, due to their low stability under chromatographic conditions. In fact, only one pure diastereoisomer was isolated by column chromatography followed by crystallization from diethyl ether. The structure **5** was assigned to this compound on the basis of the signals of 1-H and 8-H [δ 4.26 (d) and δ 3.25 (ddd)]. The crude reaction mixture was more conveniently analysed after catalytic hydrogenation followed by hydrolysis of the glucosidic bond to give the 2-unsubstituted 2-azabicyclo[4.2.0]octanes **6c** and **8c**, easily separable by column chromatography. In the NMR spectrum of the 8-cyano isomer **6c**, the signals of a minor component were also observed, suggesting the presence of compound **7c**; however many attempts at chromatographic separation were unsuccessful. The presence of **7c** is probably due to the isomerization of isomer **6c**, as in the case of **6b** described below. In order to evaluate the enantiomeric excess in the compounds **6c**–**8c**, we prepared the diastereoisomeric amides **6d**–**8d** by reaction with (R)-2-methoxy-2-trifluoromethylphenylacetyl chloride.[3]

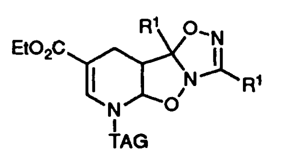
Careful chromatographic analysis of the reaction mixture allowed us to separate the individual components of the diastereoisomeric pairs of amides **6d**, **7d** and **8d**. In the NMR spectra of each compound separated from **6d** and **8d**, two series of signals, namely for 1-H, 7-H and/or 8-H and ethoxy group, were found. Dynamic NMR and saturation transfer experiments confirmed a situation of chemical exchange between two conformers, deriving from restricted rotation around the N–CO bond. Taking this fact into account, we were able to assign all the signals of 1-H to the diastereoisomers present in the crude reaction mixture. The enantiomeric excess was 45% for the 8-cyano regioisomer **6d** and 15% for the corresponding 7-cyano isomer **8d**. The same procedure performed with (*S*)-2-methoxy-2-trifluoromethylphenylacetyl chloride confirmed the attribution of the 1-H signals, as well as the values of the enantiomeric excess.

Unlike the case reported by Hoffmann *et al.*,[4] no significant temperature effect on the enantiomeric excess was found, at least in the range −40 to +20 °C.

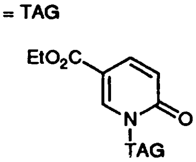
For the sake of comparison of photochemical and thermal cycloaddition, we treated the 1,4-dihydropyridines **2** and **3** with *p*-chlorobenzonitrile oxide. The reaction of **2** gave the tetrahydroisoxazolo[5,4-*b*]pyridine **10**, with high site- and regioselectivity. In contrast to the photoaddition of acrylonitrile, only the 5,6-double bond is involved in thermal cycloaddition. The reaction of compound **3** proceeds in a similar way, yielding a nearly equimolecular amount of the diastereoisomer adducts **11**; this indicates that no stereo-control is operating in the thermal reaction. We also found the pyridone **13** and the bis-adduct **12**, both of which arise from double addition of the nitrile oxide, analogously to the results previously reported by Bianchi *et al.*[5]



10 $R^1 = p\text{-}ClC_6H_4$, $R^2 = CH_2Ph$
11 $R^1 = p\text{-}ClC_6H_4$, $R^2 = TAG$



12



13

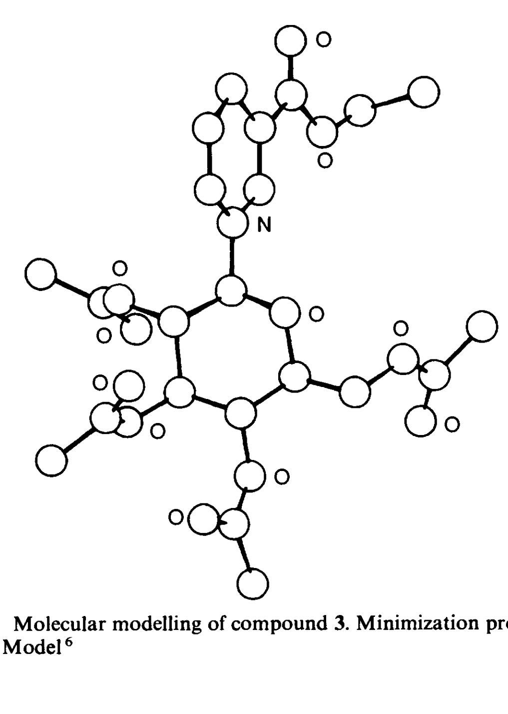
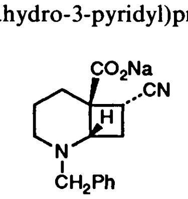


Fig. 1 Molecular modelling of compound **3**. Minimization procedure by PC Model[6]

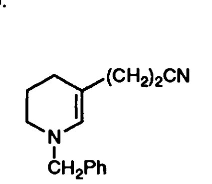
The selectivity found in the photochemical reaction of compound **3** can be rationalized bearing in mind the mechanism of the process, which probably involves an initial electron transfer from the dihydropyridine to the electron-poor alkene to give a charge-transfer complex. Fig. 1 shows a low energy conformation of compound **3** obtained by molecular mechanic calculation.[6] The acetoxy group on C-2, is responsible for the diastereotopicity of the faces of the dihydropyridine ring.

Because of the potential biological activity[7] of 2-azabicyclo-[4.2.0]octanes their chemical reactivity was also investigated, with the aim of preparing differently substituted systems with greater stability and solubility in aqueous media.

Nucleophilic attack on the ethoxycarbonyl group of compounds **6b** and **8b** is very easy. In fact, quantitative trans-esterification by CD_3O^- in CD_3OD occurred rapidly at room temperature to give the corresponding trideuteriomethyl esters. As a consequence, we tried to prepare the carboxylic acids by alkaline hydrolysis of the esters **6b** and **8b**: the 7-cyano isomer **8b** gave a stable sodium salt **14**, whereas under the same conditions, the 8-cyanoisomer **6b** gave the 3-(1-benzyl-1,4,5,6-tetrahydro-3-pyridyl)propionitrile **15**.



