PYRAZOLOQUINAZOLINES FROM 2-AMINOBENZOYLHYDRAZINE†

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Abstract - Brief treatment of 2-aminobenzoylhydrazine (2) with diethyl acetonedicarboxylate in ethanol gave 3-(benzoylhydrazono)-pentanedioic acid diethyl ester (3). However, with extended reaction times the product of this condensation was 3-amino-3,4-dihydro-4-oxo-2,2(1H)-quinazolinediacetate (5). In the latter transformation, diethyl 1,3,4,5-tetrahydro-5-oxo-2H-1,3,4-benzotriazepine-2,2-diacetate (6) is an obligatory intermediate. Cyclization of 5 with sodium carbonate in ethanol gave ethyl 2,3,4,9-tetrahydro-2,9-dioxopyrazolo[5,1-b]quinazoline-3a(1H)-acetate (8), and methylation of 8 afforded its 1-methyl derivative (9).

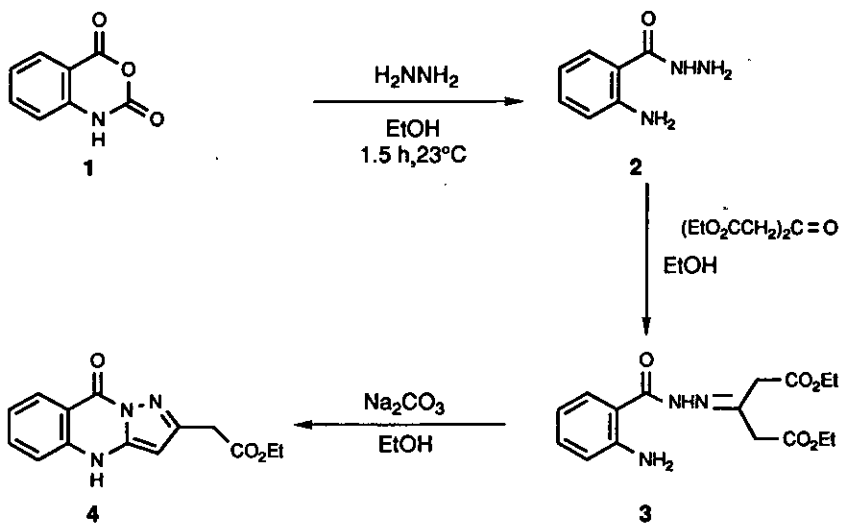
Our interest in linear, pyrazolo-fused tricyclic heterocyclic systems[1,2] prompted us to explore reactions of 2-aminobenzoylhydrazine (2) with diethyl acetonedicarboxylate. These building blocks contain all of the functionality necessary for accessing pyrazolo[5,1-b]quinazolines.

Using a procedure analogous to that reported in the patent literature by Wolfrum et al.,[3,4] 2-aminobenzoylhydrazine (2), which was prepared from isatoic anhydride (1) as described by Leiby,[5] was briefly treated with diethyl acetonedicarboxylate at room temperature to provide hydrazone (3)as shown in Scheme I. Extensive nmr studies with (3) confirmed its structure and ruled out structures of potential isomeric products

†This paper is dedicated to Professor Ted Taylor on the occasion of his 70th birthday.

(vide infra). For instance, the ^1H nmr ($CDCl_3$) spectrum of 3 showed a broad, 1-proton signal for the amide NH at δ 10.70 and a broad 2-proton signal for the NH_2 group at δ 5.65. Using nuclear Overhauser enhancement (NOE) difference spectroscopy, irradiation of the latter signal led to a large enhancement of the signal for the aromatic proton ortho to the amino group, which was consistent with structure (3). In addition, the ^{13}C nmr ($CDCl_3$) spectrum of 3 was also consistent with its structure, showing an sp^2 imine carbon signal at δ 145.20.

