Oxygen-bridged Tetrahydropyridines, Hexahydropyridines, and Dihydropyridones *via* a Hantzsch-like Synthesis with 4-(2-Hydroxyphenyl)but-3-en-2-one

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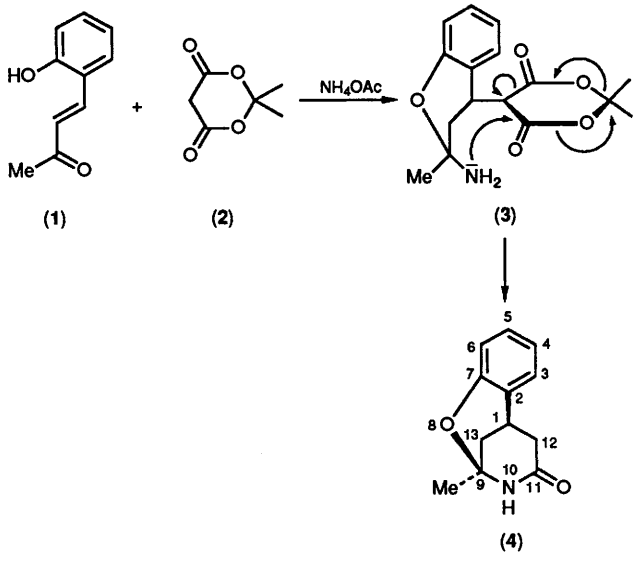
Substituted oxygen-bridged tetrahydro-2-pyridones and tetrahydropyridines (**4**) and (**7**) were synthesized by condensation of 4-(2-hydroxyphenyl)but-3-en-2-one (**1**) with Meldrum's acid (**2**) and 3-aminocrotononitrile, respectively, in the presence of ammonium acetate. Analogous cyclocondensations of (**1**) with methyl 3-amino-2,4-dicyanobut-2-enoate (**8**) and methyl 3-amino-2-cyanopentene-2-dioate (**10**) led to oxygen-bridged hexahydropyridines (**9**) and (**11**), respectively, of different stereochemistry in the piperidine rings. The dichotomy in the stereospecific routes to these oxygen-bridged heterocycles is discussed. Preparation of 4-aryl substituted dihydro-2-pyridones is also reported.

Recently considerable interest has been focussed on structural modification of the known 1,4-dihydropyridine calcium channel blockers. A variety of model compounds have been developed with the aim of studying the geometrical features that influence the biological activity of these compounds.[1] Of particular interest have been conformationally rigid analogues which represent pharmacologically attractive molecules to probe the receptor-bound conformation.[2] Another approach in the class of cardiovascular agents is represented by the design of diltiazem-like compounds as dihydropyridine mimics.[3] In keeping with recent progress we have developed a simple methodology for the synthesis of oxygen-bridged pyridines and pyrimidines,[4,5] benzothiazepines, and benzodiazepines,[6] starting from 4-(2-hydroxyphenyl)but-3-en-2-one (**1**). The objective of the present work is to extend the synthetic utility of (**1**) to stereospecific preparation of tetrahydropyridines, pyridones, and piperidines.

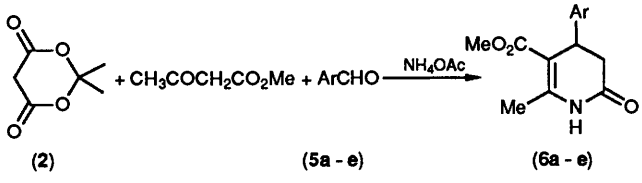
Results and Discussion

Out of a variety of active methylene compounds we first examined alkyl malonates which, however, failed to react with (**1**) under standard conditions. Condensation of (**1**) with the more reactive 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid)[7] (**2**) in refluxing ethanol afforded a crystalline product in 27% yield. On the basis of elemental analytical and NMR spectral results this was identified as the tetrahydropyridone derivative (**4**) (Scheme 1). The formation of (**4**) can be viewed as proceeding *via* Michael addition to (**1**) of the carbanion of (**2**) (a d^2 synthon) and aminal formation (**3**). Nucleophilic attack of the amine nitrogen atom at the dioxanedione ring leads to pyridone ring closure and acetone expulsion to give (**4**) (Scheme 1). By comparison, decarboxylation of 3-oxopyridazine-4-carboxylic acids, prepared from Meldrum's acid and hydrazones, required much more severe conditions, *e.g.* gas-phase pyrolysis.[8]

To further utilize the potential of the above reaction we have employed (**2**) as a second dicarbonyl component in a Hantzsch-like synthesis. Heterocyclization of methyl acetoacetate and benzaldehyde with (**2**) in the presence of ammonium acetate yielded the substituted pyridone carboxylate (**6a**) (Scheme 2).