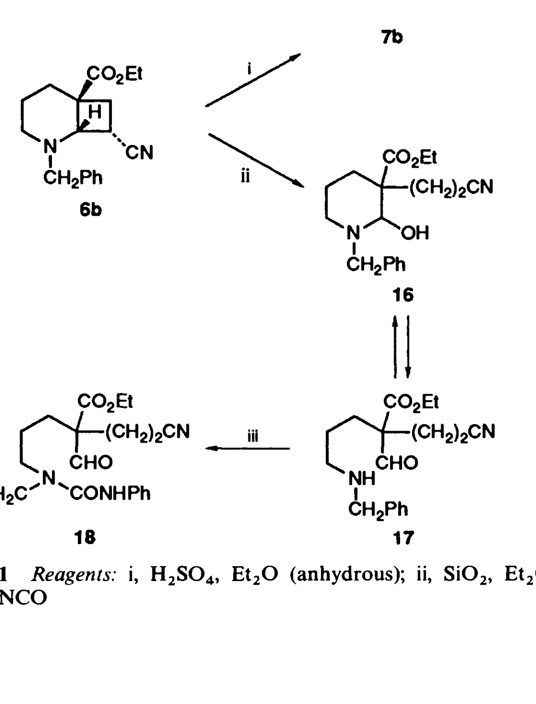
14



15

This different behaviour can be interpreted in the light of stability of the anions obtained as intermediates from compounds **6b** and **8b**. Loss of CO_2 from the 8-cyano-substituted anion and cyclobutane ring opening allow negative charge delocalization on the CN group, whereas this is not possible for the 7-cyano-substituted anion **14**.

A noteworthy difference was also found in the reactivity of compounds **6b** and **8b** towards the acids. When the 8-cyano isomer **6b** was treated with a trace of sulfuric acid in an anhydrous solvent, the corresponding isomer **7b** was obtained (Scheme 1). This change of C-8 configuration was not due to the mobility of the hydrogen at C-8. In fact, when the reaction was carried out with deuteriosulfuric acid, no hydrogen–deuterium exchange was observed by NMR spectroscopy. Under the same conditions, the corresponding **7b**→**6b** isomerization was not observed.



Scheme 1 *Reagents:* i, H_2SO_4, Et_2O (anhydrous); ii, SiO_2, Et_2O; iii, C_6H_5NCO

Two-dimensional TLC showed that the above **6b**→**7b** isomerization was also catalysed by silica gel. Under these conditions, a further main compound was found and identified as a 1:1 mixture of 2-hydroxypiperidines **16**, which are in equilibrium through the corresponding open-chain aldehyde **17**. In fact, reaction of compound **16** with phenylisocyanate quantitatively gave the urea **18**. Under the same conditions (sulfuric acid or silica gel) the 7-cyano isomer **8b** was stable.

In conclusion, photochemical attack of acrylonitrile on 1,4-dihydropyridine having a chiral auxiliary in position 1 occurs with facial selectivity, allowing the enantioselective preparation of 2-unsubstituted 2-azabicyclo[4.2.0]octanes **6c**–**8c**. These compounds may be modified under acid or basic conditions allowing access to differently substituted systems or to open-chain products.

Experimental

IR spectra were obtained for dispersion in KBr, unless otherwise stated, with a Perkin-Elmer 782 spectrometer. ^{1}H NMR spectra were recorded on a Varian XL 200 spectrometer at 200 MHz and chemical shifts are given in ppm relative to internal $SiMe_4$, coupling constants in Hz. Electron impact mass spectra (70 eV) were recorded on a VG 70 250S instrument. Optical rotation was determined at 22 °C with a Perkin-Elmer 141 polarimeter. M.p.s and b.p.s are uncorrected. Merck Kieselgel (230–400 mesh ASTM) was employed for analytical TLC, as well as for column chromatography. Photochemical reactions were carried out with a medium-pressure mercury immersion lamp (125 W) filtered and cooled with copper(II) sulfate solutions (A: 30 g dm^{-3}, cut off 300 nm; B: saturated solution, cut off 330 nm); nitrogen was constantly bubbled through the irradiated solution. Light petroleum refers to the fraction of b.p. 30–50 °C.

Irradiation of Ethyl 1-Benzyl-1,4,5,6-tetrahydronicotinate **4**.—A solution of compound **4** (1 g, 4.1 mmol) and acrylonitrile (2.6 cm^3, 40 mmol) in anhydrous ether (120 cm^3) was irradiated (filter solution A) for 16 h. The insoluble material was filtered off and the solution was evaporated to give a residue which was resolved into four components by column chromatography with ether–light petroleum (1:1.5 v/v) as eluent. The fastest running fraction was identified as compound **6b**[1] (150 mg, 14% based on compound **4**); m/z 298 (M^+, 2%), 245 (57), 216 (36), 200 (40), 172 (35), 91 (100) and 65 (22). The second band was a mixture of two compounds which was separated by a second column chromatography with benzene as eluent to give compound **8b**[1] (100 mg, 9% based on compound **4**); m/z 298 (M^+, 2%), 283 (2), 269 (2), 253 (3), 245 (33), 225 (6), 216 (19), 200 (4), 172 (11), 91 (100) and 65 (12) and *ethyl 2-benzyl-*cis*-8-cyano-*cis*-2-azabicyclo*[4.2.0]*octane-6-carboxylate* **7b** (R_f 0.58 in benzene–ether 15:1 v/v, 50 mg, 4.5% based on compound **4**), as an oil (Found: M^+, 298.1674. $C_{18}H_{22}N_2O_2$ requires M, 298.1681); ν_{max}(film)/cm^{-1} 2225 (CN) and 1730 (CO); δ_H 1.26 (3 H, t, J 7.1, Me), 1.36–1.70 (3 H, m, 4-$H_{a,e}$ and 5-H_a), 1.99 (1 H, A*B*X, J 11.0 and 8.3, 7′-H), 2.21 (1 H, *A*BX, J 11.0 and 10.0, 7-H), 2.30 (1 H, m, 3-H_a), 2.45 (1 H, m, 5-H_e), 2.75 (1 H, m, 3-H_e), 3.20 (1 H, dt, J 10.0, 8.3 and 8.2, 8-H), 3.81 and 3.59 (each 1 H, AB, J 13.8, $NCH_2C_6H_5$), 4.04 (1 H, d, J 8.2, 1-H), 4.20 (2 H, q, J 7.1, OCH_2) and 7.25–7.70 (5 H, m, C_6H_5); m/z 298 (M^+, 2%), 245 (43), 216 (20), 200 (14), 172 (18), 91 (100) and 65 (8).

