# Ring Enlargement Reactions of Tetramic Acid Derivatives



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The 4-hydroxypyridones **7** and 3-hydroxypyridones **8/9** (azagrevellins) were prepared by reaction of the pyrrolidinetrione **4** and diazoalkanes. The ring enlargement proceeded by anionotropic [1,2]-rearrangement introducing carbon between C-3 and C-4 or, to a lesser extent, between C-2 and C-3 due to the different migration aptitudes of the two acyl groups involved. In a cognate manner ring expansion between C-2 and C-3 occured by the interaction of diazomethane and the pyrrolidinetrione hydrazone **15**, to give the spiroepoxide **16** as the final product. From the reaction of trione **4** and diazomethane, however, the diepoxide **14** was obtained. In this case ring homologation must have taken place by insertion of carbon between C-4 and C-5. In a two step ring expansion the pyridones **21** and **22** were obtained from the maleineimides **17**.

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## Introduction.

The tetramic acid (2,4-pyrrolidinedione) ring system has been known since the beginning of the twentieth century [1]. It was not until the 1960s that it was realized that the heterocyclic system is a key structural unit in many natural products sequestered from microorganisms as well marine organisms [2,3]. Many of the tetramic acids display a spectrum of biological activity remarkable in its diversity [3].

## Chemistry.

As part of our investigations on γ-alkylidene tetramic acids [4,5] we have already described [6] the ring enlargement of certain tetramic acid derivatives **1** into pyridones **2** or **3** as compiled in Scheme 1.

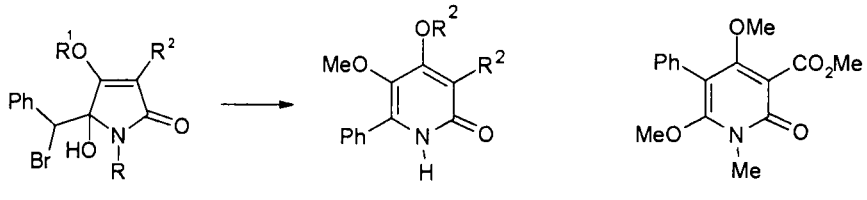
Now we observed other types of ring enlargement in the course of the reaction of pyrrolidinetrione **4** [6c] with selected diazo compounds (Scheme 2). Using phenyldiazomethane or 4-chlorophenyldiazomethane the dihydropyridones **7a** or **7b** were isolated but only in low yields. The major products in these reactions were the enolethers **8a** or **8b** respectively. Acid catalysed ether hydrolysis of these compounds led to the dihydropyridones **9a** and **9b**, structural isomers of **7a** and **7b**. Similarly the reaction of trione **4** with ethyl diazoacetate afforded the enol ether **8c** but this time as the sole product. Without purification, **8c** was easily hydrolyzed to the enol **9c**.

Compounds **9a** and **9b** bear a structural resemblance to the grevellins **13** [7-9], a family of pigments found in certain fungi, in a way that the new compounds may be called azagrevellins. As for the structural differentiation of the azagrevellins **9a/b** from their isomers **7a/b** it may be important to note that all the compounds **9** showed an intensive red color with maximum absorption at 500 nm when dissolved in concentrated sulfuric acid. This behavior is reminiscent of the color reaction described as characteristic for the grevellins in the same solvent [7f].

More significant in the structural differentiation of the isomers was the comparison of the $^{13}C$ nmr spectra of **7a** and **9a**. One of the two spectra showed three signals downfield of 145 ppm which might be attributed to C-2, C-5 and C-6 of either structure. But the other spectrum displayed four signals in the same region. This spectrum was assigned to the 4-hydroxypyridinedione **7a** on the assumption that the signal of the donor substituted C-4 in pyridone **7a** was to be found at lower field than the signal of the donor substituted C-3 in the azagrevellin **9a**.

Final structural proof produced the X-ray diffraction analysis of compound **12** (Figure 1), a derivative of the azagrevellin **9b**. This compound gave suitable crystals and was obtained by first *N*-methylation of enolether **8b** followed by acid catalyzed ether hydrolysis to enol **11** and *O*-methylation.