Scheme I

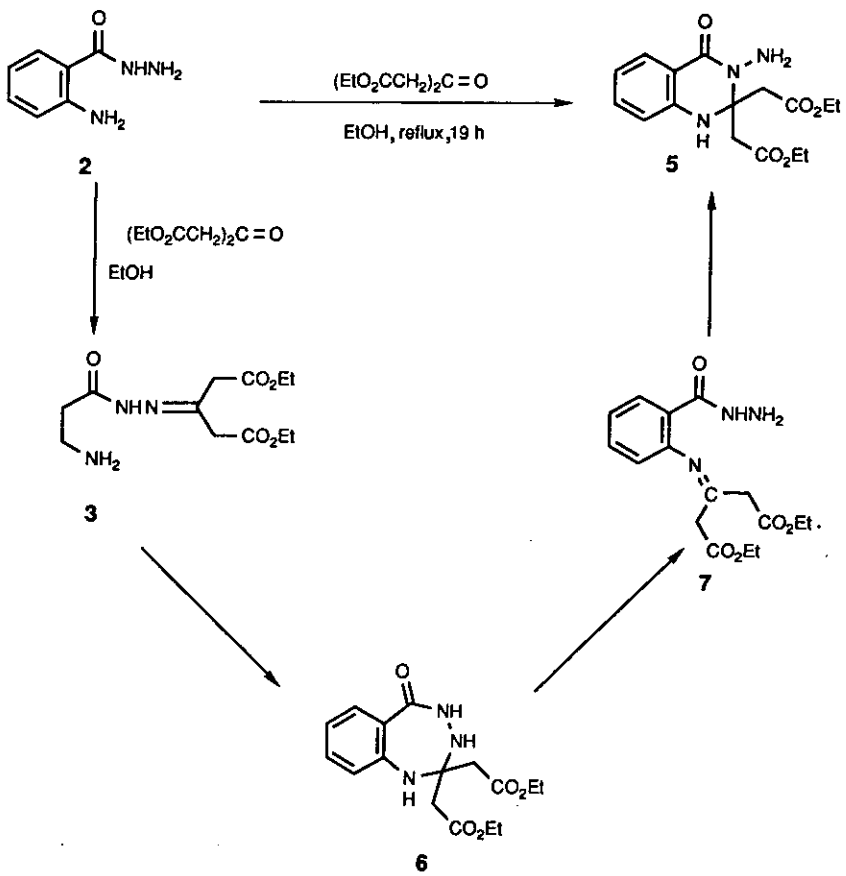


Cyclization of 3 with sodium carbonate in ethanol gave ethyl 4,9-dihydro-9-oxopyrazolo-[5,1-b]quinazoline-2-acetate (4). NOE difference spectroscopy showed a large enhancement of the protons at positions 3 and 5 when the proton on nitrogen was irradiated. Thus, the structure in solution is consistent with 4, rather than the tautomer with a proton at position one.

When 2-aminobenzoylhydrazine (2) was treated with diethyl acetonedicarboxylate for 19 h at reflux, a product different from 3 was produced. All spectral data for the new material were consistent with diethyl 3-amino-3,4-dihydro-4-oxo-2,2(1H)-quinazolinedi-acetate (5). A key piece of structural information followed from the ^{13}C nmr ($CDCl_3$) spectrum, which showed the absence of the sp^2 carbon resonance close to δ 145.20 as observed for the imine carbon of 3, and the presence of a quaternary carbon resonance at

δ 76.46, which was consistent with the expected field position for the carbon at position 2 of 5. The presence of a 1-proton NH signal at δ 5.54 in the ^{1}H nmr ($CDCl_3$) spectrum and a 2-proton NH signal at δ 4.46 support structure (5) in preference to benzotriazepinone (6), which was another potential product. Subsequent reactions performed on this material also support assignment (5) (vide *infra*).[6]