The third band was the unchanged starting material (100 mg). Finally, the slowest moving fractions afforded *ethyl 2-benzyl-*cis*-7-cyano-*cis*-2-azabicyclo*[4.2.0]*octane-6-carboxylate* **9** (R_f 0.53 in ether–light petroleum 1:1 v/v, 40 mg, 4% based on compound **4**), as an oil (Found: M^+, 298.1689. $C_{18}H_{22}N_2O_2$ requires M, 298.1681); ν_{max}(film)/cm^{-1} 2230 (CN) and 1720 (CO); δ_H 1.32 (3 H, t, J 7.3, Me), 1.54–2.52 (6 H, m, 3-$H_{a,e}$, 5-$H_{a,e}$, 5-$H_{a,e}$), 2.09 (1 H, A*B*XY, J 11.6, 7.4 and 4.3, 8′-H), 2.39 (1 H, *A*BXY, J 11.6, 8.6 and 7.4, 8-H), 3.00 (1 H, ddd, J 8.6, 4.3 and 1.1, 7-H), 3.63, 3.52 (each 1 H, AB, J 13.7, $NCH_2C_6H_5$), 3.89 (1 H, td, J 7.4 and 1.1, 1-H), 4.29 and 4.26 (each 1 H, ABq, J 10.7 and 7.3, OCH_2) and 7.25–7.35 (5 H, m, C_6H_5); m/z 298 (M^+, 4%), 297 (3), 245 (65), 225 (10), 216 (35), 200 (8), 172 (23), 91 (100) and 65 (15).

Ethyl 1-(2′,3′,4′,6′-Tetraacetyl-β-D-glucopyranosyl)-1,4-dihydronicotinate **3**.—Following the method of Haynes and Todd[8] (modified), 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (28.3 g, 68.8 mmol) and ethyl nicotinate (28.3 cm^3, 207 mmol) were heated at 100 °C for 40 min. Ether was added to give a hygroscopic solid (37 g, 95%) which was dissolved in water (0.5 dm^3) and treated under nitrogen with sodium hydrogen carbonate (10 g) and sodium hydrosulfite (17.3 g). The solution was stirred in the dark for 15 h to give a yellowish precipitate which was filtered off, dried and column chromatographed with ether to give compound **3** (12 g, 32%) as pale yellow solid, m.p. 116–118 °C (from ether); $[\alpha]_D$ −13.3 (c 4.81, MeCN) (Found: C, 54.8; H, 5.9; N, 3.0. $C_{22}H_{29}NO_{11}$ requires C, 54.65; H, 6.05; N, 2.9%); ν_{max}/cm^{-1} 1740, 1725 and 1695 (CO); δ_H 1.25 (3 H, t, J 7.1, Me), 1.99, 2.01, 2.02, 2.07 (12 H, s, MeCO), 3.02 (2 H, m, 4-H,H′), 3.73 (1 H, ddd, J 9.8, 4.7 and 2.7, 5-H_{glu}), 4.21 4.10 (2 H, AB, J 12.7, 4.7 and 2.7, 6-H,H'_{glu}), 4.14 (2 H, q, J 7.1, OCH_2), 4.34 (1 H, d, J 8.7, 1-H_{glu}), 4.83 (1 H, dt, J 8.2 and 4.4, 5-H), 5.02–5.27 (3 H, m, 2-, 3-, 4-H_{glu}), 5.87 (1 H, dq, J 8.2 and 1.6, 6-H) and 7.04 (1 H, d, J 1.7, 2-H); m/z 483 (M^+, 14%), 438 (7), 331 (25), 169 (100), 152 (11), 127 (24), 124 (21) and 109 (67).

Irradiation of Compound **3**.—A solution of **3** (5.3 g, 11 mmol) and acrylonitrile (7 cm^3, 107 mmol) in anhydrous tetrahydrofuran (250 cm^3) were irradiated (filter solution B) for 15 h. Solvent was gently removed under reduced pressure to give, by rubbing with light petroleum, a pasty residue (5.9 g).

(i) A fraction of the residue (1 g) was column chromatographed with ether as eluent. The fastest running band in ether gave, with time, ethyl 1-(2′,3′,4′,6′-tetraacetyl-β-D-*glucopyranosyl*)-trans-*8-cyano-*cis*-2-azabicyclo*[4.2.0]*oct-3-ene-6-carboxylate* **5** (0.15 g, 13%) as white crystals, m.p. 109–111 °C (ether) (Found: C, 55.7; H, 6.0; N, 5.0. $C_{25}H_{32}N_2O_{11}$ requires C, 56.0; H, 6.0; N, 5.2%); ν_{max}/cm^{-1} 2225 (CN), 1740 and 1720 (CO); δ_H 1.26 (3 H, t, J 7.0, Me), 1.97, 1.98, 2.01, 2.07 (each 3 H, 4 s, MeCO), 2.14 (1 H, dd, J 12.6 and 4.7, 7′-H), 2.42 (1 H, A*B*XY, J 16.0, 4.0 and 0.7, 5′-H), 2.54 (1 H, *A*BX, J 16.0 and 4.0, 5-H), 2.62 (1 H, dd, J 12.6 and 9.5, 7-H), 3.25 (1 H, ddd, J 9.5, 7.9 and 4.5, 8-H), 3.73 (1 H, ddd, J 7.8, 5.5 and 2.3, 5-H_{glu}), 3.99, 4.33 (each 1 H, *AB*X, J 12.2, 5.9 and 2.2, 6,6′-H_{glu}), 4.16 (2 H, q, J 7.0, OCH_2), 4.26 (1 H, d, J 7.9, 1-H), 4.37 (1 H, d, J 6.4, 1-H_{glu}), 4.70 (1 H, dt, J 8.0 and 4.0, 4-H), 5.01, 5.17 and 5.24 (each 1 H, t, J 7.8 and 6.4, 2-, 3- and 4-H_{glu}) and 6.22 (1 H, br d, J 8.0, 3-H). No pure compounds were obtained from further fractions.