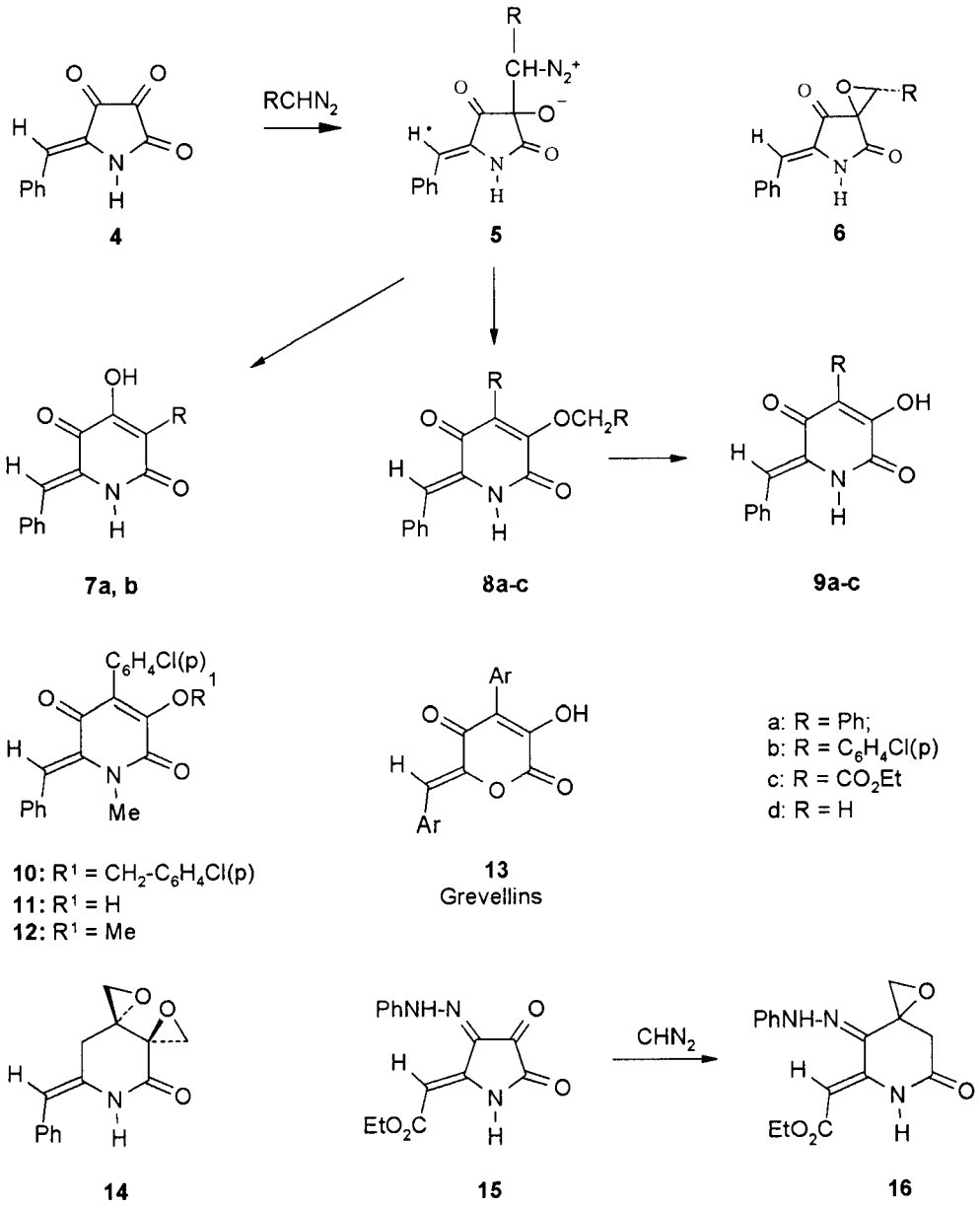
Scheme 1




**1** **2** **3**

R, $R^1$ = H, Me; $R^2$ = H, $CO_2Me$

Scheme 2




The zwitterion **5** is thought to be an intermediate in the ring enlargement reactions of trione **4**. After loss of nitrogen, it may turn into an epoxide **6** and/or undergo ring enlargement by an anionotropic [1,2]-shift of one of the two adjacent acyl groups. In fact, an epoxide has not yet been isolated and in the rearrangement reaction the two competing acyl groups showed similar migration aptitudes. As it turned out, the product of a C-4 shift was slightly favored as opposed to the product of the C-2 migration.

Homologation reactions of cyclic 1,2,3-tricarbonyl systems by means of diazoalkanes have been described already. Examples are the transformation of indanetrione into 2-hydroxynaphthoquinone [10] and the reactions of different diazoalkanes with 1,2,3,4-tetrahydro-2,3,4-quinolinetriones [11]. In the latter case, it was observed that the reaction with diazomethane led to the formation of an epoxide only, whereas the reaction with less reactive substituted diazomethanes proceeded to ring enlarged lactams. It is noteworthy that in these cases apparently only one of the two possible homologation products were obtained.

We assumed that the trione **4** would react with diazomethane in a cognate manner. However, this reaction took a different path since we isolated the piperidine **14**. The structure could be deduced from the $^1$H nmr spectrum. The neighborhood of the benzylidene and the methylene group

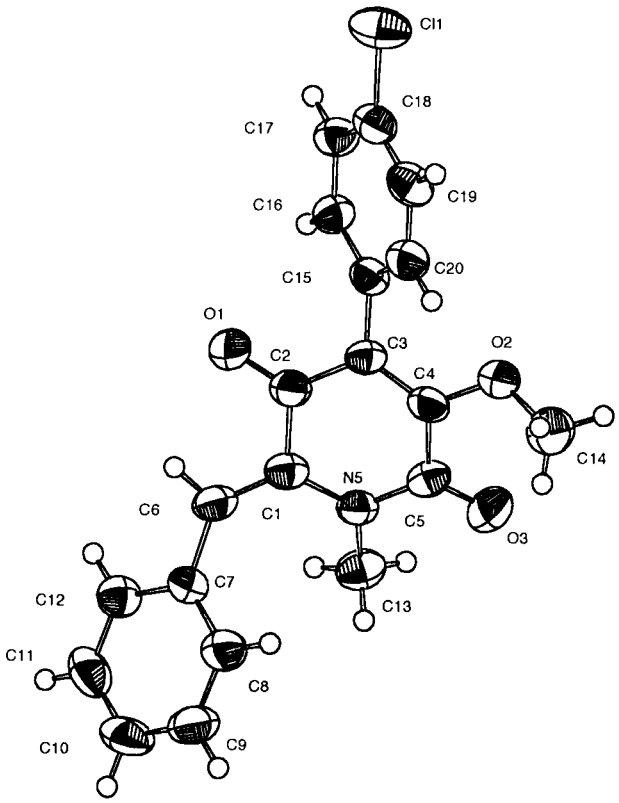



Figure 1. ORTEP plot of azagrevellin **12**.

Table 1a

Single Crystal X-Ray Crystallographic Analysis of **12**

| | |
|---|---|
| A. Crystal Parameters | |
| Formula | $C_{20}H_{16}ClNO_3$ (353.79) |
| Temperature | 293(2) K |
| Wavelength | 0.71073 Å |
| Space group | Pbca |
| Unit cell dimensions | a = 8.704(2) Å |
| | b = 18.638(4) Å |
| | c = 20.822(4) Å |
| Volume | 3377.8(11) Å$^3$ |
| Z | 8 |
| Density calcd., Mg/m$^3$ | 1.391 |
| Absorption coefficient, mm$^{-1}$ | 0.245 |
| F(000) | 1472 |
| Theta range for data collection | 2.19 to 21.66° |
| Index ranges | 0≤h≤9, 0≤k≤19, 0≤l≤21 |
| B. Refinement Parameters | |
| Reflections collected | 1976 |
| Independent reflections | 1975 [R(int) = 0.0344] |
| non-zero reflections [I>2?(I)] | 1206 |
| Absorption correction | psi-scans |
| Max. and min. transmission | 0.9994 and 0.9559 |
| Refinement method | Full-matrix least-squares on F$^2$ |
| Data / restraints / parameters | 1975 / 0 / 228 |
| Goodness-of-fit on F$^2$ | 1.104 |
| Final R indices [I>2?(I)] | R1 = 0.0618, wR2 = 0.1176 |
| R indices (all data) | R1 = 0.1097, wR2 = 0.1411 |
| Largest diff. peak and hole | 0.168 and -0.166 e.Å$^{-3}$ |
| Used program | SHELXL-93 |