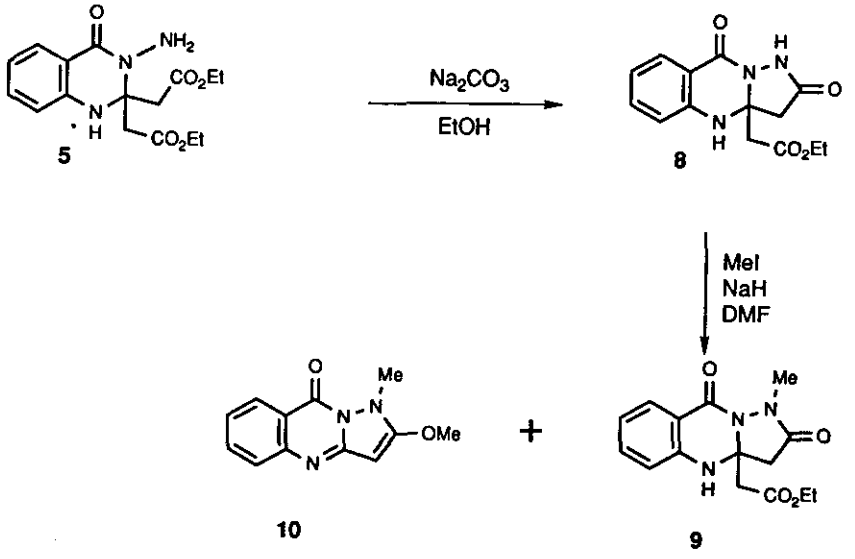
Scheme II



The formation of quinazoline (5) during the long reaction time is mechanistically interesting and suggests that quinazolinone (5) is thermodynamically more stable than acylhydrazone (3), which is presumably the first intermediate in the rearrangement process. Benzotriazepinone (6) is an obligatory intermediate in this process (Scheme II), as is Schiff base (7). Cyclization of 7 by attack of the acylated hydrazide nitrogen on the imine is the final step which produces (5) in the rearrangement process.

When quinazolinone (5) was exposed to the same conditions which produced pyrazoloquinazolinone (4) from 3, e.g. sodium carbonate in ethanol, the new tricyclic compound (8) was produced by condensation of the unsubstituted hydrazide amino group with one of the ester groups (Scheme III). The ^{1}H nmr (DMSO-d_6) spectrum of 8 displayed two NH signals at δ 11.87 and δ 7.47. Diagnostic for the quaternary carbon C-3a in 8 was the signal at δ 74.71 in the ^{13}C nmr (DMSO-d_6) spectrum. Treatment of 8 with sodium hydride in dimethylformamide followed by methyl iodide gave two products which were separated by flash chromatography. N-Methylation appeared to occur exclusively at the 1-position. The position of methylation in 9 was confirmed with a NOESY experiment, in which an NOE correlation was observed between the NH signal and the C5-H signal. Interestingly, the aromatic tricyclic structure (10) which was co-produced arose from methylation on both nitrogen and oxygen, and base-induced elimination of ethyl acetate.

Scheme III



5 8 10 9

Thus, 2-aminobenzoylhydrazine (2) and diethyl acetonedicarboxylate condensed to give the simple acylhydrazone (3) with short reaction times. However, with extended reaction times, quinazolinone (5) was produced. Subsequent transformations of 5 gave the new pyrazoloquinolinones (8) and (9)[9,10] which bear angular carboethoxymethyl groups.

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Nmr spectra were recorded with Varian Gemini 300 and Varian VXR-300 spectrometers; mass spectra were collected at 70 eV with a Finnigan TSQ46 mass spectrometer using electron impact and chemical ionization techniques and high resolution mass spectral (HRms) data were collected at 70 eV with a VG ZAB2-SE spectrometer, using computerized peak matching with perfluorokerosene as the reference and a resolution of 10,000; chemical shifts for nmr signals are reported in ppm from tetramethylsilane. NOE difference spectra were obtained using standard steady-state difference experiments. For some compounds additional one- and two-dimensional nmr spectra were obtained to aid in spectral assignments. Analytical thin layer chromatography was performed using Merck silica gel 60F-254 glass-backed plates of 0.25 mm thickness. Flash chromatography was performed using Merck silica gel, 230-400 mesh. A Model 7924T Chromatotron from Harrison Research was used for radial chromatography. Combustion analyses for C, H and N were performed by Marion Merrell Dow Analytical Laboratories.