(ii) The remaining residue (4.9 g) was dissolved in ethyl acetate (200 cm^3), Pd 10% on charcoal (0.8 g) was added and the mixture shaken in a Parr apparatus for 15 h under a hydrogen pressure of 90 psi.* Solvent was removed under reduced pressure and the oily material dissolved in hydrochloric acid (3 mol dm^{-3}; 70 cm^3) and ethanol (20 cm^3). After 0.5 h the solution was made alkaline with sodium hydrogen carbonate and extracted with chloroform. Solvent was removed under reduced pressure and the residue, dissolved in chloroform, was extracted with hydrochloric acid (3 mol dm^{-3}; 50 cm^3). The aqueous layer was made alkaline with sodium hydrogen carbonate and extracted with chloroform. Evaporation of the solvent afforded an oily

* 1 psi ≈ 6.89 × 10^3 Pa.

residue which was column chromatographed by eluting with ether to give as a single chromatographic fraction *ethyl* trans-8-*cyano*-cis-2-*azabicyclo*[4.2.0]*octane-6-carboxylate* **6c** and the corresponding *C*-8-cyano-r-1, *c*-6-isomer **7c** in the ratio 6:1 (determined by integration of the NMR signals) (R_f 0.30 in ether; 0.5 g, 28%), oil (Found: M^+, 208.1209. $C_{11}H_{16}N_2O_2$ requires *M*, 208.1212); ν_{max}(film)/cm^{-1} 3320 (NH), 2220 (CN) and 1715 (CO); δ_H 1.28, 1.29* (3 H, t, *J* 7.1, Me), 1.42–1.85 (2 H, m, 4-$H_{a,e}$), 1.95–2.32 (3 H, m, NH and 5-$H_{a,e}$), 2.05,* 2.27 (1 H, A*B*MX, *J* 11.7, 5.5 and 0.6, 7'-H), 2.30,* 2.47 (1 H, *A*BMX, *J* 11.7, 8.9 and 1.1, 7-H), 2.80, 2.95* (1 H, *A*BMXY and m,* *J* 13.1, 5.1, 3.7 and 1.0, 3-H_e), 3.20,* 3.22 (1 H, ddd, *J* 8.9, 7.8 and 5.5, 8-H), 3.35 (1 H, A*B*MX, *J* 13.1, 9.5 and 3.7, 3-H_a), 3.97, 4.02* (1 H, d, *J* 7.8 and 8.4,* 1-H) and 4.18, 4.19* (2 H, q, *J* 7.1, OCH_2); *m/z* 208 (M^+, 3%), 163 (13), 155 (87), 141 (6), 126 (100), 110 (30) and 82 (52).

Further elution of the column with ether–methanol (9:1 v/v) afforded *ethyl* trans-7-*cyano*-cis-2-*azabicyclo*[4.2.0]*octane-6-carboxylate* **8c** (R_f 0.04 in ether; 0.3 g, 17%), as an oil (Found: M^+, 208.1218. $C_{11}H_{16}N_2O_2$ requires *M*, 208.1212); ν_{max}-(film)/cm^{-1} 3310 (NH), 2220 (CN) and 1710 (CO); δ_H 1.28 (3 H, t, *J* 7.1, Me), 1.47–1.65 (2 H, m, 4-$H_{a,e}$), 2.00–2.19 (1 H, m, 5-H_a), 2.31–2.44 (1 H, m, 5-H_e), 2.33 (1 H, A*B*MX, *J* 11.0, 8.3 and 8.2, 8'-H), 2.58 (1 H, *A*BMX, *J* 11.0, 10.4 and 10.3, 8-H), 2.83 (1 H, A*B*XY, *J* 13.3, 13.0 and 4.0, 3-H_a), 2.94 (1 H, *A*BXYZ, *J* i3.3, 4.0, 3.9, 1.4, 3-H_e), 3.10 (1 H, dd, *J* 10.4, 8.2, 7-H), 3.62 (1 H, dd, *J* 10.3, 8.3, 1-H) and 4.18 (2 H, q, *J* 7.1, OCH_2); *m/z* 208 (M^+, 11%), 179 (11), 163 (43), 155 (100), 135 (39), 126 (91), 110 (20), 84 (56), 82 (49) and 56 (15).

Reaction of Compounds **6c**, **7c** *or* **8c** *with* (R)-α-*Methoxy*-α-*trifluoromethylphenylacetyl Chloride: General Procedure.*—To a cooled solution of the 2-azabicyclo[4.2.0]octane **6c**, **7c** or **8c** (0.21 g, 1 mmol) in carbon tetrachloride (8 cm^3), triethylamine (0.3 cm^3, 2.2 mmol) and freshly distilled (*R*)-α-methoxy-α-trifluoroethylphenylacetyl chloride[3] (0.56 g, 2.2 mmol) were added with stirring. After 0.5 h, a saturated solution of sodium hydrogen carbonate (10 cm^3) was added and stirring continued for 12 h. The organic layer was separated and evaporated under reduced pressure.

(i) The residue from the reaction of compounds **6c**, **7c** was resolved into two components by column chromatography with light petroleum–ether (1:1 v/v) as eluent; the first band gave a 2.7:1 diastereoisomeric mixture of *ethyl* trans-8-*cyano*-2-(α-*methoxy*-α-*trifluoromethylphenylacetyl*)-cis-2-*azabicyclo*[4.2.0]-*octane-6-carboxylate* **6d** (R_f 0.63 and 0.67 in ether–light petroleum 2:1 v/v, 0.2 g, 47%), as an oil (Found: M^+, 424.1596. $C_{21}H_{23}F_3N_2O_4$ requires *M*, 424.1610); ν_{max}(film)/cm^{-1} 2230 (CN), 1720 and 1650 (2 CO); *m/z* 424 (M^+, 1%), 371 (40), 189 (100), 182 (82) and 105 (26). Separation of the two diastereoisomers was accomplished by chromatography on Lobar (Merck Silica gel) column by eluting with light petroleum–ether (2:1 v/v).

