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Article

Reaction of Acyclic Enaminones with Methoxymethylene Meldrum's Acid. Synthetic and Structural Implications[#]

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A reação de enaminonas com o derivado metoximetilênico do ácido de Meldrum forneceu *N*-adutos e/ou *C*-adutos das enaminonas, em rendimentos moderados a bons. A regioquímica da reação se revelou dependente do substituinte do nitrogênio da enaminona, e o *C*-aduto formado é precursor para 2-piridonas. A análise da difração de raios X de dois *N*-adutos revelou que estes adutos possuem a configuração *Z-s-Z*.

The reaction of acyclic enaminones with methoxymethylene Meldrum's acid afforded *N*-adduct and/or *C*-adduct of enaminones in moderate to good yields. The regiochemistry of this reaction depends on the *N*-amino substituent of the enaminone. The *C*-adduct is a precursor to 2-pyridones. X-ray analysis of two *N*-adducts were investigated and the *Z-s-Z* configuration assigned.

Keywords: enaminones, Meldrum's acid, aza-annulation, 2-pyridone

Introduction

The fascinating chemistry of enaminones and their derivatives has attracted the attention of numerous researchers due to their ambiphilic and ambident properties and their potential in the synthesis of heterocyclic compounds.[1] In this context, the aza-annulation reaction of cyclic and acyclic enaminones has been extensively used in the preparation of a broad spectrum of nitrogen-containing compounds,[2] mainly in alkaloids[3] and conformationally constrained peptide analogues.[4] Because of these applications several protocols for the synthesis of enaminones have been developed.[5] Among them, the solid support method developed by Braibante and co-workers[6] and its systematic use in the synthesis of pyrazoles and isoxazoles derivatives is noteworthy.[7]

While the reaction of methoxymethylene Meldrum's acid (**1**) with cyclic enaminones has been documented (Scheme 1, reactions 1-4),[8] much less study has been carried out with **1** and acyclic enaminones. There is only a single paper describing two examples of reaction of **1** with enaminones **11** and **13a** (Scheme 1, reactions 5-6).[8] However, the aza-annulation of derivatives **12** and **14a** under pyrolysis conditions (Scheme 1, reaction 7) is not synthetically efficient because mixture of products and poor yields are obtained. In search for a general method of synthesis of derivatives **12** to **14** we undertook a study concerning the reactions of acyclic enaminones and methoxymethylene Meldrum's acid (**1**). In this paper we report the results of this study with emphasis on synthetic, mechanistic and structural implications.

Results and Discussion

Enaminones may act as an ambident nucleophile by reaction at the nitrogen and at the β-carbon. The reactions of enaminones and methoxymethylene Meldrum's acid depend on the *N*-amino substituent, Scheme 1. *C*-Adducts are obtained with NR_2 substituent (R = alkyl) and *N*-adducts with the NH_2 group. However, when we attempted the reaction of enaminone **13a** with **1** under the literature condition[8] a low yield of the *N*-adduct **14a** was obtained (36%, instead of the reportedly obtained 60% yield). Additionally, a small quantity of the *C*-adduct **18a** was isolated (3.2% yield, Scheme 2), which was not previously reported. The spectral data of compound **14a** here obtained were identical with those described.[8] The ^{1}H NMR spectra contained a low field N-H (13.93 ppm) which suggests its participation in intramolecular hydrogen bonding. Despite