Table 1b

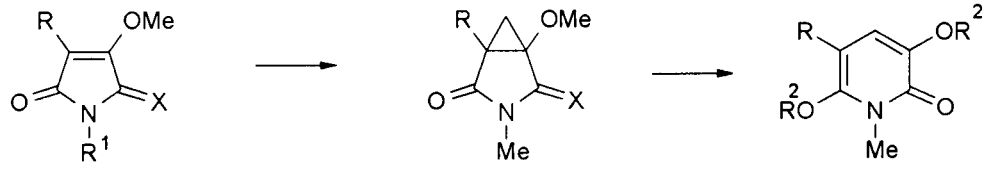
Bond Lengths (Å) and Bond Angles (°) for **12**

| | | | |
|---|---|---|---|
| Cl(1)-C(18) | 1.748(5) | C(6)-C(1)-C(2) | 116.4(5) |
| O(1)-C(2) | 1.235(6) | N(5)-C(1)-C(2) | 117.4(5) |
| O(2)-C(4) | 1.345(6) | O(1)-C(2)-C(3) | 121.2(5) |
| O(2)-C(14) | 1.434(6) | O(1)-C(2)-C(1) | 120.0(5) |
| O(3)-C(5) | 1.220(6) | C(3)-C(2)-C(1) | 118.7(5) |
| N(5)-C(5) | 1.368(6) | C(4)-C(3)-C(2) | 118.1(5) |
| N(5)-C(1) | 1.403(6) | C(4)-C(3)-C(15) | 122.9(5) |
| N(5)-C(13) | 1.471(6) | C(2)-C(3)-C(15) | 119.0(5) |
| C(1)-C(6) | 1.339(7) | C(3)-C(4)-O(2) | 120.5(5) |
| C(1)-C(2) | 1.502(7) | C(3)-C(4)-C(5) | 122.8(5) |
| C(2)-C(3) | 1.454(7) | O(2)-C(4)-C(5) | 115.5(5) |
| C(3)-C(4) | 1.338(7) | O(3)-C(5)-N(5) | 121.8(5) |
| C(3)-C(15) | 1.489(6) | O(3)-C(5)-C(4) | 120.9(5) |
| C(4)-C(5) | 1.501(7) | N(5)-C(5)-C(4) | 117.1(5) |
| C(6)-C(7) | 1.475(7) | C(1)-C(6)-C(7) | 132.3(5) |
| C(7)-C(8) | 1.382(7) | C(8)-C(7)-C(12) | 118.0(5) |
| C(7)-C(12) | 1.394(7) | C(8)-C(7)-C(6) | 122.9(5) |
| C(8)-C(9) | 1.374(7) | C(12)-C(7)-C(6) | 118.8(5) |
| C(9)-C(10) | 1.372(8) | C(9)-C(8)-C(7) | 121.8(6) |
| C(10)-C(11) | 1.379(8) | C(10)-C(9)-C(8) | 119.4(6) |
| C(11)-C(12) | 1.379(7) | C(9)-C(10)-C(11) | 120.2(6) |
| C(15)-C(16) | 1.385(6) | C(10)-C(11)-C(12) | 120.2(6) |
| C(15)-C(20) | 1.389(7) | C(11)-C(12)-C(7) | 120.4(5) |
| C(16)-C(17) | 1.393(6) | C(16)-C(15)-C(20) | 117.7(5) |
| C(17)-C(18) | 1.370(7) | C(16)-C(15)-C(3) | 120.0(5) |
| C(18)-C(19) | 1.372(7) | C(20)-C(15)-C(3) | 122.3(5) |
| C(19)-C(20) | 1.383(7) | C(15)-C(16)-C(17) | 121.8(5) |
| | | C(18)-C(17)-C(16) | 118.3(5) |
| C(4)-O(2)-C(14) | 120.8(4) | C(17)-C(18)-C(19) | 121.9(5) |
| C(5)-N(5)-C(1) | 122.4(4) | C(17)-C(18)-Cl(1) | 118.8(5) |
| C(5)-N(5)-C(13) | 115.2(4) | C(19)-C(18)-Cl(1) | 119.3(4) |
| C(1)-N(5)-C(13) | 121.3(4) | C(18)-C(19)-C(20) | 118.9(5) |
| C(6)-C(1)-N(5) | 126.2(5) | C(19)-C(20)-C(15) | 121.5(5) |

was established by allyl coupling and NOE difference spectra. The signal of one of the methylene protons was further split, thus forming a double triplet, by long range coupling with one of the epoxide's methylene protons at C-4. The latter proton, according to NOE experiments, is a neighbor to one of the second epoxide's methylene protons at C-3. The signal enhancement, however, was very weak in this case as to be expected for the 3,4-trans-diastereomer with a preferred diequatorial position of the oxygen substituents. This is an indication of the chemoselectivity of this rearrangement reaction.

The formation of **14** can be explained on the basis of the above mentioned facts as follows. The intermediate diazonium ion **5d** passed at least in part into spiro-epoxide **6d** which underwent a ring enlargement reaction with excessive diazomethane starting at the C-4 carbonyl group and causing the neighboring vinyl group to migrate. The spiro-piperidine-2,4-dione formed in this way served as precursor of the final product, the diepoxide **14**. The formation of epoxides from carbonyl compounds and diazomethane in excess is a long known reaction [12,13]. The yield of **14** was only poor. By-products and/or intermediates may be obtained in a more intensive study of this reaction at different temperatures and in the presence of Lewis acids [14].

Scheme 3



**17a, b:** $R^1$ = H
**18b:** $R^1$ = H
**19b:** $R^1$ = Me

**20a, b**

**21a, b:** $R^2$ = H
**22a, b:** $R^2$ = Me

**a:** R = $CO_2Me$
**b:** R = CN

**17,20, 21, 22:** X = O
**18, 19:** X = PhCH

The reaction of compound **15**, the monohydrazone of a trione similar to **4**, with diazomethane took a different course [15]. From a mixture of reaction products we isolated the piperidine **16**. In the $^1H$ nmr spectrum of **16** the protons of the methylene group are observed as doublets and could be identified unambigously by CH-COSY experiments. Presumably a diazonium salt analogous to zwitterion **5** was the first intermediate in this reaction. The zwitterion underwent ring expansion by insertion of carbon between C-2 and C-3 forming a piperidine-2,4-dione. The latter was finally transformed into epoxide **16** with excessive diazomethane.

Noteworthy in this context is the possibility to perform a ring enlargement with the push-pull substituted maleineimides **17** in a two step process (Scheme 3). With diazomethane in excess and prolonged reaction times the bicyclopropanes **20** were formed in good yields. Acids promoted their rearrangement into dihydroxypyridones **21**. As derivatives the enolethers **22** have been isolated in reasonable yields. The position of the methoxy substituents in

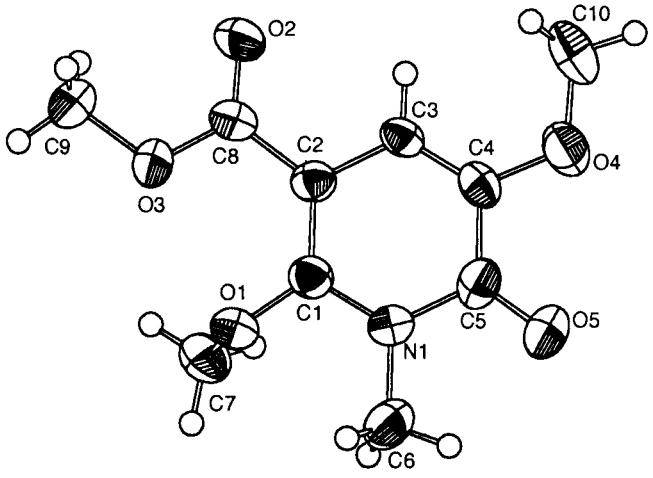



Figure 2. ORTEP plot of pyridone **22a**.