The fastest running compound, $[\alpha]_D$ −119.1 (*c* 6.58, MeCN), showed the following NMR spectrum: δ_H†(C_6D_6) 0.79, 2.95 (1 H, td, *J* 9.2, 3.2, 8-H), 0.85, 0.90 (3 H, t, *J* 7.1, Me), 1.05–2.07 (4 H, m, 4-$H_{a,e}$ and 5-$H_{a,e}$), 1.28, 1.62 (1 H, A*B*X, *J* 12.4, 3.2, 7'-H), 1.44, 1.90 (1 H, *A*BX, *J* 12.4, 9.2, 7-H), 3.37–3.62, 4.45 (4 H, m and td, *J* 13.2, 4.0, 3-$H_{a,e}$), 3.65–3.81 (3 H, q, *J* 1.8, OMe), 3.76 3.87 (2 H, q, *J* 7.1, OCH_2), 5.16, 5.37 (1 H, d, *J* 9.2, 1-H) and 6.92–7.90 (5 H, m, C_6H_5).

The slowest running compound, $[\alpha]_D$ +54.0 (*c* 8.87, MeCN), showed the following NMR spectrum: δ_H†($CDCl_3$) 1.05, 1.23 (3 H, t, *J* 7.1, Me), 1.40–1.72 (2 H, m, 4-$H_{a,e}$), 1.92–2.04 (1 H, m, 5-H_a), 2.19 (1 H, A*B*X, *J* 12.4, 3.1, 7'-H), 2.24–2.40 (1 H, m, 5-H_e), 2.59 (1 H, *A*BX, *J* 12.4, 9.5, 7-H), 2.65–2.80 (1 H, m, 3-H_a), 3.46, 3.58 (1 H, td, *J* 8.8, 3.1, 8-H), 3.68 (3 H, d, *J* 1.8, OMe), 3.85, 4.58 (1 H, dt, *J* 15.1, 5.0, 3-H_e), 4.15 (2 H, q, *J* 7.1, OCH_2), 4.50, 5.15 (1 H, d, *J* 8.8, 1-H).

The second band of the reaction residue was identified as a 2:1 diastereoisomeric mixture of *ethyl* cis-8-*cyano*-2-(α-*methoxy*-α-*trifluoromethylphenylacetyl*)-cis-2-*azabicyclo*[4.2.0]*octane-6-carboxylate* **7d** (R_f 0.37 in ether–light petroleum 2:1 v/v, 35 mg, 8%), oil (Found: M^+, 424.1624. $C_{21}H_{23}F_3N_2O_4$ requires *M*, 424.1610); ν_{max}(film)/cm^{-1} 2230 (CN), 1720 and 1650 (2 CO); *m/z* 424 (M^+, 1%), 371 (39), 235 (4), 189 (100), 182 (85) and 105 (19). Chromatographic separation of the two diastereoisomers was accomplished on Lobar (Merck Silica gel) column by eluting with light petroleum–ether 2:1 v/v.

The fastest running compound, $[\alpha]_D$ −99.3 (*c* 4.36, MeCN), showed the following NMR spectrum: δ_H(C_6D_6) 0.41–0.54 (2 H, m, 4-$H_{a,e}$), 0.78 (3 H, t, *J* 7.1, Me), 1.05–1.23 (1 H, m, 5-H_a), 1.29 (1 H, dd, *J* 9.4, 9.2, 7'-H), 1.57–1.75 (2 H, m, 3-H_a and 5-H_e), 1.94 (1 H, t, *J* 9.4, 7-H), 2.15 (1 H, q, *J* 9.4, 8-H), 3.51 (3 H, q, *J* 1.5, OMe), 3.70 (1 H, m, 3-H_e), 3.76 (2 H, q, *J* 7.1, OCH_2), 5.57 (1 H, d, *J* 9.4, 1-H), 6.98–7.14 and 7.62–7.70 (5 H, m, C_6H_5).

The slowest moving fraction, $[\alpha]_D$ −75.3 (*c* 4.54, MeCN), showed the following NMR data: δ_H(C_6D_6) 0.33–0.69 (3 H, m, 5-H_a and 4-$H_{a,e}$), 0.89 (3 H, t, *J* 7.1, Me), 1.34 (1 H, dd, *J* 10.2, 9.1, 7'-H), 1.64–1.72 (1 H, m, 5-H_e), 1.98 (1 H, dd, *J* 10.2, 9.7, 7-H), 2.16–2.30 (1 H, m, 3-H_a), 2.33 (1 H, q, *J* 9.7, 8-H), 3.43 (3 H, q, *J* 1.5, OMe), 3.44–3.59 (1 H, m, 3-H_e), 3.72–3.93 (2 H, ABq, *J* 10.7, 7.1, OCH_2), 5.82 (1 H, d, *J* 9.7, 1-H), 6.98–7.18 and 7.66–7.70 (5 H, m, C_6H_5).