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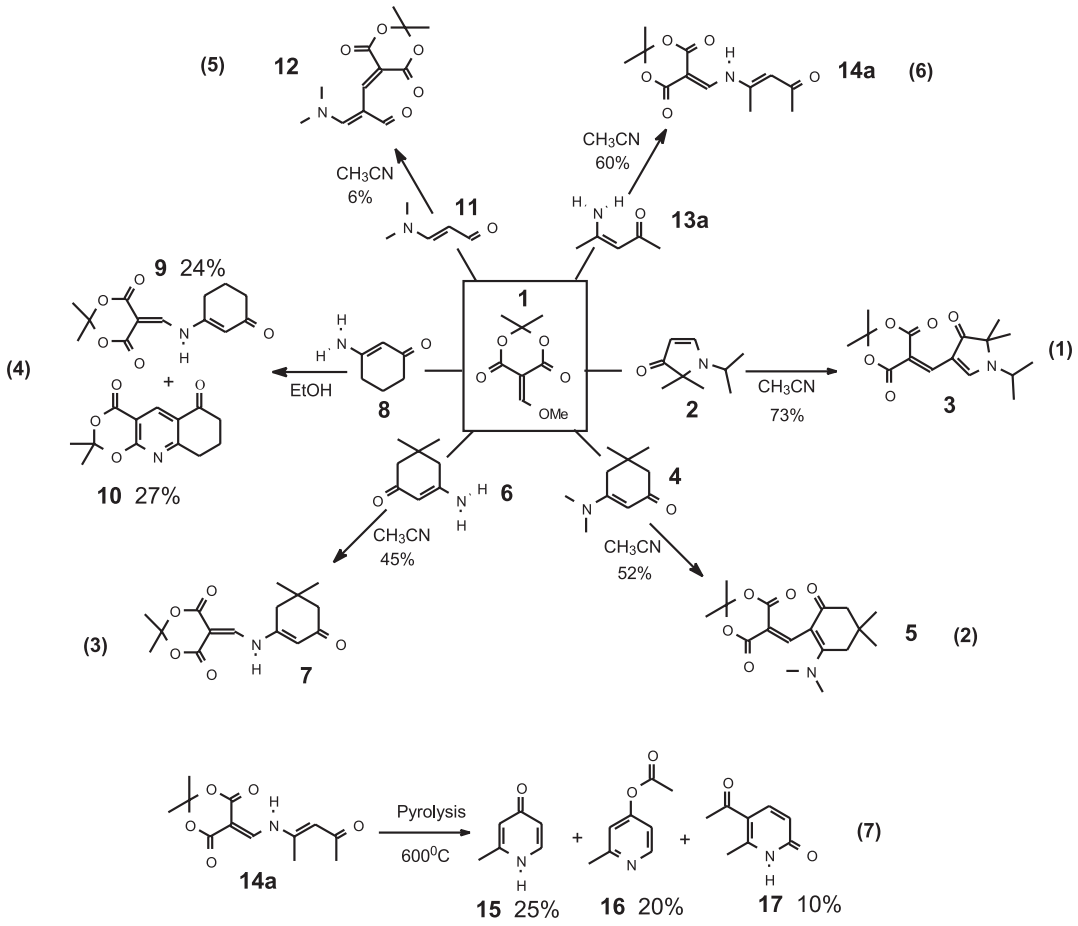
[#] Dedicated to Professor Albert James Kascheres, a great mentor and pioneer in ciclopropenone chemistry in Brazil, on the occasion of his 60th birthday.



Scheme 1.

the reportedly *E-s-E* configuration to **14a** we assigned the *Z-s-Z* configuration to the *N*-adduct because *E-s-E* and *Z-s-Z* configurational isomers of enaminones are well distinguished by typical N-H chemical shifts (*E*-isomer: 4.1-6.5 ppm; *Z*-isomer: 9.5-12.0 ppm).[9] Moreover, the structure of **14a** was unambiguously confirmed by X-ray analysis and the *Z* configuration corroborated, as shown in Figure 1.

In addition, extension of the reported protocol[8] to other enaminones afforded complex mixtures. Better results were obtained when CH_2Cl_2 was used as solvent instead of CH_3CN (Scheme 2). With this modification *N*- and *C*-adducts **14a-b** and **18a-b** were obtained in a 2:1 ratio, respectively. With enaminone **13c** only the *C*-adduct **18c** was formed in good yield.