Scheme 1.



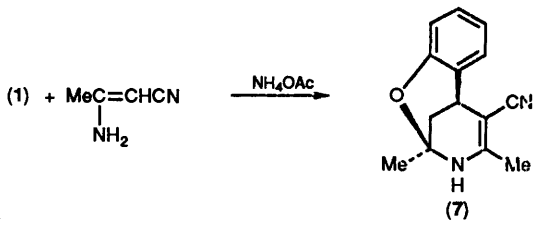
(**5a**), (**6a**) Ar = Ph
(**5b**), (**6b**) Ar = 4-$NO_2C_6H_4$
(**5c**), (**6c**) Ar = 3-$NO_2C_6H_4$
(**5d**), (**6d**) Ar = 2-$NO_2C_6H_4$
(**5e**), (**6e**) Ar = 4-$MeOC_6H_4$

Scheme 2.

The reaction proceeds well with other aromatic aldehydes, as documented by the preparation of the 4-aryl-substituted pyridones (**6b–e**). The advantage of the present method over other synthetic routes leading to substituted pyridones[9,10] is

due to the availability of the starting components and an easy work-up procedure. In spite of moderate yields, it provides a convenient entry into the chemistry of 3,4-dihydro-2(1H)-pyridones.[9,10]

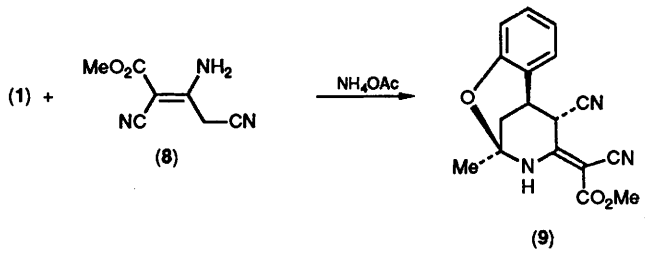
The bridged tetrahydropyridine (7) (Scheme 3) was obtained



Scheme 3.

by cyclocondensation of butenone (1) with 3-aminocrotononitrile in the presence of ammonium acetate. When the reaction was conducted in the absence of the latter, the nitrile (7) was formed in a substantially lower yield. Structure (7) was assigned from spectral data which were consistent with those of structurally related compounds synthesized previously.[4,5]

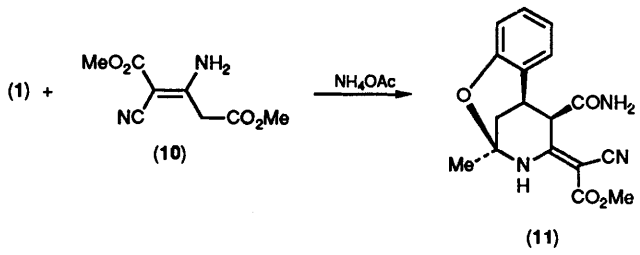
Condensation of (1) with multifunctional nucleophiles has been shown earlier to yield functionalized hexahydropyridines having a well-defined configuration of the substituents in the heterocyclic ring, and a potential for a further synthetic build-up.[5] In order to distinguish the functional groups being introduced by their reactivity, we have now examined the condensation of (1) with the co-dimer of malononitrile and methyl cyanoacetate (8), and dimeric methyl cyanoacetate (10). The reaction of (1) with (8) afforded the dinitrile (9) as a single



Scheme 4.