(ii) The residue from the reaction of compound **8c** was identified as a 1.4:1 diastereoisomeric mixture of *ethyl* trans-7-*cyano*-2-(α-*methoxy*-α-*trifluoromethylphenylacetyl*)-cis-1-2-*azabicyclo*[4.2.0]*octane-6-carboxylate* **8d**, (R_f 0.62 in ether–light petroleum 2:1 v/v, 210 mg, 50%), oil (Found: M^+, 424.1601. $C_{21}H_{23}F_3N_2O_4$ requires *M*, 424.1610); ν_{max}(film)/cm^{-1} 2230 (CN), 1720 and 1650 (2 CO); *m/z* 424 (M^+, 5%), 371 (45), 235 (30), 189 (100), 182 (72), 166 (18), 105 (30) and 84 (22). Chromatographic separation of the two diastereoisomers was accomplished on Lobar column by eluting with light petroleum–isopropyl ether (1:2 v/v). The fastest running compound, $[\alpha]_D$ −50.1 (*c* 2.69, MeCN), showed the following NMR spectrum: δ_H†(C_6D_6) 0.80, 0.89 (3 H, t, *J* 7.1, Me), 1.15–1.88 (4 H, m, 4-$H_{a,e}$ and 5-$H_{a,e}$), 1.32 (1 H, q, *J* 10.1, 8-H), 1.84 (1 H, *A*BXY, *J* 10.1, 8.2, 7.8, 8'-H), 2.10, 2.52 (1 H, dd, *J* 10.1, 8.2, 7-H), 2.25 (1 H, m, 3-H_a), 3.36, 3.63 (3 H, q, *J* 1.6, OMe), 3.72, 3.84 (2 H, q, *J* 7.1, OCH_2), 4.28–4.43 (1 H, m, 3-H_e), 4.68, 5.25 (1 H, dd, *J* 10.1, 7.8, 1-H), 7.00–7.18 and 7.47–7.50 (5 H, m, C_6H_5).

The slowest running fraction, $[\alpha]_D$ −30.2 (*c* 6.62, MeCN), showed the following NMR data: δ_H†(C_6D_6) 0.68, 0.80 (3 H, t, *J* 7.1, Me), 1.15–1.88 (4 H, m, 4-$H_{a,e}$ and 5-$H_{a,e}$), 1.65 (1 H, A*B*XY, *J* 10.3, 10.2, 10.1, 8'-H), 1.96 (1 H, *A*BXY, *J* 10.1, 8.2, 8.0, 8-H), 2.15–2.35 (1 H, m, 3-H_a), 2.43, 2.53 (1 H, dd, *J* 10.3, 8.0, 7-H), 3.17, 3.53 (3 H, q, *J* 1.6, OMe), 3.70, 3.77 (2 H, q, *J* 7.1, OCH_2), 4.08, 5.04 (1 H, dd, *J* 10.0, 8.2, 1-H), 3.56–3.69, 4.52–4.65 (1 H, m, 3-H_e), 6.99–7.18 and 7.48–7.51 (5 H, m, C_6H_5).

Reaction of 1,4-*Dihydropyridines* **2** *or* **3** *with* p-*Chlorobenzonitrile oxide. General Procedure.*—To a solution of compound **2** or **3** (10 mmol) in anhydrous ether (60 cm^3) an ethereal solution of freshly prepared *p*-chlorobenzonitrile oxide (20 mmol) was added. After 12 h solvent was removed and the residue column chromatographed as reported below.

(i) For compound **2** elution with ether–light petroleum (1:2 v/v) afforded *ethyl 7-benzyl*-3-(p-*chlorophenyl*)-3a,4,7,7a-*tetrahydroisoxazolo*[5,4-b]*pyridine-5-carboxylate* **10** (1.5 g, 38%) as

* *c*-8-Cyano-*r*-1, *c*-6-isomer.

† Some signals are doubled as a consequence of hindered rotation around CO–N moiety.

a yellow oil which crystallized by rubbing with ether–light petroleum (2:1 v/v), m.p. 93–95 °C (Found: C, 66.9; H, 5.3; N, 7.05; $C_{22}H_{21}ClN_2O_3$ requires C, 66.7; H, 5.3; N, 7.1%); ν_{max}(film)/cm^{-1} 1700 (CO); δ_H 1.21 (3 H, t, *J* 7.0, Me), 2.10 (1 H, A*B*XY, *J* 15.9, 9.4, 1.6, $H_{4'}$), 2.85 (1 H, *A*BX, *J* 15.9, 7.3, 4-H), 3.25 (1 H, ddd, *J* 9.4, 7.2, 6.9, 3-H_a), 4.51, 4.65 (each 1 H, AB, *J* 15.4, $NCH_2C_6H_5$), 5.38 (1 H, d, *J* 6.9, 7-H_a), 7.20–7.63 (4 H, m, Ar), 7.54 (1 H, d, *J* 1.6, 6-H); *m/z* 396/398 (M^+, 27/11%), 379/381 (4/1), 351/353 (7/2), 243 (23), 242 (35), 214 (56) and 91 (100).