To our surprise, when we attempted the reaction of **1** with enaminone **13d** a complex mixture was obtained, and the 2-pyridone **19d** could be isolated in 28% yield (Scheme 3, reaction. 1). Unfortunately, the pyridone **19d** was an unstable solid that precluded its complete spectral characterization. However, its structure could be assigned by comparison of its IR and ^{1}H NMR spectra with analogue **19c** (see Experimental). The formation of **19d** may be visualized as occurring through the aza-annulation of the initial *C*-adduct of the reaction of **1** and **13d**. To support this mechanistic proposal we decided to perform the thermolysis of the isolated *C*-adduct **18c**. In this way, **18c** was refluxed in toluene and the 2-pyridone **19c** was obtained in good yield (Scheme 3, reaction 2). The structure of **19c** was corroborated by analysis of a long-range heterocorrelation (COLOC) spectrum which showed correlation (^3J) of the hydrogen at C-4 with the carbonyl C-2 and with C-6 as well as the other correlations indicated in Scheme 4, which also presents the mechanistic pathway to **19c**. Interestingly, in this thermal cyclization the typical CO_2 elimination from the methylene Meldrum's acid moiety was not observed.[10] It should also be pointed out that the relative low temperature required to form the 2-pyridones **19c-d** makes this methodology synthetically attractive, contrasting with the literature pyrolysis condition for the *N*-adduct **14a**.[8]

Understanding how enaminones fit together in the solid

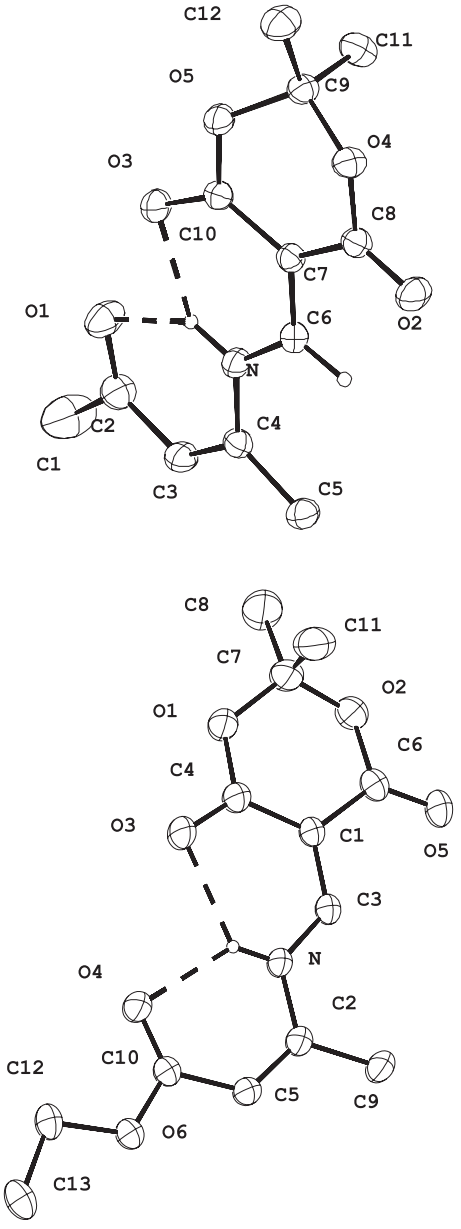
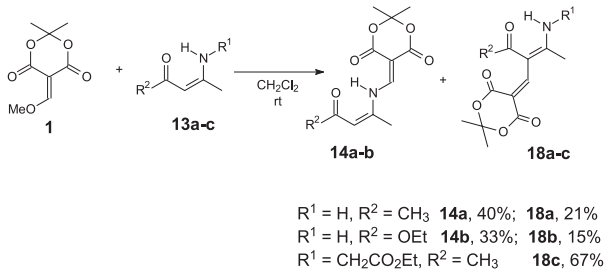
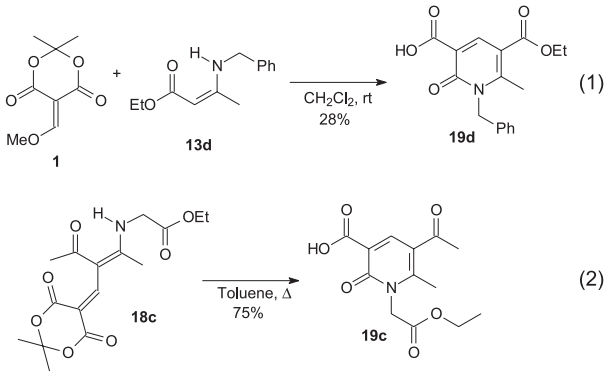


