Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 7, No. 24, pp. 3165-3170, 1997

0960-894X/97 $17.00 + 0.00

PII: S0960-894X(97)10165-2

FRIEDLÄNDER REACTION ON 2-AMINO-3-CYANO-4*H*-PYRANS: SYNTHESIS OF DERIVATIVES OF 4*H*-PYRAN [2,3-b] QUINOLINE, NEW TACRINE ANALOGUES

Angeles Martínez-Grau[1] and José L. Marco[2,*,†]

[1]Departamento de Química Orgánica I, Facultad de Química, Universidad Complutense, 28040-Madrid, Spain.
[2] Instituto de Química Orgánica General (CSIC), C/Juan de la Cierva 3, 28006-Madrid, Spain.

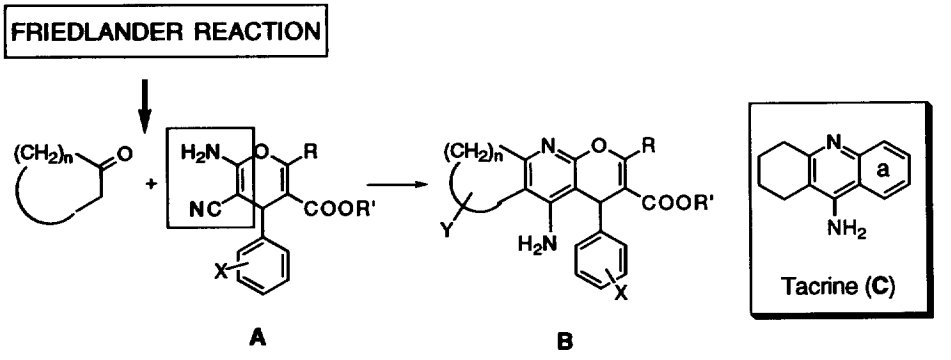
Abstract: The unprecedented Friedländer reaction of densely functionalized 2-amino-3-cyano-4*H*-pyrans (**1**) with cyclohexanone has afforded in one step and good yield 5-amino-4-aryl-3-ethoxycarbonyl-2-methyl-6,7,8,9-tetrahydro-4*H*-pyran[2,3-b]quinolines (**2**), novel amino-substituted fused pyran derivatives. These compounds are new tacrine analogues. © 1997 Elsevier Science Ltd.

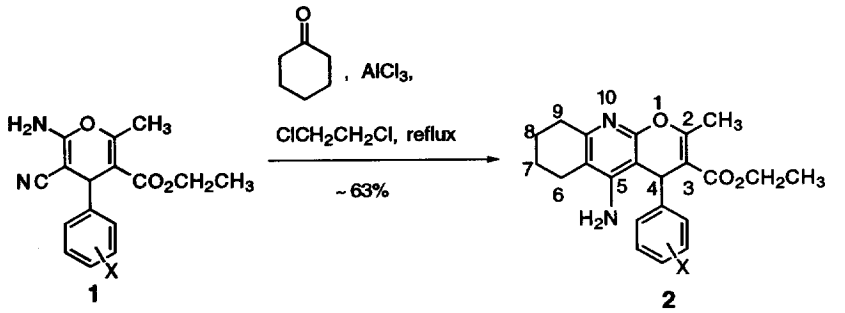
A recent report on the synthesis of some amino-substituted pyranopyranones[1] and the renewed interest for this class of compounds due to their potential HIV protease inhibition activity,[2] prompt us to report here our results on the synthesis of some novel amino-substituted fused pyran derivatives.[3]

Polyfunctionalized 2-amino-3-cyano-4*H*-pyrans[4] (**A**) are very well known compounds and their reactivity has been largely explored.[5] However, to our knowledge, the Friedländer reaction[6a] of these molecules with ketones, implementing the reactivity of the β-enaminonitrile moiety[7] of these products, has never been described.[6b] By contrast, this synthetic heteroannulation is well documented in 2-aminobenzonitriles and has been used to prepare analogues of tacrine (**C**),[8] an acetylcholinesterase inhibitor with proven efficiency in the treatment of Alzheimer desease.[9] In this Letter we report in detail the synthesis of some derivatives of 4*H*-pyran[2,3-b]quinoline (**B**), a new heterocyclic system, readily prepared *via* Friedländer reaction of 2-amino-3-cyano-4*H*-pyrans with cyclohexanone. These compounds are new tacrine (**C**) analogues, where the aromatic nucleus "**a**" has been substituted by a 4*H*-pyran ring.