stereoisomer (Scheme 4). The configuration at C-12 followed from the ^{1}H NMR spectrum. The equatorial proton 12-H appears as a doublet of doublets (Y part of an ABXY system) showing a vicinal coupling with 1-H ($J_{1,12}$ 2.3 Hz) and a long-range coupling with H_{eq}-13 ($J_{12,13}$ 1.5 Hz). The latter proton is readily identified through its long-range coupling with the nitrogen-bound proton (10-H, $J_{10,13}$ 1.6 Hz). It should be noted that the H_{eq}-13 in (9) appears at a higher field than its axial counterpart (H_{ax}-13), contrary to the usual order of chemical shifts in related compounds.[5] Complementary evidence for the configuration of the cyano group in (9) was obtained from the proton-coupled ^{13}C NMR spectrum which showed the nitrile carbon atom (δ_C 115.1) as a doublet of doublets due to splitting by coupling with H-12 (^2J 11.5 Hz) and 1-H (^3J 3.1 Hz). The configuration at the exocyclic double bond was deduced only indirectly from the large downfield shift of the NH proton (δ_H 10.18 in $CDCl_3$), which is consistent with hydrogen bonding to the ester group. The *Z*-geometry assigned to (9) is the same as in the starting compound (8).[11]

Unexpectedly, condensation of the enone (1) with the methyl cyanoacetate dimer (10) afforded a product with opposite configuration at C-12 (11) (Scheme 5). The reaction is evidently preceded by ammonolysis of one of the methoxycarbonyl groups, which is known to occur under mild conditions.[11] The



Scheme 5.

configuration at C-12 was deduced from the ^{1}H NMR spectrum which showed no long-range coupling between 12-H and 13-H_{eq}. The 12-proton appears as a pseudoquartet due to splittings by 1-H (J_{XY} 2.4 Hz) and the amide protons ($J_{Y,NH}$ 2.1 Hz). The *Z*-configuration at the exocyclic double bond was assigned indirectly from the downfield shift of the heterocyclic NH proton, and it corresponded to the same *Z*-configuration in the starting ester (10).

The different stereochemistry in the condensations of the enone (1) with the structurally related enamines (8) and (10) may be due to kinetic or thermodynamic factors. In order to distinguish these effects we have examined base-catalyzed isomerizations of (9) and (11) under conditions similar to those employed in the synthesis. The epimerization at C-12 was monitored by deuterium incorporation from the solvent (CD_3OD).

When treated with a catalytic amount of triethylamine in CD_3OD (50 °C, 5 h), the amide (11) underwent only exchange of the labile NH_2 protons. Consequently, in the ^{1}H NMR spectrum the multiplet of 12-H collapsed to a doublet, whilst its chemical shift and integrated intensity remained unchanged. This indicates that 12-H is not acidic enough to undergo exchange or epimerization under the reaction conditions. Hence, the configuration at C-12 is due to kinetic control in the formation of the C(1)–C(12) bond (see below).

By contrast, the nitrile (9) underwent complete exchange of 12-H for deuterium when treated with CD_3OD and triethylamine under the same conditions as above. This was clearly manifested by the disappearance of the 12-H signal in the ^{1}H NMR spectrum. However, the spectrum revealed that, despite the exchange, the configuration at C-12 remained unchanged as evidenced by the chemical shifts of the bridge methylene protons (13-H_{eq} and 13-H_{ax}). Since the latter are affected by the orientation of the 12-cyano group (see above), an epimerization at C-12 would have been clearly detected. It follows that the C-12 centre in (9) is prone to epimerization, so that the axial orientation of the cyano group is attributable to thermodynamic control. The preference for the axial cyano group in (9) is attributable to electrostatic repulsion of the C≡N dipoles which would be parallel in the chair conformation of an equatorial isomer of (9). The formation of the single stereoisomer of (11) necessitates a kinetic control in the transition state of the carbon–carbon bond formation. Out of a multitude of possible conformations of the reactants it appears from inspection of molecular models that the transition state with a pseudoaxial carboxamide group should experience the least steric congestion (Figure). This model further assumes a

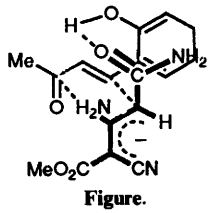


Figure.

donor–acceptor interaction of the amino group in (**10**) with the carbonyl group in (**1**),[4,5] which would lock the enone moiety in a six-membered cyclic transition state. The presumed *Z*-configuration at C(2)–C(3) in the anion of (**10**) is consistent with that in the starting compound and the product (**11**). The *Z*-configuration at C(3)–C(4) in the carbanion appears highly probable, since an *E*-isomer would be forced out of planarity because of steric interaction between the amide and cyano groups. It should be noted that such a steric congestion is less pronounced with the much smaller cyano group in (**8**). The formation of the axial *exo*-isomer (**9**) thus may be controlled kinetically, or it can result from a facile epimerization at C-12 in the cyclic product (see above).