Figure 1. X-ray crystallographic structures of compounds **14a** (top) and **14b** (bottom). Displacement ellipsoids are shown at the 30% probability level. Only the H-atoms involved in H-bonds are shown with arbitrary size. The intramolecular H-bonds are shown with broken lines.

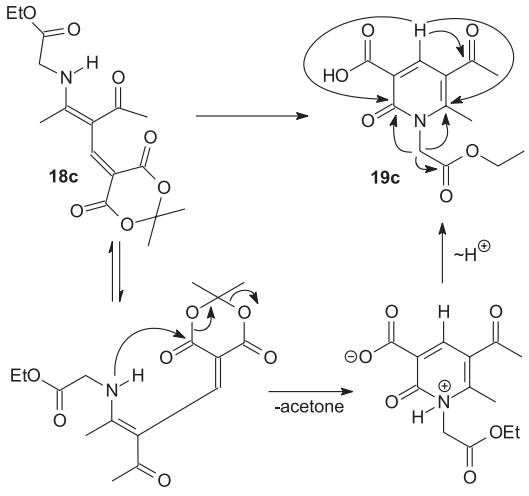


R^1 = H, R^2 = CH_3 **14a**, 40%; **18a**, 21%
R^1 = H, R^2 = OEt **14b**, 33%; **18b**, 15%
R^1 = CH_2CO_2Et, R^2 = CH_3 **18c**, 67%

Scheme 2.



Scheme 3.



Scheme 4.

state is of particular interest to recognize the relationships between structural features and pharmacological properties, e.g. the anticonvulsant activity of enaminones has been associated with the inter- and intramolecular NH...O, CH...O and CH...N hydrogen bonding in the three-dimensional structure.[11] To unambiguously assign the structure of the obtained enaminones and to gain insight into intra- and intermolecular interactions the crystal structures of **14a** and **14b** were determined, and several structural features emerged. As noted in Figure 1, which shows the molecules with labeled atoms, **14a** has one strong bifurcated intramolecular hydrogen bonding between the oxygen atoms O1 and O3 and the NH group: N-H1N...O1 [2.699(3) Å] and N-H1N...O3 [2.720(3) Å]) providing two quasi-planar pseudo six-membered rings. The major distance from the least-square plane including all the atoms of these pseudo-rings is 0.187(3) Å for atom O3. In addition, a weak C-H...O intermolecular H-bond was observed: C6-H6...O3^{i} [1/2-x,-1/2+y, z , 3.379(3)Å]. The Meldrum's acid moiety has an envelope conformation, as can be seen from

the Cremer and Pople[12] parameters: O4→C8→...C9 [Q=0.404(2) Å, $\theta = 61.0(3)^o$, $\phi = 299.0(4)^o$]. The C9 atom is 0.562(3) Å out of the plane defined by the other atoms of the ring. In a similar way, **14b** has a weak bifurcated intramolecular hydrogen bonding between the oxygen atoms O3 and O4 and the NH group: N-H2...O3 [2.763(2) Å] and N-H2...O4 [2.753(2) Å], also providing two quasi-planar pseudo six-membered rings. Here again, a weak C-H...O intermolecular H-bond was also noted: C13-H13B...O3' [1-x, y, 1-z, 3.416(3)Å].

In conclusion, the reactions of acyclic enaminones and methoxymethylene Meldrum's acid afford *N*- and/or *C*-adducts and 2-pyridones were formed from the latter through an intramolecular aza-annulation. The scope, limitations and the application of the methodology here described in natural products synthesis is under investigation in our lab and will be reported opportunely.