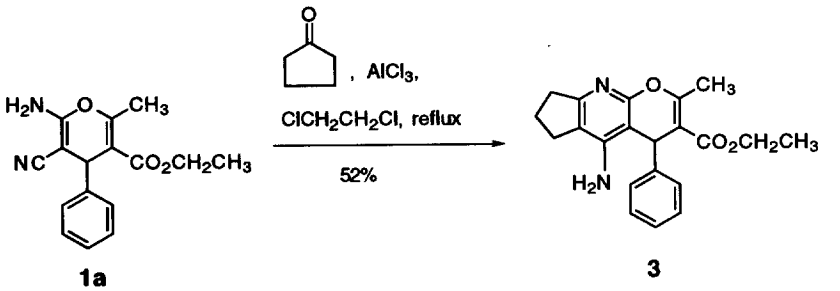
Using 4*H*-pyran **1a**,[10] an easily available starting material, and following the standard methodology for the Friedländer reaction (aluminium chloride in 1,2-dichloroethane, at reflux),[6c] a clean reaction resulted;[11] after work-up and recrystallization, compound **2a** was obtained in moderate yield (63%). The structure of this compound has been established by spectroscopic and analytical methods.[11] In fact, in the ^{1}H NMR spectrum we can observe significant signals for H4 (s, 4.84 ppm) and NH_2 (br s, 4.07 ppm); in the IR spectrum the absorption for a conjugate nitrile is absent and a carbonyl band (ester) appears at 1695 cm^{-1}. In agreement with this, in the ^{13}C NMR spectrum, typical signals for C2 (150.2 ppm) and C3 (106.5 ppm) in 4*H*-pyrans,[12] and signals for the 4-amino-pyridine nucleus[13] (C5: 153.7 ppm; C9a: 154.1 ppm, C10a: 159.6 ppm) are also present.

†Dr. José L. Marco: E-mail: iqmc21@pinar1.csic.es. Fax number: 43-1-564 48 53





(**a**: X= H, **b**: X= *p*-CH_3, **c**: *p*-Cl, **d**: *p*-CN, **e**: *p*-OCH_3, **f**: *m*-NO_2)



Under the same conditions **1b-f**[10] gave compounds **2b-f** in good yields. All these compounds showed excellent analytical and spectroscopic data,[11] in good agreement with those observed for product **2a**.

We have also tested this protocol by using cyclopentanone in the Friedländer reaction. Not surprisingly, starting from **1a** we obtained compound **3** in 52% yield. Comparison of the spectroscopic data of compound **3**[14] with those of products **2**[11] clearly supported the structure of 5-amino-7,8-dihydro-3-ethoxycarbonyl-2-methyl-6*H*-cyclopenta[e]4*H*-pyrano[2,3-b]pyridine for the new heterocycle. To our knowledge this heterocyclic system has never been previously reported.

In summary, these results cover a hole in the literature concerning the chemical reactivity of polyfunctionalized 2-amino-3-cyano-4*H*-pyrans. Note also that the resulting 5-amino-4-aryl-3-ethoxycarbonyl-3-methyl-6,7,8,9-tetrahydro-4*H*-pyran[2,3-b]quinolines incorporate the "4-aminopyridine" nucleus, a notorious pharmacophore in medicinal chemistry.[8]

The present and related products to be prepared in the future are potential and interesting new lead compounds for biological evaluation. This work is now in progress and will be reported in due course.[15]

Acknowledgment. J. L. M. thanks CICYT for financial support (Projects: SAF 94-0818-C02-02 and SAF 97-0048-C02-02) and EU (Human Capital and Mobility Programme; Contract n° ERBCHRXCT 92-0027).