In conclusion, the enone (**1**) proves to be a versatile synthon for the construction of functionalized tetrahydropyridines, hexahydropyridines, and tetrahydro-2-pyridones. The stereochemistry of the condensation depends on the nature of the electrophilic reagent. Cyano groups at C-12 tend to induce epimerization, giving rise to the more stable *exo*-axial isomers. The carboxamide group at C-12 prefers the *endo*-equatorial configuration imposed by kinetic control in the ring-forming step. The presence of several different functional groups in a conformationally locked hexahydropyridine ring appears to be promising for further stereoselective transformations which are under current study.

Experimental

M.p.s were determined on a Boetius micro hot-stage apparatus and are uncorrected. The IR spectra were recorded on a Pye-Unicam PU-9 512 spectrophotometer. ^1H and ^{13}C NMR spectra were measured on a Varian VXR-300 spectrometer using tetramethylsilane as internal standard. The abbreviations used are as follows: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintuplet, sept = septuplet, m = multiplet, and br = broad. Mass spectra were measured on a JEOL D-100 spectrometer (75 eV, direct inlet). Elemental analyses were determined at the Department of Analytical Chemistry, Slovak Technical University.

9-Methyl-8-oxa-10-azatricyclo[7.3.1.0^{2,7}]*trideca-2,4,6-trien-11-one* (**4**).—To a stirred solution of Meldrum's acid (1.44 g, 0.01 mol) in warm ethanol (25 ml) were added the butenone (**1**) (1.62 g, 10 mmol) and ammonium acetate (0.85 g, 11 mmol). The mixture was refluxed for 4 h. The crystalline material which separated upon cooling was filtered off and recrystallized from acetone; yield 0.55 g (27%), m.p. 257–258 °C (Found: C, 70.8; H, 6.6; N, 6.75. $C_{12}H_{13}NO_2$ requires C, 70.92; H, 6.45; N, 6.89%); ν_{max}(KBr) 3 200 (NH), 1 660 (lactam C=O), and 1 600 and 1 580 cm^{-1} (C=C); δ_H($CDCl_3$) 1.70 (3 H, s, CH_3), 2.10 (1 H, dd, J_{AB} 13.1, J_{BX} 2.2 Hz, B part of ABMNX, 13-H_{ax}), 2.19 (1 H, m, J_{AB} 13.1, J_{AX} 4.1, J_{AM} 1.8, and $J_{A,NH}$ 1.6 Hz, A part of ABMNX, 13-H_{eq}), 2.59 (1 H, dt, J_{MN} 17.4, J_{MX} 2.1, and J_{AM} 1.8 Hz, M part of ABMNX, 12-H_{eq}), 2.68 (1 H, dd, J_{MN} 17.4, and J_{NX} 4.6 Hz, N part of ABMNX, 12-H_{ax}), 3.24 (1 H, sept, J_{NX} 4.6, J_{AX} 4.1, J_{BX} 2.2, and J_{MX} 2.1 Hz, X part of ABMNX, 1-H), 6.31 (1 H, br s, NH), 6.78 (1 H, dd, *J* 8.4 and 1.3 Hz, 6-H), 6.91 (1 H, dt, *J* 7.4 and 1.3 Hz, 4-H), 7.09 (1 H, dd, *J* 7.6 and 1.8 Hz, 3-H), and 7.14 (1 H, dt, *J* 8 and 1.7 Hz, 5-H); δ_C[$(CD_3)_2SO$] 26.8 (q, CH_3), 28.9 (d, C-1), 32.1 (t, C-13), 40.4 (t, C-12), 82.6 (s, C-9), 116.7 (d, C-6), 120.7 (d, C-4), 125.6 (s, C-2), 128.0 (d, C-3 or C-5), 129.2 (d, C-5 or C-3), 151.2 (s, C-7), and 170.1 (s, C-11); *m/z* 204 (7%), 203 ($M^{+\cdot}$, 54), 202 (22), 188 ($C_{11}H_{10}NO_2$, 33), 160 ($C_{10}H_{10}NO$, 17), 110 (C_6H_8NO, 100), 109 (14), 97 (6), 92 (5), 91 (22), 90 (6), 89 (8), 77 (10), 65 (14), 63 (10), and 57 (40).