(ii) For compound **3** elution of the column with ether–light petroleum (2:1 v/v) gave *ethyl* 6-(2′,3′,4′,6′-*tetraacetyl*-β-D-*glucopyranos*-1′-*yl*)-3,9b-di(*p-chlorophenyl*)-5a,6,9a,9b-*tetrahydro*-9H-*isoxazolo*[4′,5′:2,3]*isoxazolo*[5,4-b]*pyridine*-8-*carboxylate* **12** (0.8 g, 10%), m.p. 172–174 °C (from ether) (Found: C, 54.75; H, 5.4; N, 2.9. $C_{36}H_{37}Cl_2N_3O_{13}$ requires C, 54.7; H, 4.7; N, 5.3%); ν_{max}(film)/cm^{-1} 1745 (CO); δ_H 1.24 (3 H, t, *J* 7.1, Me), 1.75 (1 H, A*B*XY, *J* 14.5, 12.6, 1.6, 9′-H), 1.95, 1.99, 2.01 and 2.03 (12 H, s, MeCO), 2.11 (1 H, *A*BX, *J* 14.5, 6.8, 9-H), 2.74 (1 H, ddd, *J* 12.6, 6.8, 3.2, 9a-H), 3.67–3.78 (1 H, m, 5-H_{glu}), 4.02–4.20 (4 H, m, OCH_2 and 6,6′-H_{glu}), 4.38 (1 H, d, *J* 8.5, 1-H_{glu}), 5.02–5.29 (4 H, m, 5a-H and 2,3,4-H_{glu}), 7.39 (1 H, d, *J* 1.6, 7-H), 7.33–7.46, 7.54–7.63 and 7.84–7.92 (8 H, m, Ar); *m/z* 789 (M^+, <0.1%), 760 (3), 670 (5), 428 (9), 331 (25), 277 (42), 231 (15), 169 (100) and 109 (57). Further elution of the column afforded a 1:1 mixture of diastereoisomers *ethyl* 7-(2′,3′,4′,6′-*tetraacetyl*-β-D-*glucopyranos*-1′-*yl*)-3-p-*chlorophenyl*-3a,4,7,7a-*tetrahydroisoxazolo*[5.4-b]*pyridine*-5-*carboxylate* **11** (1.34 g, 21%), m.p. 95–98 °C (from ether) (Found: C, 54.3; H, 5.4; N, 4.2. $C_{29}H_{33}ClN_2O_{12}$ requires C, 54.7; H, 5.2; N, 4.4%); ν_{max}(film)/cm^{-1} 1745 (CO); δ_H 1.26, 1.27 (3 H, t, *J* 7.1, Me), 1.82–1.98 (1 H, m, 4-H′), 2.00, 2.01, 2.02, 2.03, 2.04, 2.06, 2.07, 2.08 (12 H, s, MeCO), 2.88, 2.90 (1 H, dd, *J* 16.0, 6.8, 4-H), 3.15 (1 H, ddd, *J* 9.4, 6.8, 6.4, 3a-H), 3.76–3.85 (1 H, m, 5-H_{glu}), 4.06–4.30 (4 H, m, OCH_2 and 6,6′-H_{glu}), 4.76, 4.65 (1 H, d, *J* 8.8, 1-H_{glu}), 5.10–5.40 (3 H, m, 2,3,4-H_{glu}), 5.53, 5.64 (1 H, d, *J* 6.4, 7a-H), 7.48, 7.54 (1 H, d, *J* 1.5, 6-H) and 7.37–7.65 (m, Ar); *m/z* 636/638 (M^+, 8/2%), 591 (1), 483 (2), 331 (30), 305 (2), 169 (100), 127 (11) and 109 (47).

Elution with ether gave *ethyl* 1-(2′,3′,4′,6′-*tetraacetyl*-β-D-*glucopyranos*-1′-*yl*)-1,2-*dihydro*-2-*oxopyridine*-3-*carboxylate* **13** (0.1 g, 10%) as white crystals, m.p. 78–81 °C (from ether), $[\alpha]_D$ +20.3 (*c* 6.20, MeCN) (Found: C, 52.9; H, 5.4; N, 2.9. $C_{22}H_{27}NO_{12}$ requires C, 53.1; H, 5.4; N, 2.8%); ν_{max}(film)/cm^{-1} 1750 and 1670 (CO); δ_H 1.38 (3 H, t, *J* 7.1, Me), 1.91, 2.01, 2.06, 2.09 (12 H, s, MeCO), 3.98 (1 H, ddd, *J* 10.1, 4.3, 2.4, 5-H_{glu}), 4.17 and 4.25 (2 H, AB, *J* 12.8, 4.3, 2.4, 6,6′-H_{glu}), 4.34 (2 H, q, *J* 7.1, OCH_2), 5.20, 5.21, 5.45 (3 H, t, *J* 9.8, 2-, 3- and 4-H_{glu}), 6.29 (1 H, d, *J* 9.8, 1-H_{glu}), 6.48 (1 H, *J* 9.5, 5-H), 7.83 (1 H, dd, *J* 9.5, 2.0, 4-H) and 8.22 (1 H, d, *J* 2.0, 2-H); *m/z* 497 (M^+, 6%), 452 (2), 331 (31), 262 (5), 169 (100), 127 (16), 122 (12) and 109 (62).

Sodium 2-*Benzyl*-trans-7-*cyano*-cis-2-*azabicyclo*[4.2.0]*octane*-6-*carboxylate* **14**.—To sodium hydroxide (68 mg, 1.7 mmol) in ethanol (5 cm^3) compound **8b** (100 mg, 0.33 mmol) was added and the mixture kept at room temperature for 24 h. Solvent was then removed and the residue was dissolved in water and the solution neutralized with concentrated hydrochloric acid. Extraction with dichloromethane and solvent evaporation gave the white sodium salt **14** (65 mg, 67%), m.p. 144–150 °C after washing with ether (Found: C, 65.5; H, 6.4; N, 9.1. $C_{16}H_{17}N_2NaO_2$ requires C, 65.7; H, 5.9; N, 9.6%); ν_{max}(film)/cm^{-1} 2235 (CN) and 1630 (CO); δ_H 1.70–1.88 (2 H, m, 4-$H_{a,e}$), 1.90–2.03 (1 H, m, 5-H_a), 2.38–2.76 (4 H, m, 3-H_a, 5-H_e and 8-H,H′), 2.66 (1 H, m, 5-H_e), 2.95 (1 H, m, 3-H_a), 3.37, 4.34 (2 H, AB, *J* 12.2, $CH_2C_6H_5$), 3.40 (1 H, dd, *J* 10.0 and 7.9, 7-H), 4.34 (1 H, dd, *J* 10.3, 7.7, 1-H) and 7.38–7.51 (5 H, m, C_6H_5); *m/z* 217 (52%), 172 (21), 91 (100) and 65 (14).

1-*Benzyl*-3-(2-*cyanoethyl*)-1,4,5,6-*tetrahydropyridine* **15**.—To sodium hydroxide (68 mg, 1.7 mmol) in ethanol (5 cm^3), compound **6b** (100 mg, 0.33 mmol) was added and the mixture kept for 24 h at room temperature. Solvent was removed under reduced pressure and the residue treated with water was extracted with chloroform. Evaporation of the organic layer left a liquid residue which was distilled *in vacuo* to give compound **15** as a yellow oil, b.p. 146 °C at 0.03 mmHg (60 mg, 80%) (Found: C, 79.3; H, 8.2; N, 12.1. $C_{15}H_{18}N_2$ requires C, 79.6; H, 8.0; N, 12.4%); ν_{max}(film)/cm^{-1} 2240 (CN) and 1665 (C=N); δ_H 1.78–1.95 (4 H, m, 4-H,H′ and 5-H,H′), 2.26–2.37 (4 H, A_2B_2X, *J* 7.0, 1.2, CH_2CH_2CN), 2.75–2.84 (2 H, m, 6-H,H′), 3.92 (2 H, s, $CH_2C_6H_5$), 5.94 (1 H, quint, *J* 1.1, 2-H) and 7.25–7.34 (5 H, m, C_6H_5); *m/z* 226 (M^+, 22%), 186 (95), 91 (100) and 65 (18).

