70. An Efficient Synthesis of Racemic 4-Hydroxy-2-oxo-1-pyrrolidineacetamide (Oxiracetam) Using Tetramic-Acid Intermediates

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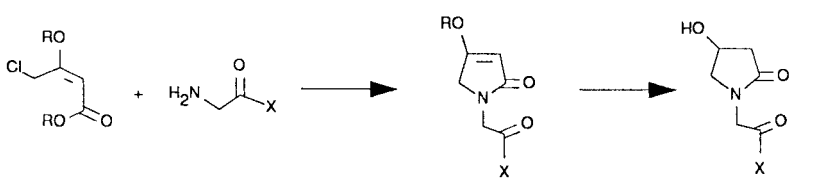
The title compound, **1a**, has been synthesised in racemic form from ethyl (*E*)-4-chloro-3-ethoxybut-2-enoate in 43% overall yield in five steps. Several routes to the final product are described, but the most efficient involves hydrogenation of a C(5)-unsubstituted tetramic acid **5b**. The instability of this class of compounds required the use of a catalyst which could operate under very acidic aqueous conditions, a role that was successfully filled by a 5% Ru/C catalyst.

Introduction. – Oxiracetam (=4-hydroxy-2-oxo-1-pyrrolidineacetamide; **1a**) has attracted considerable synthetic interest [1] due to its effectiveness in improving learning and memory, *e.g.* in the treatment of *Alzheimer*'s disease [2–4]. Compounds of similar structure, differing in the nature of the amide, continue to appear as possible agents for counteracting the effects of senility [5]. Our interest in the synthesis of oxiracetam was stimulated by the possibility of constructing the molecule from an alkyl (*E*)-3-alkoxy-4-chlorobut-2-enoate (**2** or **3**), the chemistry of which we have been investigating for several years [6].

We describe here a synthesis, which can produce oxiracetam of the requisite purity for a pharmaceutical synthesis, and which is noteworthy for the simplicity of both the synthetic route and operations. As outlined in *Scheme 1*, the synthetic strategy was to build the framework by coupling an (*E*)-3-alkoxy-4-chlorobutenoate, **2** or **3**, with a suitable glycine derivative to give an alkyl tetramate **4**. Removal of the alkyl group

Scheme 1



2 R = Me
3 R = Et

4a R = Me, X = NH_2
b R = Me, X = OH
c R = Me, X = EtO
d R = Et, X = OH
e R = Bn, X = NH_2

1a X = NH_2
b X = OH
c X = EtO
d X = BuO

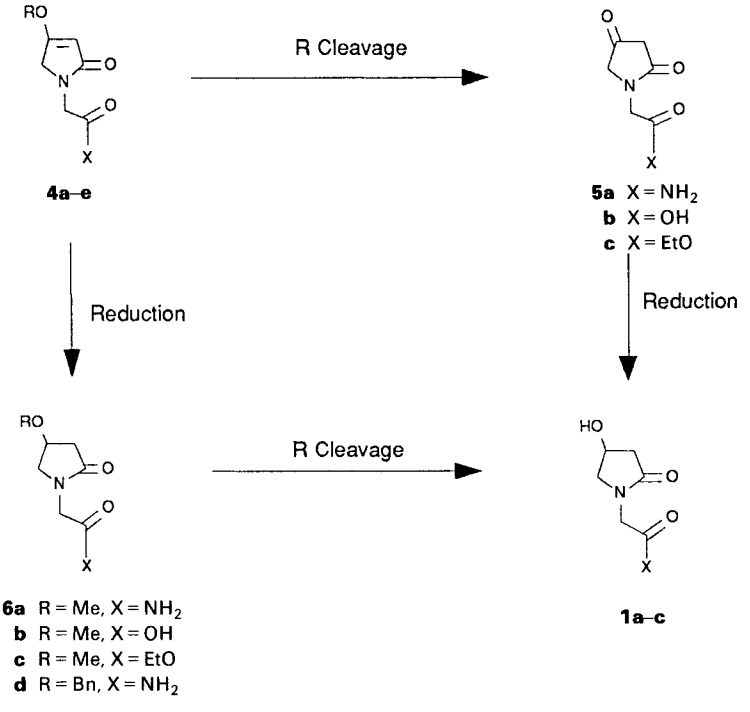
followed by a reduction, or *vice versa*, giving 4-hydroxypyrrolidinone **1**, should then leave only manipulation of the carboxy derivative to give oxiracetam (**1a**). Three different types of glycine derivatives were considered during the work: the amide, an ester, either ethyl or butyl, and the acid (*Scheme 1*).