Experimental

Melting points were determined on a Karl Kolb apparatus and are uncorrected. Infrared spectra were recorded as KBr discs on a FT-IR BOMEM MB100 instrument. NMR spectra were obtained for ^{1}H at 300 MHz and for ^{13}C at 75 MHz using a Varian Gemini 300 or a Bruker AC300P spectrometers at Instituto de Química, UNICAMP. Chemical shifts are reported in ppm units downfield from reference (internal TMS). MS spectra were measured on a SHIMADSU CG-MS QP-5050 spectrometer at 70 eV. Elemental analyses were performed on a 2400 CHN Perkin Elmer instrument at Instituto de Química, UNICAMP. Enaminones **13a-b**,[6] **13c**,[13] **13d**,[6] Meldrum's acid[13] and methoxymethylene Meldrum's acid[13] were prepared according to known procedures. The single crystal X-ray data collections were carried out on a Nonius CAD-4 diffractometer at Departamento de Química, UFSC.

General synthetic procedure

A solution of 2 mmol of Meldrum's acid in 2 mL of trimethyl orthoformate was heated at reflux for 2 h after which time the solvent was evaporated. The solid that formed was dissolved in 5 mL of CH_2Cl_2 and 2 mmol of enaminone was added and the solution was allowed to stand at room temperature for 24 h. The solvent was evaporated and the crude residue was treated as indicated in each case.

2,2-dimethyl-5-[(Z)-1-methyl-3-oxo-1-butenylaminomethylene]-1,3-dioxane-4,6-dione (**14a**).Purified by silica gel column chromatography (benzene/ethyl acetate 20%), pale orange needles, mp 193-196 ºC. IR (KBr): ν_{max}/cm^{-1} 3079, 1736, 1690, 1664, 1600, 1580. ^{1}H NMR ($CDCl_3$): 1.74 (6H, s); 2.22 (3H, s); 2.26 (3H, s); 5.75 (1H, s); 8.35 (1H, d, *J* 14.3Hz); 13.93 (1H, br s). ^{13}C NMR ($CDCl_3$): 18.1 (CH_3); 27.3 (CH_3); 30.8 (CH_3); 90.8 (C); 105.0 (C); 109.7 (CH); 148.4 (C); 150.8 (CH); 162.8 (C); 163.7 (C); 199.0 (C). MS, m/z (%): 253 [M$^+$, 41%], 195 (100%), 149 (99%); 136 (56%), 108 (37%). Anal. Calcd. for $C_{12}H_{15}NO_5$: C, 56.90%; H, 5.95%; N, 5.55%. Found: C, 56.97%; H, 6.01%; N, 5.54%.

5-[(Z)-2-acetyl-3-amino-2-butenylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**18a**). Purified by silica gel column chromatography (benzene/ethyl acetate 50%), pale yellow needles, mp 158-161 ºC. IR (KBr): ν_{max}/cm^{-1} 3420, 3200, 1728, 1690, 1631. ^{1}H NMR ($CDCl_3$): 1.75 (6H, s); 2.24 (3H, s); 2.39 (3H, s); 7.97 (1H, br s); 8.64 (1H, s); 10.60 (1H, br s). ^{13}C NMR ($CDCl_3$): 21.5 (CH_3); 27.4 (CH_3); 28.5 (CH_3); 99.7 (C); 103.5 (C); 110.9 (C); 155.1 (CH); 163.0 (C); 164.6 (C); 172.4 (C); 199.4 (C). MS, m/z (%): 253 [M$^+$, 70%], 195 (48%), 151 (97%), 149 (37%), 136 (57%), 123 (84%), 108 (100%), 95 (65%), 80 (75%). Anal. Calcd. for $C_{12}H_{15}NO_5$: C, 56.90%; H, 5.95%; N, 5.55%. Found: C, 56.97%; H, 6.01%; N, 5.54%.