Preparation of 4-Aryl-1,4,5,6-tetrahydropyridine-3-carboxylates (**6a–e**): *General Procedure*.—A mixture of an aromatic aldehyde (10 mmol), Meldrum's acid (10 mmol), methyl acetoacetate (10 mmol), and ammonium acetate (11 mmol) in ethanol (20 ml) was refluxed for 6 h. The solvent was removed under reduced pressure and the oily residue was triturated with methanol. Recrystallization of the precipitate from methanol afforded a sample of analytical quality.

Methyl 1,4,5,6-tetrahydro-2-methyl-6-oxo-4-phenylpyridine-3-carboxylate (**6a**). Yield 26%, m.p. 197–198 °C (Found: C, 68.35; H, 5.9; N, 5.9. $C_{14}H_{15}NO_3$ requires C, 68.56; H, 6.16; N, 5.71%); ν_{max}(KBr) 1 705 and 1 690 cm^{-1} (C=O); δ_H($CDCl_3$) 2.42 (3 H, s, CH_3), 2.70 (1 H, dd, J_{AB} 16.5, J_{BX} 1.5 Hz, B part of ABX), 2.92 (1 H, dd, J_{AB} 16.5, J_{AX} 7.9 Hz, A part of ABX), 3.67 (3 H, s, ester CH_3), 4.26 (1 H, dd, X part of ABX), 7.17–7.32 (5 H, m, Ph), and 7.75 (1 H, br s, NH).

Methyl 1,4,5,6-tetrahydro-2-methyl-4-(4-nitrophenyl)-6-oxopyridine-3-carboxylate (**6b**). Yield 27%, m.p. 223–225 °C (Found: C, 58.1; H, 4.7; N, 9.6. $C_{14}H_{14}N_2O_5$ requires C, 57.93; H, 4.86; N, 9.65); ν_{max}(KBr) 1 700 (C=O) and 1 515 and 1 350 cm^{-1} (NO_2); δ_H($CDCl_3$) 2.46 (3 H, s, CH_3), 2.49 (1 H, dd, J_{AB} 16.5, J_{BX} 1.8 Hz, B part of ABX), 3.00 (1 H, dd, J_{AX} 8 Hz, A part of ABX), 3.64 (3 H, s, ester CH_3), 4.29 (1 H, dd, X part of ABX), 7.35 (2 H, dd), 7.58 (1 H, br s, NH), and 8.17 (2 H, dd).

Methyl 1,4,5,6-tetrahydro-2-methyl-4-(3-nitrophenyl)-6-oxopyridine-3-carboxylate (**6c**). Yield 24%, m.p. 206–207 °C (Found: C, 57.8; H, 4.7; N, 9.9. $C_{14}H_{14}N_2O_5$ requires C, 57.93; H, 4.86; N, 9.65%); ν_{max}(KBr) 1 700 (C=O) and 1 535 cm^{-1} (NO_2); δ_H($CDCl_3$) 2.46 (3 H, s, CH_3), 2.67 (1 H, dd, J_{AB} 16.3, J_{BX} 1.5 Hz, B part of ABX), 3.02 (1 H, dd, J_{AX} 7.9 Hz, A part of ABX), 3.58 (3 H, s, ester CH_3), 4.37 (1 H, dd, X part of ABX), 7.49 (2 H, m), 8.07 (2 H, m), and 8.24 (1 H, m, NH).

Methyl 1,4,5,6-tetrahydro-2-methyl-4-(2-nitrophenyl)-6-oxopyridine-3-carboxylate (**6d**). Yield 26%, m.p. 205–207 °C (Found: C, 57.8; H, 4.7; N, 9.75. $C_{14}H_{14}N_2O_5$ requires C, 57.93; H, 4.86; N, 9.65%); ν_{max}(KBr) 1 710 and 1 685 (C=O) and 1 350 cm^{-1} (NO_2); δ_H($CDCl_3$) 2.47 (3 H, s, CH_3), 2.83 (1 H, dd), 3.06 (1 H, dd), 3.52 (3 H, s, ester CH_3), 4.77 (1 H, dd), 7.28 (1 H, d), 7.34 (1 H, t), 7.50 (1 H, t), 7.85 (1 H, d), and 8.00 (1 H, br s, NH); δ_C($CDCl_3$) 19.2 (q, CH_3), 33.5 (d, C-4), 37.1 (t, C-5), 51.5 (q, ester CH_3), 106.1 (s, C-3), 124.9 (d, C_{ar}-3), 128.1, 128.2 (d, C_{ar}-4 and C_{ar}-6), 133.4 (d, C_{ar}-5), 137.1 (s, C_{ar}-1), 147.7, 149.0 (s, C_{ar}-2 and C-2), 166.5 (s, ester C=O), and 169.9 (s, lactam C=O).