Due to the difficulty of handling C(5)-unsubstituted tetramic acids such as **5** [7] [8], previous syntheses of oxiracetam (**1a**) have concentrated on formation of the secondary OH group at C(4) before lactamisation, which inevitably leads to several protecting and deprotecting steps. A prerequisite for success in our approach was to ensure that tetramic-acid intermediates should be generated only under conditions in which they were stable, and that they should be immediately, if possible *in situ*, reacted further.

Results and Discussion. – Coupling of **2** or **3** and a glycine derivative proved straightforward and high-yielding (**4b** in 80, **4c** in 79, and **4d** in 87% yield). The reaction with glycine was particularly attractive, as it could be carried out in H_2O using NaOH as base. Isolation of the free acid required only acidification of the crude aqueous solution with HCl, which precipitated out acid of sufficient purity to be used directly in the following steps. The amide **4a** was prepared from the ester by treatment with NH_3 in MeOH (95% yield).

Of the two possible dealkylation and reduction routes leading to the key hydroxypyrrolidinone **1** outlined in *Scheme 2*, the reduction of the alkyl tetramate before dealkylation initially appeared to be more attractive, since each intermediate should be a stable

Scheme 2

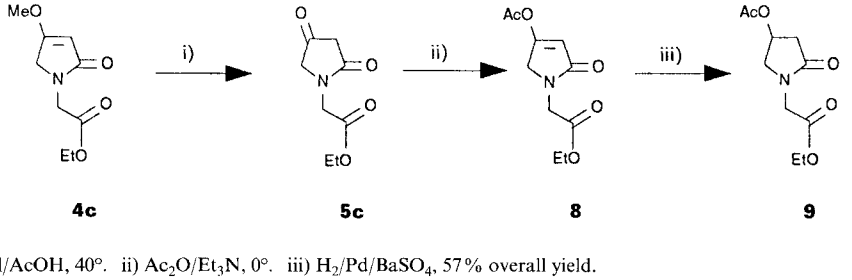


product. Reduction of **4a–c** to the 4-methoxy-pyrrolidinones **6a–c** was cleanly achieved by hydrogenation using Pd/C as catalyst (5% Pd/C, 10 bar; yield of **6c**, 93%; yield of **6a**, > 96%, 80% recryst.). Use of other catalysts resulted in varying amounts of the hydrogenolysis products **7a–c**, most notably Pt/C gave **7a** (piracetam) and **7c** in quantitative yields. Unfortunately, removal of the Me group proved extremely difficult; the usual strong *Lewis*-acid or mineral-acid methods utilised for methyl-ether hydrolysis were totally unsuccessful in this case, generally leading to a > 90% recovery of starting material. Success was finally achieved on **6c** using *Olah*'s conditions ($MeSiCl_3$/NaI in MeCN) [9]. This required a larger excess of NaI (1.44 equiv.) and much harsher conditions (80°, 24 h) than are usually employed. As a consequence, numerous silylated by-products were produced, and the isolated yield was only modest (for **6c**, 57%). These points argued against persevering with these methyl-ether intermediates.