Table 2a

Single Crystal X-Ray Chrystallograhic Analysis of **22a**

| | |
|---|---|
| A. Crystal Parameters | |
| Formula | $C_{10}H_{13}NO_5$ (227.21) |
| Crystal size, mm | 0.53 x 0.33 x 0.27 |
| Temperature | 293(2) K |
| Wavelength | 0.71073 Å |
| Space group | $P2_1$ |
| Cell dimensions | a = 14.239(8) Å<br>b = 9.828(5) Å ? = 98.51(2)°<br>c = 7.7510(9) Å |
| Volume | 1072.8(8) $Å^3$ |
| Z | 4 |
| Density calcd., $Mg/m^3$ | 1.407 |
| Absorption coefficient, $mm^{-1}$ | 0.114 |
| F(000) | 480 |
| Theta range for data collection | 2.53 to 23.98° |
| Index ranges | -16≤h≤16, -11≤k≤11, -8≤l≤8 |
| B. Refinement Parameters | |
| Reflections collected | 3869 |
| Independent reflections | 3355 [R(int) = 0.0247] |
| non-zero reflections [I>2?(I)] | 2714 |
| Absorption correction | None |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 3355 / 1 / 297 |
| Goodness-of-fit on $F^2$ | 1.138 |
| Final R indices [I>2?(I)] | R1 = 0.0421, wR2 = 0.1174 |
| R indices (all data) | R1 = 0.0538, wR2 = 0.1473 |
| Largest diff. peak and hole | 0.181 and -0.187 $e.A^{-3}$ |
| Used program | SHELXL-93 |

compounds **22** could not be deduced unambiguously from spectroscopical data. But the question was answered by X-ray structure determination of a single crystal diffraction analysis of pyridone **22a** (Figure 2). In comparison to imide **17b**, the analoguously substituted arylidene tetramic acid derivative **18b** was less reactive against diazomethane. In a slow reaction and only in the presence of methanol the *N*-methylated tetramic acid derivative **19b** was formed.

Compounds of type **7** as well as azagrevellins **9**, **11** and **12** are interesting not only structurally but also with respect to their physiological actions, especially because of

Table 2b

Bond Lengths (Å) and Bond Angles (°) for **22a**

| | | | |
|---|---|---|---|
| O(1)-C(1) | 1.331(7) | O(1)-C(1)-C(2) | 125.4(5) |
| O(1)-C(7) | 1.455(6) | O(1)-C(1)-N(1) | 114.8(5) |
| O(2)-C(8) | 1.182(6) | C(2)-C(1)-N(1) | 119.6(5) |
| O(3)-C(8) | 1.318(7) | C(1)-C(2)-C(3) | 117.6(5) |
| O(3)-C(9) | 1.456(6) | C(1)-C(2)-C(8) | 125.8(5) |
| O(4)-C(4) | 1.360(8) | C(3)-C(2)-C(8) | 116.6(5) |
| O(4)-C(10) | 1.411(8) | C(4)-C(3)-C(2) | 122.6(5) |
| O(5)-C(5) | 1.225(6) | C(3)-C(4)-O(4) | 126.6(5) |
| N(1)-C(1) | 1.373(7) | C(3)-C(4)-C(5) | 121.2(5) |
| N(1)-C(5) | 1.415(7) | O(4)-C(4)-C(5) | 112.2(5) |
| N(1)-C(6) | 1.443(7) | O(5)-C(5)-N(1) | 119.2(5) |
| C(1)-C(2) | 1.383(7) | O(5)-C(5)-C(4) | 125.6(5) |
| C(2)-C(3) | 1.433(8) | N(1)-C(5)-C(4) | 115.3(5) |
| C(2)-C(8) | 1.465(8) | O(2)-C(8)-O(3) | 122.2(6) |
| C(3)-C(4) | 1.325(8) | O(2)-C(8)-C(2) | 122.9(6) |
| C(4)-C(5) | 1.431(7) | O(3)-C(8)-C(2) | 114.8(5) |
| O(1A)-C(1A) | 1.354(7) | C(1A)-O(1A)-C(7A) | 115.0(4) |
| O(1A)-C(7A) | 1.433(6) | C(8A)-O(3A)-C(9A) | 117.0(5) |
| O(2A)-C(8A) | 1.219(7) | C(4A)-O(4A)-C(10A) | 117.6(5) |
| O(3A)-C(8A) | 1.325(7) | C(1A)-N(1A)-C(5A) | 123.7(5) |
| O(3A)-C(9A) | 1.420(6) | C(1A)-N(1A)-C(6A) | 120.4(5) |
| O(4A)-C(4A) | 1.361(8) | C(5A)-N(1A)-C(6A) | 115.9(5) |
| O(4A)-C(10A) | 1.430(7) | C(2A)-C(1A)-O(1A) | 124.4(5) |
| O(5A)-C(5A) | 1.225(6) | C(2A)-C(1A)-N(1A) | 121.0(5) |
| N(1A)-C(1A) | 1.376(7) | O(1A)-C(1A)-N(1A) | 114.5(5) |
| N(1A)-C(5A) | 1.387(7) | C(1A)-C(2A)-C(3A) | 118.8(5) |
| N(1A)-C(6A) | 1.492(6) | C(1A)-C(2A)-C(8A) | 125.9(5) |
| C(1A)-C(2A) | 1.345(7) | C(3A)-C(2A)-C(8A) | 115.3(5) |
| C(2A)-C(3A) | 1.412(8) | C(4A)-C(3A)-C(2A) | 120.8(6) |
| C(2A)-C(8A) | 1.477(7) | O(4A)-C(4A)-C(3A) | 126.7(6) |
| C(3A)-C(4A) | 1.373(8) | O(4A)-C(4A)-C(5A) | 112.4(5) |
| C(4A)-C(5A) | 1.446(7) | C(3A)-C(4A)-C(5A) | 120.8(6) |
| | | O(5A)-C(5A)-N(1A) | 121.8(5) |
| C(1)-O(1)-C(7) | 113.8(4) | O(5A)-C(5A)-C(4A) | 123.3(5) |
| C(8)-O(3)-C(9) | 115.9(5) | N(1A)-C(5A)-C(4A) | 114.9(5) |
| C(4)-O(4)-C(10) | 116.0(5) | O(2A)-C(8A)-O(3A) | 121.9(6) |
| C(1)-N(1)-C(5) | 123.5(5) | O(2A)-C(8A)-C(2A) | 121.6(6) |
| C(1)-N(1)-C(6) | 120.4(5) | O(3A)-C(8A)-C(2A) | 116.4(5) |
| C(5)-N(1)-C(6) | 116.1(5) | | |

the ability of some of the new compounds to bind at the NMDA receptor. Work is in progress to prepare azagrevellin-type compounds with other substitution patterns for the purpose of biological testing.