Ethyl (Z)-3-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidenmethylamino)-2-butenoate (**14b**). Purified by silica gel column chromatography (benzene/ethyl acetate 20%), colorless solid, mp 193-194 ºC. IR (KBr): ν_{max}/cm^{-1} 3136, 1741, 1698, 1651, 1603cm^{-1}. ^{1}H NMR ($CDCl_3$): 1.31 (3H, t, *J* 7.1Hz); 1.74 (6H, s); 2.22 (3H,s); 4.31 (2H, q, *J* 7.1Hz); 5.37 (1H, s); 8.32 (1H, d, *J* 14.3Hz); 13.39 (1H, br s). ^{13}C NMR ($CDCl_3$): 14.2 (CH_3); 18.1 (CH_3); 27.1 (CH_3); 60.7 (CH_2); 90.1 (C); 103.0 (CH); 105.1 (C); 148.8 (C); 150.5 (CH); 163.5 (C); 163.9 (C); 167.1 (C). MS, *m/z* (%): 283 [M$^+$, 22%], 259 (22%), 225 (71%), 196 (100%). Anal. Calcd. for $C_{13}H_{17}NO_6$: C, 55.12%; H, 6.01%; N, 4.95%. Found: C, 54.83%; H, 5.96%; N, 4.32%.

Ethyl (Z)-3-amino-2-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidenmethyl)-2-butenoate (**18b**). Purified by silica gel column chromatography (benzene/ethyl acetate 30%), yellow needles, mp 172-174 ºC. IR (KBr): ν_{max}/cm^{-1} 3317, 3109, 1725, 1668. ^{1}H NMR ($CDCl_3$): 1.23 (3H, t, *J* 7.1Hz); 1.66 (6H, s); 2.38 (3H, s); 4.17 (2H, q, *J* 7.1Hz); 7.04 (1H, br s); 8.40 (1H, s); 9.38 (1H, br s). ^{13}C NMR ($CDCl_3$): 14.4 (CH_3); 21.0 (CH_3); 27.4 (CH_3); 60.7 (CH_2); 101.6 (C); 101.7 (C); 103.8 (C); 153.5 (CH); 163.3 (C); 165.5 (C); 169.2 (C); 170.8 (C). MS, *m/z* (%): 283 [M$^+$, 48%], 225 (36%), 181 (100%), 153 (91%), 136 (31%), 124 (57%). Anal. Calcd. for $C_{13}H_{17}NO_6$: C, 55.12%; H, 6.01%; N, 4.95%. Found: C, 55.23%; H, 6.07%; N, 4.72%.

Ethyl 2-[(Z)-2-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidenmethyl)-1-methyl-3-oxo-1-butenylamino]acetate (**18c**). Recrystallized from CH_2Cl_2/petroleum ether, yellow

solid, mp 139-142 ºC. IR (KBr): ν_{max}/cm^{-1} 3224, 1736, 1690, 1647. ^{1}H NMR ($CDCl_3$): 1.34 (3H, t, *J* 7.1Hz); 1.74 (6H, s); 2.22 (3H, s); 2.42 (3H, s); 4.26 (2H, d, *J* 5.1Hz); 4.32 (2H, q, *J* 7.1Hz); 8.72 (1H, s); 12.64 (1H, br s). ^{13}C NMR ($CDCl_3$): 14.1 (CH_3); 18.6 (CH_3); 27.4 (CH_3); 27.7 (CH_3); 46.1 (CH_2); 62.7 (CH_2); 99.3 (C); 103.3 (C); 111.2 (C); 154.9 (CH); 162.3 (C); 164.5 (C); 166.6 (C); 173.5 (C); 197.5 (C). MS, *m/z* (%): 339 [M$^+$, 34%], 281 (62%), 237 (56%), 135 (100%). Anal. Calcd. for $C_{16}H_{21}NO_7$ C, 56.64%; H, 6.19%; N, 4.13%. Found: C, 56.47%; H, 6.09%; N, 4.04%.