2-Aminobenzoylhydrazine (2). A suspension of 32.6 g (0.200 mol) of isatoic anhydride (1) in 100 ml of 95% ethanol was treated, by slow addition, with 15.0 ml (47.3 mmol) of anhydrous hydrazine. Gas evolution was vigorous. Midway through the addition gas evolution ceased and the mixture turned to paste. The mixture was cooled in an ice bath and the solid was collected, dried and recrystallized from toluene (600 ml) to give 17.5 g (59%) of 2 as white, fluffy needles, mp 117-118° (lit.,[5] mp 122-123°).

3-[2-Aminobenzoylhydrazono]pentanedioc Acid Diethyl Ester (3). To an ice-cold slurry of 6.04 g (40.0 mmol) of 2 and 35 ml of ethanol was added a solution of 8.09 g (40.0 mmol) of diethyl acetonedicarboxylate in 15 ml of ethanol. The ice bath was removed and the mixture was stirred for 1.5 h, during which time the character of the solid had changed and the mixture became thick. The solid was collected, washed with ethanol and air-dried

to give 7.41 g (55%) of 3. Recrystallization of a portion from ethanol-water gave 3 as fine white needles, mp 113.5-114°; ^{1}H nmr ($CDCl_3$): δ 10.70 (br s, 1H, NH), 7.50 (dd, 1H, J=7.9 Hz, 1.3 Hz, aromatic C6-H), 7.21 (ddd, 1H, J=8.2 Hz, 7.2 Hz, 1.5 Hz, aromatic C4-H), 6.69 - 6.61 (m, 2H, aromatic C3-H and C5-H), 5.65 (br s, 2H, NH_2), 4.21 (q, 2H, J=7.2 Hz, OCH_2), 4.13 (q, J=7.2 Hz, 2H, OCH_2), 3.53 (s, 2H, CH_2CO), 3.49 (s, 2H, CH_2CO), 1.26 (t, J=7.2 Hz, 3H, CH_3), 1.23 (t, J=7.2 Hz, 3H, CH_3); ^{13}C nmr ($CDCl_3$): δ 169.41 (ester C=O), 168.93 (ester C=O), 166.38 (hydrazide C=O), 149.86 (aromatic C2), 145.20 (C=N), 133.04 (aromatic C4), 127.26 (aromatic C6), 117.37 (aromatic C3), 116.50 (aromatic C5), 113.40 (aromatic C1), 62.47 (OCH_2), 61.27 (OCH_2), 43.93 ($\underline{C}H_2CO$), 38.13 ($\underline{C}H_2CO$), 14.09 (CH_3), 13.99 (CH_3); ms: (chemical ionization, methane) m/z 336 (M^+ + 1), 364 (M^+ + 29), 376 (M^+ + 41). Anal. Calcd for $C_{16}H_{21}N_3O_5$: C, 57.30; H, 6.31; N, 12.53. Found: C, 57.48; H, 6.40; N, 12.37.