## EXPERIMENTAL

Melting points were determined using a Gallenkamp Melting Point apparatus and are uncorrected. The $^1$H nmr spectra were recorded at 400 MHz using tetramethylsilane as internal standard on a JEOL GSX 400 Spectrometer. The solvent was hexadeuteriodimethylsulfoxide if not indicated otherwise. Mass spectra were obtained with a Hewlett Packard 5989A Mass Spectrometer. Infrared spectra were measured as potassium bromide plates using a FT-IR-Spectrometer PARAGON 1000 (Perkin Elmer). The uv analysis was performed in methanolic solution if not stated otherwise on Uvikon 810 Anakomp 220 (Kontron) and UV/VIS Spectrometer Lambda 20 (Perkin Elmer). Microanalyses were carried out applying an Analysator CHN-O-Rapid from Heraeus or were done by I. Beetz, Mikroanalytisches Laboratorium; Kronach, Germany.

(*Z*)-6-Benzylidene-4-hydroxy-3-phenyl-1,2,5,6-tetrahydropyridine-2,5-dione (**7a**).

A solution of excessive phenyldiazomethane [16] in hexane was added to a solution of 0.40 g (2 mmoles) of compound **4** [6c] in dioxane (50 ml). The yellow precipitate was collected after 30 minutes. The mother liquor contained compound **8a**. Yield 10%, yellow crystals, mp 210° (methanol); ir: ν 3316, 1650, 1554 cm$^{-1}$; uv: λ max (log ε) 375 nm (4.004); $^1$H nmr: δ 10.65 (s, 1 H), 9.89 (s, 1 H), 7.69 - 7.34 (m, 10 H), 7.01 (s, 1 H); $^{13}$C nmr: δ 176.3 (C-5), 161.8 (C-2), 153.9 (C-6), 149.7 (C-4), 119.4 (C-3), 117.3 (C-7); ms: m/z 291 [M$^+$].

*Anal.* Calcd. for $C_{18}H_{13}NO_3$ (291.31): C, 74.22; H, 4.49; N, 4.80. Found: C, 73.99; H, 4.64; N, 4.89.

(*Z*)-6-Benzylidene-4-hydroxy-3-(4-chlorophenyl)-1,2,5,6-tetrahydropyridine-2,5-dione (**7b**).

This compound was prepared analogously to **7a** from 0.4 g (2 mmoles) of compound **4** and 4-chlorophenyldiazomethane [16]. The mother liquor contained compound **8b**. Yield 10%, yellow crystals, mp 242° (methanol); ir: ν 3310, 1649, 1594, 1551 cm$^{-1}$; uv: λ max (log ε) 324 (3.952), 374 nm (3.922); $^1$H nmr: δ 9.94 (s, 1 H), 7.69 - 7.37 (m, 9 H), 7.00 (s, 1 H); ms: m/z 325 [M$^+$].

*Anal.* Calcd. for $C_{18}H_{12}ClNO_3$ (325.75): C, 66.37; H, 3.71; N, 4.30. Found: C, 66.54; H, 3.68; N, 4.23.

(*Z*)-6-Benzylidene-3-benzyloxy-4-phenyl-1,2,5,6-tetrahydropyridine-2,5-dione (**8a**).

This compound is a by-product in the preparation of compound **7a**. The mother liquor was freed from excess of phenyldiazomethane by addition of a few drops of acetic acid. Then the volatile components were removed *in vacuo* and the residue was crystallized from diisopropyl ether/ethanol 1:1. Yield 25%, yellow crystals, mp 196°; ir: ν 3060, 1670, 1655, 1587 cm$^{-1}$; uv: λ max (log ε) 341 (3.972), 392 nm (3.986); $^1$H nmr: δ 10.85 (s, 1 H), 7.62 - 7.21 (m, 15 H), 6.89 (s, 1 H), 5.33 (s, 2 H); ms: m/z 381 [M$^+$].

*Anal.* Calcd. for $C_{25}H_{19}NO_3$ (381.43): C, 78.72; H, 5.02; N, 3.67. Found: C, 78.48; H, 5.21; N, 3.71.

(*Z*)-6-Benzylidene-3-(4-chlorobenzyloxy)-4-(4-chlorophenyl)-1,2,5,6-tetrahydropyridine-2,5-dione (**8b**).

This compound is a by-product in the preparation of compound **7b** and was isolated from the mother liquor analogously to **8a**. Yield 30%, yellow crystals, mp 154° (diisopropyl ether/ethanol 1:1); ir: ν 3379, 1686, 1660, 1586 cm$^{-1}$; uv: λ max (log ε) 337 (3.985), 394 nm (3.991); $^1$H nmr: δ 10.65 (s, 1 H), 7.64 - 7.22 (m, 13 H), 6.90 (s, 1 H), 5.36 (s, 2 H); ms: m/z 450 [M$^+$].

*Anal.* Calcd. for $C_{25}H_{17}Cl_2NO_3$ (450.32): C, 66.68; H, 3.80; N, 3.11. Found: C, 66.87; H, 3.80; N, 2.91.

(*Z*)-6-Benzylidene-3-hydroxy-4-phenyl-1,2,5,6-tetrahydropyridine-2,5-dione (**9a**).

A solution of 0.38 g (1 mmole) of compound **8a** in trifluoroacetic acid (3 ml) was stirred for 10 minutes. Then the volatile components were removed *in vacuo* and the residue was recrystallized from diisopropyl ether/ethanol 1:1. Yield 75%, faintly yellow crystals, mp 217°; ir: ν 3285, 1675, 1652, 1630, 1588 cm$^{-1}$; uv: λ max (log ε) 242 (4.230), 340 nm (4.138); $^1$H nmr: δ 11.32 (s, 1 H), 10.68 (s, 1 H), 7.60 - 7.33 (m, 10 H), 6.95 (s, 1 H); $^{13}$C nmr: δ 178.7 (C-5), 157.2 (C-2), 154.9 (C-6), 133.9 (C-3), 121.0 (C-4), 117.3 (C-7); ms: m/z 291 [M$^+$].