5-acetyl-1-ethyloxycarbonylmethyl-6-methyl-2-oxo-1,2-dihydro-3-pyridinecarboxylic acid (**19c**). A solution of 85.1 mg (0.25 mmol) of **18c** in 10 mL of toluene was heated at reflux for 24 h, after which time the solvent was evaporated and the residue was recrystallized from CH_2Cl_2/petroleum ether to give 52.9 mg (75% yield) of **19c** as colorless needles, mp 121-123 ºC. ^{1}H NMR ($CDCl_3$): 1.34 (3H, t, *J* 7.1Hz), 2.62 (3H, s), 2.74 (3H, s), 4.31 (2H, q, *J* 7.1Hz), 5.03 (2H, s), 8.90 (1H, s), 13.42 (1H, l). ^{13}C NMR ($CDCl_3$): 14.1 (CH_3), 18.4 (CH_3), 29.6 (CH_3), 46.4 (CH_2), 62.8 (CH_2), 113.9 (C), 119.7 (C), 145.3 (CH), 157.3 (C), 163.9 (C), 164.3 (C), 166.1 (C), 196.4 (C). MS, *m/z* (%): 281 [M$^+$, 43%], 207 (100%). Anal. Calcd. for $C_{13}H_{15}NO_6$ C, 55.52%; H, 5.34%; N, 4.98%. Found: C, 55.44%; H, 5.19%; N, 5.14%.

1-benzyl-5-ethyloxycarbonyl-6-methyl-2-oxo-1,2-dihydro-3-pyridinecarboxylic acid (**19d**). Recrystallized from CH_2Cl_2/petroleum ether, colorless solid, mp 135-137 ºC. IR (KBr): ν_{max}/cm^{-1} 1735, 1720, 1670, 1620. ^{1}H NMR ($CDCl_3$): 1.38 (3H, t, *J* 7.2Hz), 2.86 (3H, s), 4.35 (2H, q, *J* 7.2Hz), 5.55 (2H, s), 7.11-7.15 (2H, m), 7.32-7.42 (3H, m), 9.07 (1H, s), 13.95 (1H, br s).

Crystal structure of **14a**. $C_{12}H_{15}NO_5$, M_w = 253.25, orthorhombic, space group Pbca [nr. 61], Z = 8, a = 14.321(3), b = 9.261(2), c = 19.064(4) Å, V = 2528.4(9) Å,^{3} d_c = 1.331 Mg m^{-3}, λ (Mo Kα) = 0.71073 Å, μ = 0.104 mm^{-1}, 2835 measured reflections, 2473 unique (R_{int} = 0.0) of which 1579 were considered as observed with $I \geq 2\sigma(I)$. The single crystals were obtained by diffusion of petroleum ether into a solution of **14a** in CH_2Cl_2 at room temperature.

Crystal structure of **14b**. $C_{13}H_{17}NO_6$, M_w = 283.28, monoclinic, space group C2/m [nr. 12], Z = 4, a = 18.015(4), b = 6.600(1), c = 12.056(2) Å, V = 1430.7(5) Å,^{3} d_c = 1.315 Mg m^{-3}, λ (Mo Kα) = 0.71073 Å, μ = 0.105 mm^{-1}, 3066 measured reflections, 1535 unique (R_{int} = 0.016) of which 1225 were considered as observed with $I \geq 2\sigma(I)$. The molecule is placed on the mirror symmetry plane, except the atoms O1, O2, C8 and C11, that are disordered. The single crystals were obtained by diffusion of petroleum ether into a solution of **14b** in CH_2Cl_2 at room temperature. The structures were solved with direct methods using SHELXS97[14] and refined anisotropically with full-matrix least-squares on F^2 using SHELXL97.[15] The hydrogen atoms were placed at calculated position except those involved in H-bonds, found on difference maps and refined. Final indices: $R_1(F_o)$ = 0.043, wR_2 (F^2) = 0.131 for 172 refined parameters and $R_1(F_o)$ = 0.048, wR_2 (F^2) = 0.128 for 145 refined parameters, for **14a** and **14b**, respectively.

The crystallographic data (excluding structure factors) for structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 179109 and CCDC 179108, for **14a** and **14b**, respectively. Copies of the data can be obtained, free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, CCDC, 12 Union Road, Cambridge, CB21EZ, UK (fax +44 1223 336033) or e-mail: deposit@ccdc.camac.uk.)

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