Ethyl 1,9-Dihydro-9-oxopyrazolo[5,1-b]quinazoline-2-acetate (4). To a slurry of 6.65 g (19.8 mmol) of 3 and 100 ml of ethanol was added 5.00 g (47.2 mmol) of sodium carbonate and the mixture was stirred at room temperature for 2 h. Tlc of an aliquot diluted with ethanol to effect solution showed only the presence of hydrazone (3). The mixture was heated to reflux for 35 min, after which time tlc showed the absence of 3 and the presence of a higher R_f spot. The mixture was cooled and concentrated and the residue was partitioned between methylene chloride and water. The organic layer was concentrated and the residue was triturated with ether to give 0.66 g (12%) of 4. The low yield of 4 is presumably due to hydrolysis to the free acid corresponding to 4 which partitioned into the aqueous phase. Recrystallization of 4 from ethanol gave 0.38 g of 4 as pale violet needles, mp 247-249°; ^{1}H nmr (DMSO-d_6): δ 12.23 (br s, 1H, NH), 8.19 (dd, J=8.1 Hz, 1.4 Hz, 1H, C8-H), 7.76 (ddd, J=8.4 Hz, 7.0 Hz, 1.5 Hz, 1H, C6-H), 7.39 (d, J=8.3 Hz, 1H, C5-H), 7.26 (ddd, J=8.1 Hz, 7.0 Hz, 1.0 Hz, 1H, C7-H), 6.04 (s, 1H, C3-H), 4.13 (q, J=7.1 Hz, 2H, OCH_2), 3.80 (s, 2H, CH_2CO), 1.22 (t, J=7.1 Hz, 3H, CH_3); ^{13}C nmr (DMSO-d_6): δ 169.63 (ester C=O), 155.38 (C9), 151.38 (C2), 142.59 (C3a), 139.61 (C4a), 134.70 (C6), 127.56 (C8), 121.35 (C7), 115.91 (C5), 111.44 (C8a), 87.08 (C3), 60.52 (OCH_2), 34.62 ($\underline{C}H_2CO$), 14.06 (CH_3); ms: (chemical ionization, methane) m/z 272 (M^+ + 1), 300 (M^+ + 29), 312 (M^+ + 41). Anal. Calcd for $C_{14}H_{13}N_3O_3$: C, 61.98; H, 4.83; N, 15.49. Found: C, 62.26; H, 4.77; N, 15.46.

Diethyl 3-Amino-3,4-dihydro-4-oxo-2,2(1H)-quinazolinediacetate (5). A solution of 3.02 g

(20.0 mmol) of 2 and 4.04 g (20.0 mmol) of diethyl acetonedicarboxylate in 40 ml of anhydrous ethanol was heated at reflux for 19 h. The cherry red solution was concentrated to dryness to give a red-orange oil. Trituration with hexane-ether gave 5.55 g (82%) of crude 5 as an orange solid. Purification by flash chromatography on silica gel (600 ml dry volume), eluting with 2:1::hexane:ethyl acetate (4 l) and 1:1::hexane:ethyl acetate (21) gave 4.21 g (63%) of 5 as white needles, mp 84-86°; ^{1}H nmr ($CDCl_3$): δ 7.84 (dd, J=7.8 Hz, 1.2 Hz, 1H, C5-H), 7.29 (tm, J=7.5 Hz, 1H, C7-H), 6.83 (tm, J=7.6 Hz, 1H, C6-H), 6.65 (dm, J=8.2 Hz, 1H, C8-H), 5.54 (s, 1H, NH), 4.46 (s, 2H, NH_2), 4.10 (q, J=7.2 Hz, 4H, both OCH_2), 3.06 (s, 4H, both CH_2CO), 1.22 (t, J=7.2 Hz, 6H, both CH_3); ^{13}C nmr ($CDCl_3$): δ 170.09 (CO_2), 163.38 (C4), 144.03 (C8a), 133.96 (C7), 128.04 (C5), 119.13 (C6), 114.65 (C8), 113.48 (C4a), 76.46 (C2), 61.03 (OCH_2), 41.18 ($\underline{C}H_2CO$), 13.99 (CH_3); ms: (electron impact) m/z 335 (molecular ion). Anal. Calcd for $C_{16}H_{21}N_3O_5$: C, 57.30; H, 6.31; N, 12.53. Found: C, 57.58; H, 6.44; N, 12.27.