*Anal.* Calcd. for $C_{18}H_{13}NO_3$ (291.31): C, 74.22; H, 4.49; N, 4.80. Found: C, 74.34; H, 4.57; N, 4.88.

(*Z*)-6-Benzylidene-3-hydroxy-4-(4-chlorophenyl)-1,2,5,6-tetrahydropyridine-2,5-dione (**9b**).

This compound was prepared analogously to **9a** from 0.45 g (1 mmole) of compound **8b**. Yield 80%, yellow crystals, mp 235° (diisopropyl ether/ethanol 1:1); ir: ν 3314, 1671, 1651, 1618, 1584 $cm^{-1}$; uv: λ max (log ε) 250 (4.229), 351 nm (4.177); $^1H$ nmr: δ 10.71 (s, 1 H), 7.55 - 7.28 (m, 9 H), 6.95 (s, 1 H); ms: m/z 325 [M+].

*Anal.* Calcd. for $C_{18}H_{12}ClNO_3$ (325.75): C, 66.37; H, 3.71; N, 4.30. Found: C, 66.18; H, 3.67; N, 4.09.

(*Z*)-Ethyl 6-Benzylidene-2,5-dioxo-3-hydroxy-1,2,5,6-tetrahydropyridine-4-carboxylate (**9c**).

A solution of 0.40 g (2 mmoles) of compound **4** in dioxane (10 ml) was heated in a sealed tube with 1.14 g (10 mmoles) of ethyl diazoacetate to 80° for one hour. The solvent was removed and the residue dissolved in trifluoroacetic acid (5 ml). After 30 minutes the solvent was evaporated and the residue crystallized from diisopropyl ether/ethanol 1:1. Yield 20%, light yellow crystals, mp 140°; ir: ν 3446, 1696, 1623, 1560 $cm^{-1}$; uv: λ max (log ε) 237 (4.039), 349 nm (4.154); $^1H$ nmr: δ 10.68 (s, 1 H), 7.57 - 7.36 (m, 5 H), 6.89 (s, 1 H), 4.22 (q, 2 H), 1.22 (t, 3 H); ms: m/z 287 [M+].

*Anal.* Calcd. for $C_{15}H_{13}NO_5$ (287.27): C, 62.71; H, 4.56; N, 4.87. Found: C, 62.77; H, 4.66; N, 4.76.

(*Z*)-6-Benzylidene-3-(4-chlorobenzyloxy)-4-(4-chlorophenyl)-1-methyl-1,2,5,6-tetrahydropyridine-2,5-dione (**10**).

To a stirred solution of 0.45 g (1 mmole) of compound **8b** in dimethylformamide (20 ml) were added 0.08g (2 mmoles) of sodium hydride (as 60% suspension in mineral oil). After 30 minutes at room temperature 0.28 g (2 mmoles) of methyl iodide were added and the mixture was again stirred for one hour. The reaction mixture was diluted with 100 ml of water and twice extracted with dichloromethane. The combined organic layers were dried over sodium sulfate. After removal of the solvent the residue was crystallized from diisopropyl ether/ethanol 1:1. Yield 55%, light yellow crystals, mp 129°; ir: ν 1648, 1587 $cm^{-1}$; uv: λ max (log ε) 220 (4.418), 332 nm (4.018); $^1H$ nmr: δ 7.48 - 7.29 (m, 13 H), 7.04 (s, 1 H), 5.36 (s, 2 H), 2.97 (s, 3 H); ms: m/z 464 [M+].

*Anal.* Calcd. for $C_{26}H_{19}Cl_2NO_3$ (464.35): C, 67.25; H, 4.12; N, 3.02. Found: C, 67.44; H, 4.21; N, 3.20.

(*Z*)-6-Benzylidene-4-(4-chlorophenyl)-3-hydroxy-1-methyl-1,2,5,6-tetrahydropyridine-2,5-dione (**11**).

This compound was prepared analogously to **9a** from 0.46 g (1 mmole) of compound **10**. Yield 70%, light yellow crystals, mp 184° (diisopropyl ether/ethanol 1:1); ir: ν 3297, 1657, 1637, 1586 $cm^{-1}$; uv: λ max (log ε) 245 (4.250), 330 nm (4.107); $^1H$ nmr: δ 8.03 (s, 1 H), 7.47 - 7.39 (m, 9 H), 7.13 (s, 1 H), 2.96 (s, 3 H); ms: m/z 339 [M+].

*Anal.* Calcd. for $C_{19}H_{14}ClNO_3$ (339.78): C, 67.16; H, 4.15; N, 4.12. Found: C, 66.93; H, 4.08; N, 3.98.

(*Z*)-6-Benzylidene-4-(4-chlorophenyl-3-methoxy)-1-methyl-1,2,5,6-tetrahydropyridine-2,5-dione (**12**).

Compound **11** (0.68 g, 2 mmoles) was treated with an excess of an etheral solution of diazomethane. After the evolution of nitrogen had ceased the solution was evaporated to dryness and the residue crystallized from diisopropyl ether/ethanol 1:1. Yield 75%, light yellow crystals, mp 133°; ir: ν 2938, 1659, 1607 $cm^{-1}$; uv: λ max (log ε) 240 (4.279), 333 nm (4.005); $^1H$ nmr: δ 8.29 (s, 1 H), 7.49 - 7.32 (m, 8 H), 7.04 (s, 1 H), 3.97 (s, 3 H), 2.95 (s, 3 H); ms: m/z 353 [M+].

*Anal.* Calcd. for $C_{20}H_{16}ClNO_3$ (353.80): C, 67.89; H, 4.56; N, 3.96. Found: C, 68.09; H, 4.62; N, 3.70.

X-ray Diffraction Analysis of Azagrevellin **12**.

Data collection: CAD4 Diffractometer, crystal mounted in a glass capillary, cell constants from 25 centered reflections. Mo-$K_\alpha$ radiation , λ = 0.71073 Å, graphite monochromator, ω-scan, scan width $(0.77 + 0.59 \tan \Theta)^2$, maximum measuring time 60 s, intensity of three standard reflections checked every two hours. Structure solution by SHELXS-86 [17] and refinement by SHELXL-93 [18], non-hydrogen atoms refined anisotropically, hydrogens with $U_i = 1.2 \times U_{eq}$ of the adjacent carbon atom. Full-matrix refinement against $F^2$. Weight: SHELXL-93. Maximum and minimum of the final difference Fourier synthesis 0.199 and -0.234 e $Å^{-3}$. The drawing (Figure 1) was made by ZORTEP [19]. Selected data are given in tables 1. The complete data are available from the Cambridge Crystallographic Data Centre [22]. The deposition number is CCDC 140102.