References and Notes

1. Piao, M.-Z.; Imafuku, K. *Tetrahedron Lett.* **1997**, *38*, 5301.
2. See, for instance: Wang, S.; Milne, G. W. A.; Yang, X.; Posey, I. J.; Nicklaus, M. C.; Graham, L.; Rice, W. G. *J. Med. Chem.* **1996**, *39*, 2047.
3. The reactivity of the β-enaminonitrile moiety of 2-amino-3-cyano-4*H*-pyrans has been previously analyzed by several authors and the most significant results are resumed in:
   (A) The synthesis of pyrano[2,3-d]pyrimidine type of compounds after reaction with acetic anhydride in pyridine, or formamide or formamide in formic acid: a) Elagamey, A. A.; El-Taweel, F. M. A-A.; Khodeir, M. N. M.; Elnagdi, M. H. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 464; b) Khalil, Z. H.; Abdel-Hafez, A. A.; Geies, A. A.; Kamal El-Dean, A. M. *Bull. Chem. Soc. Jpn.* **1991** *64*, 668; c) Khodeir, M.; El-Taweel, F.; Elagamey, A. *Pharmazie* **1992**, *47*, 486.
   (B) The synthesis of benzopyrano[3',2':5,6]pyrano[2,3-b]pyridines after reaction with malononitrile, or malononitrile and aldehydes, or arylidenemalononitriles: d) Shaker, R. M. *Pharmazie* **1996**, *51*, 148.
   (C) The reaction with benzonitriles and orthoesteres has also been covered in the paper cited in ref. 3d.
4. Kuthan, J. *Adv. Heterocyclic Chem.* **1983**, *34*, 146.
5. Martín, N.; Martínez-Grau, A.; Seoane, C.; Marco, J. L.; Albert, A.; Cano, F. H. *J. Heterocyclic Chem.* **1996**, *33*, 27, and references cited therein.
6. a) Cheng, C. C.; Yan, S. J. *Org. React.* **1982**, *28*, 37; b) Aguado, F.; Badía, A.; Baños, J. E.; Bosch, F.; Bozzo, C.; Camps, P.; Contreras, J.; Dierssen, M.; Escolano, C.; Görbig, D. M.; Muñoz-Torrero, D.; Pujol, M. D.; Simón, M.; Vázquez, M. T.; Vivas, N. M. *Eur. J. Med. Chem.* **1994**, *29*, 205; c) Kawakami, H.; Ohuchi, M.; Kitano, M.; Ono, K. EP Appl. **1987** A1-0 268 871.
7. Taylor, E. C.; McKillop, A. *The Chemistry of Cyclic Enaminonitriles and o-Aminonitriles*, in Advances in Organic Chemistry, Vol 7; Taylor, E. C. Ed; Wiley & Sons; **1970**, New York.

8. Crismon, M. L. *Ann. Pharmacother.* **1994**, *28*, 744.
9. Hershenson, F. M.; Moos, W. H. *J. Med. Chem.* **1986**, *29*, 1125.
10. Quinteiro, M.; Seoane, C.; Soto, J, L. *Tetrahedron Lett.* **1977**, 1835.
11. **General Method** for the synthesis of compounds **2a-f** and **3**: In a typical experiment, aluminium chloride (1.1 equiv.) was suspended in dry 1,2-dichloroethane (10 mL/mmol) at room temperature under argon. The corresponding 2-amino-4*H*-pyran (**1a-f**) (1 equiv.) and the ketone (cyclohexanone or cyclopentanone; 1.1 equiv.) were added. The reaction mixture was heated at reflux (2-8 h). When the reaction was over (TLC analysis), a mixture of THF/H_2O (2:1) was added dropwise at rt. An aqueous solution of sodium hydroxide (10%) was added dropwise to the mixture until the aqueous solution was basic. After stirring for 30 min, the mixture was extracted twice with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, filtered and the solvent was evaporated. The solid obtained was washed with cold ether and recrystallized from ethyl acetate/hexane mixtures to give pure compounds **2a-f** and **3**. These compounds showed good elemental analysis in agreement with their structures.

5-Amino-3-ethoxycarbonyl-2-methyl-4-phenyl-6,7,8,9-tetrahydro-4*H*-pyran[2,3-b]quinoline (2a).
Following the **General Method** compound **1a** (400 mg, 1.48 mmol) [$AlCl_3$ (217 mg, 1.63 mmol), $ClCH_2CH_2Cl$ (15 mL), cyclohexanone (160 mg, 0.17 mL, 1.63 mmol)] afforded product **2a** (340 mg, 63%): mp 209-211 °C; IR (KBr) υ 3430, 3350, 3220, 2920, 1740, 1670, 1640, 1595, 1570, 1450, 1295, 1210, 1060 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.32-7.1 (m, 5 H, C_6H_5), 4.84 (s, 1 H, H4), 4.15-4.07 (m, 4 H, $CO_2CH_2CH_3$, NH_2), 2.74 (m, 2 H, H9), 2.45 (s, 3 H, CH_3), 2.18 (m, 2 H, H6), 1.77 (m, 4 H, H7, H8), 1.25 (t, *J*= 6.7 Hz, 3 H, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.7 ($CO_2CH_2CH_3$), 159.6 (C10a), 154.1 (C9a), 153.7 (C5), 150.2 (C2), 143.8, 128.4, 128.3, 126.9 (C_6H_5), 113.5 (C5a), 106.5 (C3), 99.5 (C4a), 60.1 ($CO_2CH_2CH_3$), 38.4 (C4), 32.3 (C9), 22.7, 22.4, 22.2 (C6, C7, C8), 19.5 (CH_3), 14.1 ($CO_2CH_2CH_3$); MS (70 eV) m/z 364 (M^+, 19), 335 (18), 287 (100), 259 (21), 241 (7), 185 (3), 169 (2) 115 (2), 105 (1), 77 (5).