The benzyloxy derivative **6d** should allow for a simple hydrogenolytic cleavage of the protecting $PhCH_2$ group after reduction. The corresponding **4e** was prepared in two steps from **4c** in good yield (83%). Only Rh/Al_2O_3 catalysts were suitable for the hydrogenation of the C=C bond (**4e** → **6d**). Competing reactions observed with other catalysts included hydrogenation of the Ph ring, debenzylation prior to reduction of the C=C bond or, again in the case of Pt catalysts, hydrogenolysis to **7a** (see later). With Rh/Al_2O_3 catalyst in MeOH under 1 bar pressure of H_2 (higher pressures resulted in some Ph-group hydrogenation), the benzyloxy derivative was formed in 82% yield. Debenzylation was surprisingly difficult, only taking place in HCOOH with Pd/C catalysis and producing *O*-formylated oxiracetam in 84% yield. This formyl group could not be selectively hydrolysed in the presence of the acetamide side chain, and was, therefore, removed as formamide with NH_3. Although all these steps are high-yielding, the number of steps involved in changing the nature of the O-substituent, first from Me to $PhCH_2$, then to formyl, and lastly to free OH, is inelegant and robs the synthesis of its essential simplicity.

As the hydrogenation of the alkyl tetramate had worked well, it seemed worthwhile studying other *O*-substituted tetramates as possible oxiracetam precursors. As an alternative, the acetate **8** was synthesised by acetylation of the tetramic acid **5c** resulting from

Scheme 3



4c **5c** **8** **9**

i) HCl/AcOH, 40°. ii) Ac_2O/Et_3N, 0°. iii) $H_2/Pd/BaSO_4$, 57% overall yield.

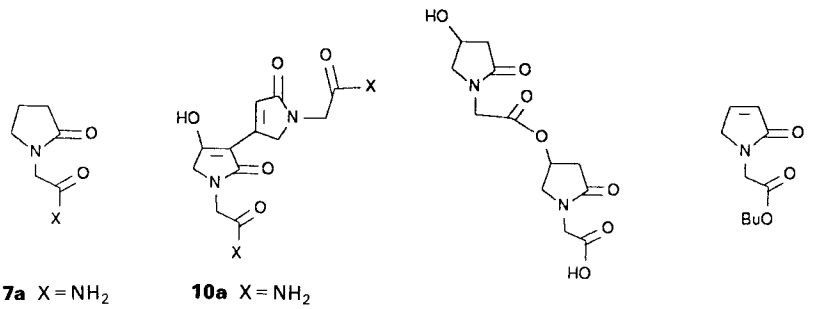
a hydrolysis of **4c** (*Scheme 3*). The hydrolysis proceeded easily in AcOH saturated with HCl, needing only catalytic quantities of H_2O; if 1 equiv. of H_2O was added, the ethyl ester was also hydrolysed. Removal of the AcOH gave the tetramic acid, which was immediately dissolved in CH_2Cl_2 and acetylated with Ac_2O/Et_3N to give **8** in 62% yield over the two steps, after recrystallisation. Hydrogenation of **8** was again a question of

controlling the selectivity between hydrogenation to the acetate **9** and hydrogenolysis to **7c**. This could be achieved using $Pd/C/BaSO_4$ in AcOEt (10 bar, 92% yield, **9**/**7c** 15:1), but the selectivity of the hydrogenation was critically dependent on the purity of **8**. Due to the instability of **5c**, coupled to the difficult recrystallisation of **8**, this purity was difficult to achieve consistently. The acetylation had to be performed as quickly as possible after the generation of **5c**, in order to minimise decomposition, and this became increasingly difficult with increasing scale, therefore, making it unsuitable for an industrial process.

Having exhausted the viable routes proceeding *via* reduction of a protected tetramic acid, we turned our attention to reduction of a tetramic acid itself. As mentioned above, handling of the tetramic acid could be a major problem, so its instability must be of major importance in determining the conditions for its generation and also for its reduction. As a general rule, C(5)-unsubstituted tetramic acids (substituted ones are relatively stable) are more stable in acidic media, the major decomposition product being derived from a self-condensation (→**10**) [7] [9] [10].