(3R,*4S,Z*)-9-Benzylidene-1,5-dioxa-8-aza-dispiro[2.0.2.4]decan-7-one (**14**).

This compound was prepared analogously to **12** from 0.60 g (3 mmoles) of compound **4** and diazomethane and crystallized from methanol. Yield 10%, colorless crystals, mp 180°; ir: ν 3224, 1675, 1457, 1389 $cm^{-1}$; uv: λ max (log ε) 272 nm (4.109); $^1H$ nmr ($CDCl_3$): δ 9.90 (s, 1 H), 7.38 (m, 3 H), 7.21 (m, 2 H, NOE: signal amplification at 9.90, 5.68), 5.68 (d, 1 H, $^4J$ = 1.5 Hz), 3.25 (dt, 1 H, $^2J$ = 13.7 Hz, $^4J$ = 1.5 Hz, $^4J$ = 1.1 Hz), 3.03 (d, 1 H, $^2J$ = 7.3 Hz), 2.87 (d, 1 H, $^2J$ = 7.2 Hz, NOE: signal amplification at 3.03), 2.84 (d, 1 H, $^2J$ = 5.3 Hz), 2.81 (dd, 1 H, $^2J$ = 5.3 Hz, $^4J$ = 1.1 Hz, NOE: signal amplification at 3.03, 2.84), 2.59 (d, 1 H, $^2J$ = 13.7 Hz, NOE: signal amplification at 5.68, 3.25, 2.84); ms: m/z 243 [M+].

*Anal.* Calcd. for $C_{14}H_{13}NO_3$ (243.26): C, 69.12; H, 5.39; N, 5.76. Found: C, 69.21; H, 5.30; N, 5.67.

(*Z*)-Ethyl (7-Oxo-4-phenylhydrazono-6-aza-1-oxaspiro[2,5]-octan-5-ylidene)-acetate (**16**).

Compound **15** (0.57 g, 2 mmoles) [15] was treated with an excess of an etheral solution of diazomethane. After ten hours the volatile components were removed and the residue was purified on a silica gel column, using ethyl acetate/cyclohexane 1:2 as eluent. Yield 20%, orange crystals, mp 189° (ethyl acetate); ir: ν 3302, 2975, 1698, 1662, 1636 $cm^{-1}$; uv: λ max (log ε) 255 (4.112), 383 nm (4.202); $^1H$ nmr ($CDCl_3$): δ 11.35 (s, 1 H), 7.77 (s, 1 H), 7.32 - 6.97 (m, 5 H), 5.98 (s, 1 H), 4.21 (q, 2 H, J = 7.1 Hz), 3.28 (d, 1 H, $^2J$ = 6.0 Hz), 3.00 (d, 1 H, $^2J$ = 16.7 Hz), 2.88 (d, 1 H, $^2J$ = 6.0 Hz), 2.87 (d, 1 H, $^2J$ = 16.7 Hz), 1.31 (t, 3 H, J = 7.1 Hz); $^{13}C$ nmr ($CDCl_3$): δ 168.6, 146.6, 143.0, 129.5, 127.8, 122.4, 113.9, 89.6, 60.4, 54.6, 51.6, 30.0, 14.3; $^1H^{13}C$-COSY ($CDCl_3$): 86.6 and 5.98, 54.6 and 3.28/ 2.88, 30.0 and 3.00/2.87; ms: m/z 315 [M+].

*Anal.* Calcd. for $C_{16}H_{17}N_3O_4$ (315.34): C, 60.94; H, 5.43; N, 13.33. Found: C, 60.95; H, 5.43; N, 13.32.

Methyl 4-Methoxy-2,5-dioxo-3-pyrroline-3-carboxylate (**17a**).

A solution of 1.17 g (10 mmoles) of methyl aminocarbonylacetate [20], 1.18 g (10 mmoles) of dimethyl oxalate and 0.54 g (20

mmoles) of sodium methylate in methanol (50 ml) was refluxed. The yellow precipitate was isolated and its methanolic suspension stirred with Amberlite® IR-120 (strongly acidic) for one hour. After filtration the solvent was removed *in vacuo* and the colorless residue suspended in diethyl ether. Then a solution containing an equimolar amount of diazomethane in diethyl ether was added dropwise. After the evolution of nitrogen had ceased the solution was evaporated to dryness and the residue crystallized from ethyl acetate. Yield 62%, colorless crystals, mp 155° ; ir: ν 3265, 3190, 1735, 1680, 1625 $cm^{-1}$; uv: λ max (log ε) 235 (4.225), 329 nm (3.395); $^1H$ nmr: δ 10.95 (s, 1 H), 4.33 (s, 3 H), 3.88 (s, 3 H); ms: m/z 185 [M+].

*Anal.* Calcd. for $C_7H_7NO_5$ (185.14): C, 45.41; H, 3.81; N, 7.57. Found: C, 45.27; H, 3.80; N, 7.47.

(*Z*)-5-Benzylidene-4-methoxy-2-oxo-3-pyrroline-3-carbonitrile (**18b**).

This compound was prepared analogously to **12** from 0.63 g (3 mmoles) of 5-benzylidene-4-hydroxy-2-oxo-3-pyrroline-3-carbonitrile [4] and recrystallized from methanol. Yield 75%, colorless crystals, mp 237°; ir: ν 3177, 2223, 1690, 1654 $cm^{-1}$; uv: λ max (log ε) 343 nm (4.451); $^1H$ nmr: δ 10.51 (s, 1 H), 7.64 - 7.36 (m, 5 H), 6.52 (s, 1 H), 4.35 (s, 3 H); ms: m/z 226 [M+].

*Anal.* Calcd. for $C_{13}H_{10}N_2O_2$ (226.23): C, 69.01; H, 4.45; N, 12.38. Found: C, 69.20; H, 4.44; N, 12.44.

(*Z*)-5-Benzylidene-4-methoxy-1-methyl-2-oxo-3-pyrroline-3-carbonitrile (**19b**).

An etheral solution of excessive diazomethane was added to a solution of 0.22 g (1 mmole) **18b** in methanol. After ten hours the solution was evaporated to dryness and the residue crystallized from methanol. The second fraction contained the new compound. Yield 10%, colorless crystals, mp 160°; ir: ν 3177, 2223, 1702, 1645 $cm^{-1}$; uv: λ max (log ε) 322 nm (4.239); $^1H$ nmr: δ 7.46 - 7.39 (m, 5 H), 6.80 (s, 1 H), 4.37 (s, 3 H), 2.77 (s, 3 H); ms: m/z 240 [M+].

*Anal.* Calcd. for $C_{14}H_{12}N_2O_2$ (240.26): C, 69.98; H, 5.03; N, 11.66. Found: C, 69.89; H, 5.00; N, 11.60.