5-Amino-3-ethoxycarbonyl-2-methyl-4-*p*-methylphenyl-6,7,8,9-tetrahydro-4*H*-pyran[2,3-b]quinoline (2b).
Following the **General Method** compound **1b** (500 mg, 1.68 mmol) [$AlCl_3$ (245 mg, 1.84 mmol), $ClCH_2CH_2Cl$ (17 mL), cyclohexanone (181 mg, 0.19 mL, 1.84 mmol)] afforded product **2b** (389 mg, 61%): mp 199-201 °C; IR (KBr) υ 3450, 3370, 3250, 2940, 1695, 1645, 1605, 1575, 1455, 1300, 1210, 1065 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.20 and 7.07 (two d, *J*= 7.2 Hz, 2 H, 2 H, *p*-$CH_3C_6H_4$), 4.80 (s, 1 H, H4), 4.14 (q, *J*= 6.7 Hz, 2 H, $CO_2CH_2CH_3$), 4.11 (s, 2 H, NH_2), 2.74 (m, 2 H, H9), 2.45 (s, 3 H, CH_3), 2.28 (m, 5 H, 2 H6, $CH_3C_6H_4$), 1.80 (m, 4 H, H7, H8), 1.27 (t, 3 H, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.9 ($CO_2CH_2CH_3$), 159.6 (C10a), 154.2 (C9a), 153.8 (C5), 150.2 (C2), 140.9, 136.6, 129.3, 128.3 (*p*-$CH_3C_6H_4$), 113.5 (C5a), 106.7 (C3), 99.4 (C4a), 60.2 ($CO_2CH_2CH_3$), 38.1 (C4), 32.4 (C9), 22.8, 22.5, 22.3 (C6, C7, C8), 21.0 (*p*-$CH_3C_6H_4$), 19.6 (CH_3), 14.2 ($CO_2CH_2CH_3$); MS (70 eV) m/z 378 (M^+, 24), 349 (25), 305 (9), 287 (100), 241 (7), 185 (3), 145 (2), 91 (3), 65 (5).

5-Amino-4-*p*-chlorophenyl-3-ethoxycarbonyl-2-methyl-6,7,8,9-tetrahydro-4*H*-pyran[2,3-b]quinoline (2c).

Following the **General Method** compound **1c** (500 mg, 1.57 mmol) [$AlCl_3$ (230 mg, 1.73 mmol), $ClCH_2CH_2Cl$ (16 mL), cyclohexanone (169 mg, 0.18 mL, 1.73 mmol)] afforded product **2c** (421 mg, 67% yield): mp 223-6 °C; IR (KBr) υ 3450, 3370, 3260, 2950, 1695, 1650, 1610, 1580, 1500, 1460, 1390, 1380, 1310, 1215, 1070 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.32 (m, 4 H, *p*-ClC_6H_4), 4.87 (s, 1 H, H4), 4.22-4.08 (m, 4 H, $CO_2CH_2CH_3$, NH_2), 2.78 (m, 2 H, H9), 2.49 (s, 3 H, CH_3), 2.40-2.27 (m, 2 H, H6), 1.83 (m, 4 H, H7, H8), 1.30 (t, *J*= 6.7 Hz, 3 H, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.6 ($CO_2CH_2CH_3$), 160.0 (C10a), 154.1 (C9a, C5), 150.0 (C2), 142.3, 132.7, 129.3, 128.3 (ClC_6H_4), 113.6 (C5a), 106.2 (C3), 99.0 (C4a), 60.3 ($CO_2CH_2CH_3$), 37.8 (C4), 32.4 (C9), 22.8, 22.4, 22.2 (C6, C7, C8), 19.7 (CH_3), 14.1 ($CO_2CH_2CH_3$); MS (70 eV) m/z 398 (M^+, 19), 369 (24), 318 (18), 287 (100), 259 (20), 207 (42), 179 (14), 153 (9), 91(3), 101 (7).