Ethyl 2,3,4,9-Tetrahydro-2,9-dioxopyrazolo[5,1-b]quinazoline-3a(1H)-acetate (8). A solution of 4.21 g (12.6 mmol) of quinazolinone 5 in 50 ml of ethanol was treated with 6.00 g (56.6 mmol) of sodium carbonate and the mixture was heated at reflux for ca. 20 h. The mixture was concentrated and treated with 50 ml of water. The insoluble white solid was collected to give 3.04 g (83%) of 8, mp 188-190° (ethanol); ^{1}H nmr (DMSO-d_6): δ 11.87 (br s, 1H, NH), 7.62 (dd, J=7.7 Hz, 1.4 Hz, 1H, C8-H), 7.47 (br s, 1H, NH), 7.32 (tm, J=7.7 Hz, 1H, C6-H), 6.85-6.77 (m, 2H, C5-H and C7-H), 3.97-3.80 (m, 2H, OCH_2), 3.16 (d, J=16.3 Hz, 1H, C3-H), 2.98 (d, J=16.3 Hz, 1H, C3-H), 2.75 (s, 2H, CH_2CO_2), 1.09 (t, J=7.1 Hz, 3H, CH_3); ^{13}C nmr (DMSO-d_6): δ 168.29 (ester C=O), 167.37 (C2), 153.00 (C9), 144.90 (C4a), 133.24 (C6), 126.86 (C8), 118.58 (C7), 115.11 (C5), 114.48 (C8a), 74.71 (C3a), 60.57 (OCH_2), 42.01 ($\underline{C}H_2CO_2$), 13.67 (CH_3); ms: (chemical ionization) m/z 290 ($M^+ + 1$), 318 ($M^+ + 29$), 330 ($M^+ + 41$). Anal. Calcd for $C_{14}H_{15}N_3O_4$: C, 58.12; H, 5.23; N, 14.53. Found: C, 57.97; H, 5.37; N, 14.66.

Ethyl 2,3,4,9-Tetrahydro-1-methyl-2,9-oxopyrazolo[5,1-b]quinazoline-3a(1H)-acetate (9) and 2-Methoxy-1-methylpyrazolo[5,1-b]quinazolin-9(1H)-one (10). To a mixture of 0.168 g (7.00 mmol) of sodium hydride and 10 ml of dimethylformamide cooled in an ice bath was added a slurry of 1.36 g (5.00 mmol) of 8 in 10 ml of dimethylformamide. Gas evolved and a clear, golden solution resulted. After 5 min of stirring, a solution of 1.00 g (7.00 mmol) of methyl iodide in 3 ml of dimethylformamide was added and the solution was

stirred in an ice bath and allowed to warm to room temperature over 5 h. The cloudy solution was concentrated by Kugelrohr distillation and the residue was partitioned between water (containing ca. 1 g of ammonium chloride) and methylene chloride. The organic layer was dried (sodium sulfate) and concentrated and applied (in methylene chloride. The organic layer was dried (sodium sulfate) and concentrated and applied (in methylene chloride) to a 500 g (dry volume) column of flash chromatography silica gel. Elution with 1:1::hexane:ethyl acetate (2 l) and 1:3::hexane:ethyl acetate (2 l) gave, as the first product to elute, 510 mg (34%) of **9**, mp 98-100°; ^{1}H nmr ($CDCl_3$): δ 7.79 (dd, J=7.8 Hz, 1.6 Hz, 1H, C8-H), 7.34 (ddd, J=8.1 Hz, 7.5 Hz, 1.6 Hz, 1H, C6-H), 6.93 (td, J=7.5 Hz, 1.0 Hz, 1H, C7-H), 6.71 (dm, J=8.1 Hz, 1H, C5-H), 5.68 (s, 1H, NH), 4.23-4.07 (m, 2H, OCH_2), 3.58 (s, 3H, NCH_3), 3.22 (br d, J=16.4 Hz, 1H, C3-H), 3.04 (dd, J=16.4 Hz, 1.6 Hz, 1H, $CHCO_2$), 2.90 (d, J=16.4 Hz, 1H, C3-H), 2.80 (d, J=16.4 Hz, 1H, $CHCO_2$), 1.25 (t, J=7.2 Hz, 3H, $OCH_2\underline{CH_3}$); ^{13}C nmr ($CDCl_3$): δ 169.61 (CO_2), 168.02 (C2), 157.79 (C9), 143.79 (C4a), 139.99 (C6), 127.87 (C8), 120.37 (C7), 115.62 (C8a), 114.90 (C5), 75.46 (C3a), 61.51 (OCH_2), 44.86 (C3), 40.78 ($\underline{CH_2}CO_2$), 34.93 (NCH_3), 13.93 ($OCH_2\underline{CH_3}$); ms: (chemical ionization) m/z 304 (M^+ + 1), 332 (M^+ + 29), 344 (M^+ + 41). *Anal.* Calcd for $C_{15}H_{17}N_3O_4$: C, 59.39; H, 5.65; N, 13.86. Found: C, 59.43; H, 5.72; N, 13.86.