Methyl 5-Methoxy-3-methyl-2,4-dioxo-3-azabicyclo[3.1.0]-hexane-1-carboxylate (**20a**).

Compound **17a** (1.85 g , 10 mmoles ) was treated with an excess of an etheral solution of diazomethane. After the evolution of nitrogen had ceased the solution was evaporated to dryness and the residue crystallized from methanol. Yield 80%, colorless crystals, mp 108°; ir: ν 3100, 3010, 2950, 1735, 1705 $cm^{-1}$; uv: λ max (log ε) 230 nm (3.749); $^1H$ nmr ($CDCl_3$): δ 3.90 (s, 3 H), 3.60 (s, 3 H), 2.97 (s, 3 H), 2.68 (d, 1 H, $^2J$ = 6.0 Hz), 2.03 (d, 1 H, $^2J$ = 6.0 Hz); ms: m/z 213 [M+].

*Anal.* Calcd. for $C_9H_{11}NO_5$ (213.19): C, 50.71; H, 5.20; N, 6.57. Found: C, 50.63; H, 5.13; N, 6.63.

5-Methoxy-3-methyl-2,4-dioxo-3-azabicyclo[3.1.0]hexane-1-carbonitrile (**20b**).

This compound was prepared analogously to **20a** from 1.52 g (10 mmoles) of compound **17b** [21] and crystallized from methanol. Yield 80%, colorless crystals, mp 128°; ir: ν 3100, 3020, 2945, 2250, 1785, 1720, 1710 $cm^{-1}$; uv: λ max (log ε) 219 nm (4.117); $^1H$ nmr ($CDCl_3$): δ 3.80 (s, 3 H), 3.00 (s, 3 H), 2.48 (d, 1 H, $^2J$ = 6.0 Hz), 2.28 (d, 1 H, $^2J$ = 6.0 Hz); ms: m/z 180 [M+].

*Anal.* Calcd. for $C_8H_8N_2O_3$ (180.16): C, 53.33; H, 4.48; N, 15.55. Found: C, 53.48; H, 4.59; N, 15.68.

Methyl 3,6-Dihydroxy-1-methyl-2-oxo-1,2-dihydropyridine-5-carboxylate (**21a**).

To a stirred solution of 1.06 g (5 mmoles) of compound **20a** in acetone (25 ml) 15 ml of concentrated hydrochloric acid were added. The slowly appearing precipitate was crystallized from methanol. Yield 75%, colorless crystals, mp 196°; ir: ν 3240, 2960, 1660, 1630, 1565 $cm^{-1}$; uv: λ max (log ε) 313 nm (4.157); $^1H$ nmr: δ 7.00 (s, 1 H), 3.90 (s, 3 H), 3.45 (s, 3 H); ms: m/z 199 [M+].

*Anal.* Calcd. for $C_8H_9NO_5$ (199.16): C, 48.25; H, 4.56; N, 7.03. Found: C, 48.28; H, 4.66; N, 7.08.

3,6-Dihydroxy-1-methyl-2-oxo-1,2-dihydropyridine-5-carbonitrile (**21b**).

To a stirred solution of 0.90 g (5 mmoles) of compound **20b** in acetone (25 ml) 15 ml of concentrated hydrochloric acid were added. After three hours the solution was diluted with water and extracted twice with dichloromethane. The combined organic layers were dried over sodium sulfate. Evaporation gave colorless crystals. Yield 40%, mp 195°; ir: ν 3280, 2225, 1710, 1655, 1585 $cm^{-1}$; uv: λ max (log ε) 267 nm (3.798), 334 (3.762); $^1H$ nmr: δ 6.83 (s, 1 H), 3.50 (s, 3 H); ms: m/z 166 [M+].

*Anal.* Calcd. for $C_7H_6N_2O_3$ (166.14): C, 50.61; H, 3.64; N, 16.86. Found: C, 50.51; H, 3.91; N, 16.96.

Methyl 3,6-Dimethoxy-1-methyl-1,2-dihydropyridine-5-carboxylate (**22a**).

Compound **21a** (1.00 g, 5 mmoles) was treated with an excess of an etheral solution of diazomethane. After the evolution of nitrogen had ceased the solution was evaporated to dryness and the residue crystallized from diethyl ether. Yield 56%, colorless crystals, mp 96°; ir: ν 3000, 2950, 1660, 1620, 1555 $cm^{-1}$; uv: λ max (log ε) 286 nm (4.162); $^1H$ nmr ($CDCl_3$): δ 7.12 (s, 1 H), 3.97 (s, 3 H), 3.87 (s, 3 H), 3.82 (s, 3 H), 3.55 (s, 3 H); ms: m/z 227 [M+].

*Anal.* Calcd. for $C_{10}H_{13}NO_5$ (227.22): C, 52.86; H, 5.77; N, 6.16. Found: C, 52.84; H, 5.62; N, 6.16.

X-ray Diffraction Analysis of Pyridone **22a**.

Data collection: CAD4 Diffractometer, crystal mounted in a glass capillary, cell constants from 25 centered reflections. Mo-$K_\alpha$ radiation, λ = 0.71073 Å, graphite monochromator, ω-scan, scan width $(0.77 + 0.59 \tan \Theta)^2$, maximum measuring time 60 s, intensity of three standard reflections checked every two hours. Structure solution by SHELXS-86 [17] and refinement by SHELXL-93 [18], non-hydrogen atoms refined anisotropically, hydrogens with $U_i = 1.2 \times U_{eq}$ of the adjacent carbon atom. Full-matrix refinement against $F^2$. Weight: SHELXL-93. Maximum and minimum of the final difference Fourier synthesis 0.199 and -0.234 e $Å^{-3}$. The drawing (Figure 2) was made by ZORTEP [19]. Selected data are given in tables 2. The complete data are available from the Cambridge Crystallographic Data Centre [22]. The deposition number is. CCDC 140103.

3,6-Dimethoxy-1-methyl-2-oxo-1,2-dihydropyridine-5-carbonitrile (**22b**).

This compound was prepared analogously to **21a** from 0.83 g (5 mmoles) of compound **21b** and crystallized from diethyl ether. Yield 52%, colorless needles, mp 156°; ir: ν 2960, 2250, 1680, 1625, 1560 $cm^{-1}$; uv: λ max (log ε) 273 nm (3.869); $^1H$ nmr ($CDCl_3$): δ 6.61 (s, 1 H), 4.33 (s, 3 H), 3.83 (s, 3 H),3.53 (s, 3 H); ms: m/z 194 [M+].

*Anal.* Calcd. for $C_9H_{10}N_2O_3$ (194.19): C, 55.67; H, 5.19; N, 14.43. Found: C, 55.61; H, 5.16; N, 14.45.

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