Methyl 1,4,5,6-tetrahydro-2-methyl-4-(4-methoxyphenyl)-6-oxopyridine-3-carboxylate (**6e**). Yield 15%, m.p. 188–190 °C (Found: C, 65.3; H, 6.2; N, 5.25. $C_{15}H_{17}NO_4$ requires C, 65.44; H, 6.22; N, 5.09%); ν_{max}(KBr) 1 690 cm^{-1} (C=O); δ_H($CDCl_3$) 2.38 (1 H, s, CH_3), 2.63 (1 H, dd), 2.92 (1 H, dd), 3.65 (3 H, s), 3.76 (3 H, s), 4.19 (1 H, d), 6.80 (2 H, dd), 7.10 (2 H, dd), and 8.80 (1 H, br s, NH).

9,11-Dimethyl-8-oxa-10-azatricyclo[7.3.1.0^{2,7}]*trideca-2,4,6,11-tetraene-12-carbonitrile* (**7**).—A solution of butenone (**1**) (1.62 g, 10 mmol), 3-aminocrotononitrile (0.82 g, 10 mmol), and ammonium acetate (0.85 g, 11 mmol) in ethanol (25 ml) was refluxed for 3 h. The solid precipitated upon cooling was filtered off and washed with ether to give (**7**) (0.82 g). An additional crop (0.15 g) was obtained from the mother liquor; total yield 0.97 g (43%), m.p. 271–273 °C (from ethanol) (Found: C, 74.3; H, 6.35; N, 12.3. $C_{14}H_{14}N_2O$ requires C, 74.31; H, 6.24; N, 12.38%); ν_{max}(KBr) 3 300 (NH), 2 175 (CN), and 1 610 and 1 578 cm^{-1} (C=C); δ_H[$(CD_3)_2SO$] 1.67 (3 H, s, 9-CH_3), 1.87 (3 H, s, 11-CH_3), 1.88 (1 H, dd, J_{AB} 12.7, J_{BX} 3.1 Hz, B part of ABX, 13-H_{ax}), 2.00 (1 H, ddd, J_{AX} 3.1, $J_{A,NH}$ 1 Hz, A part of ABX, 13-H_{eq}), 3.54 (1 H, t, X part of ABX, 1-H), 6.74 (1 H, dd, 6-H), 6.81 (1 H, dt, 4-H), 7.03 (1 H, dd, 3-H), 7.06 (1 H, dt, 5-H), and 7.96 (1 H, br s, NH); δ_C[$(CD_3)_2SO$] 17.8 (q, 11-CH_3), 26.2 (q, 9-CH_3), 30.8 (t, C-13), 31.1 (d, C-1), 78.6 (s, C-12), 81.0 (s, C-9), 115.9 (d, C-6), 119.9 (d, C-4), 121.4 (s, CN), 126.9 (s, C-2), 127.3, 127.4 (d, C-3, C-5), 151.9, and 152.1 (s, C-7, C-11).