Fractions containing the second component were combined to give 230 mg of white solid which contained a small amount of an impurity. Purification by radial chromatography (silica gel; 4 mm plate) was accomplished by elution with isopropanol:hexane (300 ml of 1:4; 200 ml of 3:7; 200 ml of 1:1; and 200 ml of 3:1) to give 220 mg (19%) of **10** as white, fluffy needles, mp 255-256°; ^{1}H nmr ($CDCl_3$): δ 8.49 (dd, J=8.0 Hz, 1.6 Hz, C8-H), 7.72 (ddd, J=8.4 Hz, 7.2 Hz, 1.6 Hz, 1H, C6-H), 7.31-7.24 (m, 2H, C5-H and C7-H), 5.44 (s, 1H, C3-H), 4.11 (s, 3H, OCH_3), 3.66 (s, 3H, NCH_3); ^{13}C nmr ($CDCl_3$): δ 167.27 (C9), 155.40 (C3a), 145.69 (C4a), 140.18 (C2), 134.61 (C6), 129.55 (C8), 122.00 (C7), 114.26 (C8a), 112.33 (C5), 75.52 (C3), 56.32 (OCH_3), 34.42 (NCH_3); ms: (chemical ionization) m/z 230 (M^+ + 1), 258 (M^+ + 29), 270 (M^+ + 41); ms: (electron impact) m/z 229 (molecular ion); HRms (chemical ionization) calcd for $C_{12}H_{11}N_3O_2$ (M^+ +1), 230.0930; found 230.0919.

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4. Wolfrum *et al.*[3] used dimethyl acetone dicarboxylate and thus produced compound **(3)** as the corresponding methyl ester.
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6. When benzoylhydrazine was employed instead of 2 using the conditions of Scheme II, followed by treatment with sodium carbonate, products of disproportionation were observed. Thus, 5.45 g (40.0 mmol) of benzoylhydrazine was treated with 8.09 g (40.0 mmol) of diethyl acetonedicarboxylate in ethanol at reflux for 21 h. A 3-g quantity of sodium carbonate was added and reflux was continued for 2 h. The mixture was filtered and the filtrate was concentrated and partitioned between water and methylene chloride. A 200-mg quantity of fluffy white solid, insoluble in both layers, was collected and shown to be 1,2-dibenzoylhydrazine, mp 236-237° (lit.,[7] mp 241°]; ^{1}H nmr (DMSO-d_6): δ 11.00 (s, 2H, NHNH), 8.65-8.30 (m, 4H, ortho aromatic protons), 8.30-7.85 (m, 6H, remaining aromatic). The organic phase and the extract from the acidified aqueous phase were flash-chromatographed on silica gel (600 ml dry volume) with chloroform:methanol (1 l of 9:1, 1.5 l of 85:15) to give 4.15 g of a mobile oil followed by 890 mg of ethyl 1,2-dihydro-5-oxo-1H-pyrazole-3-acetate, mp 114-117° (lit.,[8] mp 116-118°); ^{1}H nmr ($CDCl_3$ and DMSO-d_6): δ 9.90 (s, 1H, NH, D_2O-exchangeable), 5.50 (s, 1H, OH, D_2O-exchangeable), 4.14 (q, J=7 Hz, 2H, OCH_2), 3.60 (s, 2H, CH_2CO_2), 1.30 (t, J=7 Hz, 3H, CH_3); ms: (chemical ionization, methane) m/z 171 (M^+ + 1), 199 (M^+ + 29), 211 (M^+ + 41).
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9. Attempted hydrolysis of **9** with ethanolic sodium hydroxide at room temperature consumed **9** but did not produce the corresponding carboxylic acid.
10. Compound **(9)** was readily resolved into its component enantiomers on a Chiralcel OD analytical hplc column. Elution was effected with 4:1::hexane:isopropanol; the isopropanol contained 1% diethylamine.

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