Transformation of Compound **6b** *into* **7b**.—A solution of compound **6b** (200 mg, 0.66 mmol) in anhydrous ether (10 cm^3) containing a catalytic amount of concentrated sulfuric acid was kept at room temperature for 72 h. TLC analysis of the reaction mixture showed the presence of both **6b** and **7b** isomers. The solution was neutralized with sodium hydrogen carbonate and organic layer on evaporation yielded a residue which was column chromatographed with ether–light petroleum 1:1 (v/v) to give starting material (80 mg, 40%) and compound **7b** (90 mg, 45%), as oils.

Ethyl 1-*Benzyl*-3-(2-*cyanoethyl*)-2-*hydroxypiperidine*-3-*carboxylate* **16**.—A solution of compound **6b** (500 mg, 1.7 mmol) in ether (10 cm^3) was added with silica gel (1 g) and kept at room temperature with stirring until the starting material disappeared (TLC). Solvent was evaporated *in vacuo* and the residue purified by column chromatography with ether–light petroleum 2:1 v/v to give compounds **16** (R_f 0.29 in ether–light petroleum 1:2 v/v, 400 mg, 74%) as a single chromatographic fraction, a yellowish oil (Found: C, 67.7; H, 7.6; N, 8.5. $C_{18}H_{24}N_2O_3$ requires C, 68.3; H, 7.65; N, 8.85%); ν_{max}(film)/cm^{-1} 3500 (OH), 2245 (CN) and 1725 (CO); δ_H 1.23, 1.24 (3 H, 2 t, *J* 7.1, Me), 1.46–2.43 (9 H, m, 4-H,H′, 5-H,H′, 6′-H and CH_2CH_2CN), 2.66 (1 H, m, 6-H), 2.91, 3.08 (1 H, 2 exch. d, *J* 5.3, OH), 3.52, 3.80 (2 H, 2 AB, *J* 13.5, $CH_2C_6H_5$), 4.11, 4.22 (2 H, m, CH_2CH_3), 4.41, 4.70 (1 H, 2 d, *J* 5.3, 2-H) and 7.20–7.45 (5 H, m, C_6H_5); *m/z* 316 (M^+, 5%), 299 (4), 298 (4), 225 (4), 207 (3), 134 (12), 105 (16), 91 (100), 77 (8) and 65 (10).

Ethyl 6-(1-*Benzyl*-3-*phenylureido*)-1-*cyano*-3-*formylhexane*-3-*carboxylate* **18**.—Phenyl isocyanate (0.5 cm^3, 4.5 mmol) was added to compound **16** (300 mg, 0.9 mmol) and the mixture was kept at room temperature for 0.5 h. The resulting solution was washed with light petroleum and the insoluble material column chromatographed by eluting first with light petroleum–ether 1:1 v/v and then with light petroleum–ether 1:2 v/v to give *compound* **18** as an oil (R_f 0.38 in ether–light petroleum 1:2 v/v, 300 mg, 76%) (Found: C, 69.2; H, 6.7; N, 9.5. $C_{25}H_{29}N_3O_4$ requires C, 68.9; H, 6.7; N, 9.65); ν_{max}(film)/cm^{-1} 3340 (NH), 2235 (CN), 1710 and 1640 (CO); δ_H 1.25 (3 H, t, *J* 7.1, Me), 1.51 (2 H, m, 4-H,H′), 1.78 (2 H, m, 3-H,H′), 2.09 (2 H, m, CH_2CH_2CN), 2.27 (2 H, m, CH_2CN), 3.34 (2 H, t, *J* 7.0, NCH_2), 4.21 (2 H, q, *J* 7.1, OCH_2), 4.49 (2 H, s, $NCH_2C_6H_5$), 6.62 (1 H, exch. br s, NH), 6.96–7.38 (10 H, m, 2 C_6H_5) and 9.65 (1 H, m, CHO); *m/z* 435 (M^+, 2), 355 (2), 300 (6), 298 (5), 260 (9), 209 (8), 141 (47), 135 (19), 119 (84), 113 (25), 108 (10), 95 (11), 91 (100), 67 (12) and 64 (19).

Acknowledgements

We thank the Progetto Finalizzato Chimica Fine II, CNR, Rome for financial support and the Centro di Analisi e Determinazioni Strutturali, University of Siena, Italy for use of the mass spectrometer.

References

1 (*a*) G. Adembri, D. Donati, S. Fusi and F. Ponticelli, *Heterocycles*, 1985, **23**, 2885; (*b*) G. Adembri, D. Donati, S. Fusi and F. Ponticelli, *Heterocycles*, 1987, **26**, 3221; (*c*) D. Donati, M. Fiorenza, S. Fusi and F. Ponticelli, *Acta Crystallogr., Sect C, Cryst. Struct. Commun.*, 1989, **45**, 317.
2 W. Oppolzer, *Acc. Chem. Res.*, 1982, **15**, 135.
3 J. A. Dale, D. L. Dull and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543.
4 N. Hoffmann, H. D. Scharf and J. Runsink, *Tetrahedron Lett.*, 1989, **30**, 2637.
5 G. Bianchi, C. De Micheli and R. Gondolfi, *J. Chem. Soc., Perkin Trans. 1*, 1972, 1711.
6 PCMODEL, SERENA Software, Bloomington, IN 47402-3076, 1987.
7 G. Adembri, D. Donati, S. Fusi and F. Ponticelli, *Atti VI Conv. Div. Chim. Farm., Sassari (Italy)*, 1986, 8.
8 L. J. Haynes and A. R. Todd, *J. Chem. Soc.*, 1950, 303.

Paper 2/00154C
Received 13*th January* 1992
Accepted 14*th April* 1992