The benzyloxy (**4e**), ethoxy (**4d**), and methoxy (**4a–c**) derivatives were considered as possible precursors to a tetramic-acid derivative **5**. Unlike **4a–d**, **4e** could be used to generate **5** under non-hydrolytic conditions.

By-products



7a X = NH_2
b X = OH
c X = OEt
d X = OBu

10a X = NH_2
b X = OH
c X = OEt

11

12

Hydrogenolysis of the $PhCH_2$ group in **4e** was achieved easily with 5% Pd/C as catalyst in DMF, DMA, MeOH, or AcOH, giving **5a** as a solution which could be used immediately. Relatively little decomposition was noted in DMF or DMA, but hydrogenation of the oxo group at C(4) to an OH group was impossible. Instead, a reduction with $NaBH_4$ was carried out without any problem, giving oxiracetam (**1a**) in good yield (75%). However, purification of the crude product, particularly removal of salts, was exceedingly difficult, as **1a** is very soluble in H_2O and insoluble in nearly all organic solvents. Hence, it was decided to investigate routes generating **1a** free from salts, *e.g.* from a hydrogenation of tetramic-acid derivatives **5a–c** or by amidation of an already purified ester, **1c** or **1d**.

The results of hydrogenation of **5** are shown in the *Table*. Compound **5a** could be formed in two ways, as above by debenzylation of **4e** or by hydrolysis of **4a** in HCl/

Table. *Results of Hydrogenation of* **5**

Entry	Tetramic-acid derivative	Solvent	Catalyst[a])	$p(H_2)$/bar	Reaction time/h	Yield [%] **1a–c**	**1/7**
1	**5a**	MeOH	5% *A*	15	17	41 **1a**	19:1
2	**5a**	MeOH	5% *B*	10	18	56 **1a**	12:1
3	**5a**	MeOH	5% *A* +5% $MeSO_3H$	15	14	20 **1a**	1:3
4	**5a**·HCl	H_2O, pH 1	5% *C*	25	18	69 **1a**/**b** 2:1	15:1
5	**5c**	H_2O/AcOH 1:1	5% *C*	25	23	86 **1c**/**b** 2:1	25:1
6	**5c**	H_2O/AcOH/EtOH 1:10:10	5% *C*	25	20	59 **1c**	12:1
7	**5b**	2N HCl	10% *C*	10	69	82[b]) **1b**	10:1
8	**5b**	1N HCl	10% *C*	10	24	78[b]) **1b**	15:1
9	**5b**	H_2O, pH 1	7% *C*	10	14	84[b]) **1b**	20:1

[a]) *A*: Pt/Al_2O_3; *B*: Rh/Al_2O_3; *C*: Ru/C. [b]) Yield after esterification.

AcOH, which, in contrast to the other cases, gave **5a** as a stable, crystalline HCl salt. Two main by-products were expected, and observed, in these hydrogenations, the hydrogenolysis product **7** and the self-condensation product **10**. No hydrogenation was possible in non-protic solvents, and for Ru/C catalysis some H_2O was necessary. In protic solvents, acid is required to minimise self-condensation, and only the 5% Ru/C catalyst was capable of maintaining a high **1/7** (> 15:1) ratio under strongly acidic conditions. This problem is exemplified by the use of Pt/Al_2O_3 catalysis in MeOH (*Entries 1* and *3*). In MeOH using 5% of 5% Pt/Al_2O_3, the selectivity of the catalyst is 19:1 in favour of oxiracetam (**1a**), but the yield is only 41% because of rapid self-condensation of **5a**. Stabilisation of the intermediate **5a** by the addition of 5 mol-% $MeSO_3H$ reversed the sense of the catalyst selectivity to 1:3 in favour of **7a**. Resubmission of oxiracetam to the hydrogenation conditions led to a > 90% recovery of oxiracetam, showing that elimination of H_2O and hydrogenation of the unsaturated lactam had not occurred.