11-(1-*Cyano-2-methoxy-2-oxoethylidene*)-9-*methyl*-8-*oxa*-10-*azatricyclo*[7.3.1.0^{2,7}]*trideca*-2,4,6-*triene*-12-*carbonitrile* (**9**).—A solution of the butenone (**1**) (1.62 g, 10 mmol), co-dimer (**8**) (1.65 g, 10 mmol), and ammonium acetate (0.85 g, 11 mmol) in ethanol (60 ml) was refluxed for 4 h. A small amount of polymeric material was filtered off from the warm ethanol solution and the filtrate was allowed to crystallize. The separated crystals were washed with ether and recrystallized from ethanol; yield 1.55 g (50%), m.p. 195–197 °C (Found: C, 66.2; H, 4.7; N, 13.55. $C_{17}H_{15}N_3O_3$ requires C, 66.01; H, 4.89; N, 13.58%); ν_{max}(KBr) 2 250 and 2 210 (CN), 1 680 (C=O), and 1 595 cm^{-1} (C=C); δ_H($CDCl_3$) 1.86 (3 H, s, CH_3), 2.25 (1 H, m, J_{AB} 14, J_{AX} 4.4, $J_{A,NH}$ 1.6, J_{AY} 1.5 Hz, A part of ABXY, 13-H_{eq}), 2.53 (1 H, dd, J_{AB} 14, J_{BX} 2.1 Hz, B part of ABXY, 13-H_{ax}), 3.63 (1 H, qui, J_{AX} 4.4, J_{BX} 2.1, J_{XY} 2.3 Hz, X part of ABXY, 1-H), 3.74 (3 H, s, ester CH_3), 4.11 (1 H, dd, J_{XY} 2.3 Hz, Y part of ABXY, 12-H), 6.83 (1 H, dd, 6-H), 7.02 (1 H, dt, 4-H), 7.20 (1 H, dd, 3-H), 7.25 (1 H, dt, 5-H), and 10.18 (1 H, br s, NH); δ_C($CDCl_3$) 27.3 (q, ester CH_3), 29.0 (t, C-13), 31.9 (d, C-1), 37.5 (d, C-12), 52.1 (q, ester CH_3), 75.4 (s, exocyclic methylene), 80.6 (s, C-9), 115.1 (s, ^2J 11.8, ^3J 3.1 Hz, CN at C-12), 115.7 (s, exocyclic CN), 117.8 (d, C-6), 119.5 (s, C-2), 122.6 (d, C-4), 129.2 (d, C-5), 130.4 (d, C-3), 151.0 (s, C-7), 159.0 (s, C-11), and 167.2 (s, C=O); *m/z* 309 ($M^{+\cdot}$).

9-*Methyl*-11-(1-*cyano*-2-*methoxy*-2-*oxoethylidene*)-8-*oxa*-10-*azatricyclo*[7.3.1.0^{2,7}]*trideca*-2,4,6-*triene*-12-*carboxamide* (**11**).—A solution of the butenone (**1**) (1.62 g, 0.01 mol), methyl cyanoacetate dimer (**10**) (1.98 g, 0.01 mol), and ammonium acetate (0.85 g, 0.011 mol) in ethanol (25 ml) was refluxed for 3 h. The solvent was evaporated and the oily residue was triturated with ether. The crystalline product (0.6 g, 18%) was filtered off and recrystallized from ethanol, m.p. 268–271 °C (Found: C, 62.2; H, 5.35; N, 12.9. $C_{17}H_{17}N_3O_4$ requires C, 62.38; H, 5.24; N, 12.84%); ν_{max}(KBr) 3 500–2 700 (NH_2, NH), 2 200 (CN), 1 680 (ester C=O), 1 660 (amide C=O), and 1 580 cm^{-1} (C=C); δ_H[$(CD_3)_2SO$] 1.75 (3 H, s, CH_3), 2.24 (1 H, dd, J_{AB} 13, J_{BX} 5.5 Hz, B part of ABXY, 13-H_{ax}), 2.31 (1 H, dd, J_{AB} 13, J_{AX} 10 Hz, A part of ABXY, 11-H_{eq}), 3.61 (3 H, s, ester CH_3), 3.70 (m, J_{XY} 2.4, $J_{Y,CONH2}$ 2.1 Hz, Y part of ABXY, 12-H), 4.05 (1 H, ddd, J_{AX} 10, J_{BX} 5.5, J_{XY} 2.4 Hz, X part of ABXY, 1-H), 6.70 (1 H, dt, 4-H), 6.84 (1 H, dd, 6-H), 6.95 (1 H, dd, 3-H), 7.07 (1 H, dt, 5-H), 9.27 (1 H, br s, $CONH_2$), 9.74 (1 H, br s, $CONH_2$), 9.76 (1 H, s, NH); δ_C[$(CD_3)_2SO$] 20.7 (q, CH_3), 32.0 (d, C-1), 40.7 (t, C-13), 51.5 (q, ester CH_3), 53.5 (d, C-12), 68.7, 70.4 (s, exocyclic methylene and C-9), 115.3 (d, C-6), 117.1 (s, CN), 118.9 (d, C-4), 125.1 (s, C-2), 126.5 (d, C-3), 128.4 (d, C-5), 155.3 (s, C-7), 166.3, 166.5, and 169.6 (s, C-11, ester and amide C=O); *m/z* 327 ($M^{+\cdot}$).

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