5-Amino-4-*p*-cyanophenyl-3-ethoxycarbonyl-2-methyl-6,7,8,9-tetrahydro-4*H*-pyran[2,3-b]quinoline (2d).

Following the **General Method** compound **1d** (250 mg, 0.81 mmol) [$AlCl_3$ (118 mg, 0.89 mmol), $ClCH_2CH_2Cl$ (9 mL), cyclohexanone (87 mg, 0.09 mL, 0.89 mmol)] afforded product **2d** (201 mg, 64% yield): mp 235-8 °C; IR (KBr) υ 3440, 3380, 3250, 2950, 2250, 1695, 1645, 1610, 1580, 1460, 1380, 1305, 1215, 1060 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.50 and 7.37 (two d, *J*= 7.8 Hz, 2 H, 2 H, *p*-CNC_6H_4), 4.86 (s, 1 H, H4), 4.11-4.02 (m, 4 H, $CO_2CH_2CH_3$, NH_2), 2.70 (m, 2 H, H9), 2.42 (s, 3 H, CH_3), 2.40-2.17 (m, 2 H, H6), 1.80 (m, 4 H, H7, H8), 1.21 (t, *J*= 6.7 Hz, 3 H, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.4 ($CO_2CH_2CH_3$), 160.9 (C10a), 154.5 (C9a), 154.1 (C5), 149.9 (C2), 149.1, 132.0, 129.1, 110.8 (*p*-CNC_6H_4), 118.5 (CN), 113.7 (C5a), 105.6 (C3), 99.3 (C4a), 60.5 ($CO_2CH_2CH_3$), 38.5 (C4), 32.4 (C9), 22.8, 22.3, 22.1 (C6, C7, C8), 19.8 (CH_3), 14.1 ($CO_2CH_2CH_3$); MS (70 eV) m/z 389 (M^+, 20), 360 (25), 287 (100), 259 (19), 241 (7), 116 (1), 145 (2), 67 (3).

5-Amino-3-ethoxycarbonyl-4-*p*-methoxyphenyl-2-methyl-6,7,8,9-tetrahydro-4*H*-pyran[2,3-b]quinoline (2e).

Following the **General Method** compound **1e** (500 mg, 1.59 mmol) [$AlCl_3$ (233 mg, 1.75 mmol), $ClCH_2CH_2Cl$ (16 mL), cyclohexanone (172 mg, 0.18 mL, 1.75 mmol)] afforded product **2e** (396 mg, 63%): mp 176-9 °C; IR (KBr) υ 3450, 3380, 3240, 2940, 1690, 1645, 1610, 1575, 1510, 1450, 1380, 1375, 1300, 1210, 1060 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.17 and 6.74 (two d, *J*= 8.2 Hz, 2 H, 2 H, *p*-$CH_3OC_6H_4$), 4.75 (s, 1 H, H4), 4.09-4.02 (m, 4 H, $CO_2CH_2CH_3$, NH_2), 3.70 (s, 3 H, *p*-$CH_3OC_6H_4$), 2.70 (m, 2 H, H9), 2.40 (s, 3 H, CH_3), 2.37-2.17 (m, 2 H, H6), 1.75 (m, 4 H, H7, H8), 1.22 (t, *J*= 6.7 Hz, 3 H, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.9 ($CO_2CH_2CH_3$), 159.3 (C10a), 154.1 (C9a), 153.7 (C5), 150.2 (C2), 158.4, 135.9, 129.4, 113.8 (*p*-$OCH_3C_6H_4$), 113.5 (C5a), 106.7 (C3), 99.7 (C4a), 60.2 ($CO_2CH_2CH_3$), 55.1 (*p*-$CH_3OC_6H_4$), 37.5 (C4), 32.3 (C9), 22.7, 22.4, 22.2 (C6, C7, C8), 19.6 (CH_3), 14.1 ($CO_2CH_2CH_3$); MS (70 eV) m/z 394 (M^+, 35), 365 (44), 321 (20), 287 (100), 259 (23), 185 (3), 77 (5).

5-Amino-3-ethoxycarbonyl-2-methyl-4-*m*-nitrophenyl-6,7,8,9-tetrahydro-4*H*-pyran[2,3-b]quinoline (2f).

Following the **General Method** compound **1f** (500 mg, 1.52 mmol) [$AlCl_3$ (222 mg, 1.67 mmol), $ClCH_2CH_2Cl$ (16 mL), cyclohexanone (164 mg, 0.17 mL, 1.67 mmol)] afforded product **2f** (380 mg,

62% yield): mp 202-4 °C; IR (KBr) υ 3440, 3360, 3240, 2940, 1690, 1645, 1610, 1575, 1530, 1460, 1380, 1355, 1300, 1210, 1070 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.18 (s, 1H), 8.08 (d, *J*= 5.5 Hz, 1 H), 7.58 (d, *J*= 5.5 Hz, 1 H), 7.41 (t, *J*= 5.5 Hz, 1 H), (*m*-$NO_2C_6H_4$), 4.94 (s, 1 H, H4), 4.13 (q, *J*= 6.7 Hz, 2 H, $CO_2CH_2CH_3$), 4.01 (s, 2 H, NH_2), 2.78 (m, 2 H, H9), 2.46 (s, 3 H, CH_3), 2.40-2.17 (m, 2 H, H6), 1.78 (m, 4 H, H7, H8), 1.25 (t, 3 H, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.3 ($CO_2CH_2CH_3$), 161.2 (C10a), 154.6 (C9a), 154.1 (C5), 149.8 (C2), 148.0, 145.9, 134.5, 129.6, 123.1, 122.1 (*m*-$NO_2C_6H_4$), 113.8 (C5a), 105.6 (C3), 98.2 (C4a), 60.6 ($CO_2CH_2CH_3$), 38.1 (C4), 32.4 (C9), 22.8, 22.4, 22.2 (C6, C7, C8), 19.8 (CH_3), 14.1 ($CO_2CH_2CH_3$); MS (70 eV) m/z 409 (M^+, 11), 392 (40), 287 (100), 259 (27), 241 (10), 185 (4), 77 (3).

12. Pascual, C.; Martín, N.; Seoane, C. *Mag. Res. Chem.* **1985**, *23*, 793.
13. Levy, G. C.; Nelson, G. L. *Carbon-13 Nuclear Magnetic Resonance for Organic Chemists*, Wiley & Sons, **1972**, p 113.
14. **5-Amino-7,8-dihydro-3-ethoxycarbonyl-2-methyl-6*H*-cyclopenta[e]4*H*-pyrano[2,3-b]pyridine (3).** Following the **General Method** compound **1a** (600 mg, 2.22 mmol) [$AlCl_3$ (325 mg, 2.44 mmol), $ClCH_2CH_2Cl$ (22 mL), cyclopentanone (239 mg, 0.25 mL, 2.44 mmol)] afforded product **3** (405 mg, 52%) that was isolated by flash chromatography (hexane/ethyl acetate, 7:3): mp 205-6 °C; IR (KBr) υ 3440, 3360, 3240, 2980, 1690, 1645, 1610, 1580, 1480, 1460, 1445, 1430, 1375, 1340, 1220, 1080 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.22-7.18 (m, 5 H,C_6H_5), 4.78 (s, 1 H, H4), 4.15-4.00 (q, *J*= 6.7 Hz, 2 H, $CO_2CH_2CH_3$), 3.94 (s, 2 H, NH_2), 2.90-2.70 (m, 2 H, H8), 2.80-2.60 (m, 2 H, H6), 2.38 (s, 3 H, CH_3), 2.00 (m, 2 H, H7), 1.18 (t, 3 H, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.8 ($CO_2CH_2CH_3$), 162.0 (C9a), 159.7 (C8a), 156.3 (C5), 148.3 (C2), 143.9, 128.3, 128.2, 127.0 (C_6H_5), 118.1 (C5a), 106.5 (C3), 99.8 (C4a), 60.2 ($CO_2CH_2CH_3$), 38.4 (C4), 34.1 (C8), 26.9 (C6), 22.2 (C7), 19.5 (CH_3), 14.1 ($CO_2CH_2CH_3$); MS (70 eV) m/z 350 (M^+, 17), 321 (18), 273 (100), 245 (25), 227 (9), 77 (7).
15. Dr. Baños (Dpto. de Fisiología, Facultad de Medicina, Universidad Autónoma de Barcelona, Bellaterra, Spain), to be published elsewhere.

(*Received in Belgium* 25 *September* 1997; *accepted* 10 *November* 1997)