A substantial by-product in hydrogenations of **5a** or **5c** was the acid **1b** resulting from hydrolysis of the side-chain ester or amide. It was, therefore, decided to carry the carboxylic acid through the synthesis (*via* **4b** or **4d**) and perform the esterification and subsequent amidation at the end.

For the hydrolysis of **4b** or **4d**, strong acid (> 1N HCl) and 50° were needed. Higher temperatures or lower concentrations of HCl led to immediate self-condensation of **5b**. For the hydrogenation, at room temperature, the pH of the solution had to be adjusted to pH 1 with NaOH (aq.) in order to maintain sufficient activity and selectivity of the Ru/C catalyst (14 h with 7% by weight of 5% Ru/C, > 20:1 selectivity). Higher pH values led to a drastic drop in yield, as self-condensation became predominant. After removal of the catalyst and removal of the major part of the H_2O, the crude material contained not only

1b and **7b** but also the ester **11** formed from **1b**. Esterification was achieved simply by azeotropically removing H_2O with BuOH, which also transformed **11** into the desired ester **1d**. At this point, the NaCl present could be substantially removed by filtration of the BuOH solution. If the crude solution of the starting tetramate, **4b** or **4d**, was used, the major part of all the salt produced in this synthesis could be removed at this stage by filtration. Over the three steps, hydrolysis, hydrogenation, and esterification, the crude yield of **1d** was 88% (based on HPLC).

It was important to purify **1d** thoroughly before conversion into oxiracetam, as impurities could only be removed with great difficulty from the final product. The non-polar impurities could be removed by washing an aqueous solution of the butyl ester with toluene, and the polar impurities were left in the aqueous phase after extracting out the ester with CH_2Cl_2. To achieve high purity, a wiped film distillation was also necessary; other types of distillation resulted in appreciable quantities of the unsaturated butyl ester **12** resulting from a dehydration. Production of **12** was not totally avoidable, so it was necessary to perform this distillation before the extractions. This purification proceeded in 76% yield with the major loss of **1d** lying in the toluene phase. Re-extraction of this allowed for recovery of a further 10% **1d**, giving a yield of 86% in the purification and a total yield of 75% from **4d**.

Amidation occurred quite simply with NH_3 in EtOH in an autoclave at 50°. With ester purified as described above, the oxiracetam precipitated out of the reaction mixture in 93% yield and good purity (98.7% pure, HPLC). Recrystallisation (65% yield), with active charcoal treatment, from H_2O gave very pure (99.6% pure by HPLC, 0.3% H_2O) and essentially salt-free (Cl^- and NH_4^+ < 50 ppm) oxiracetam (**1a**).

Conclusion. – This synthesis (**3**→**4d**→**5b**→**1b**→**1d**→**1a**) produces oxiracetam (**1a**) in 43% overall yield (66% before recrystallisation) from **3** in five steps, each of which is suitable to scale-up. The purity is excellent, even though only one of the intermediates, **1d**, is purified. Of great practical importance is the nature of the waste; the main solvent used in this route is H_2O, and the only inorganic waste produced is NaCl. It has also demonstrated that the difficulties usually associated with syntheses using tetramic acids are not insurmountable.

Experimental Part

General. Solvents and reagents were purchased from *Fluka*, except for 5% Pd/C and 5% Pt/Al_2O_3 from *Johnson Matthey*, 5% Rh/C from *Degussa*, and 5% Ru/C from *Heraeus*. M.p.: *Büchi 535* apparatus, uncorrected. IR Spectra: *Nicolet Model 20 SXB* spectrometer; absorptions in cm^{-1}. NMR Spectra: *Varian Unity 400* (400 MHz for ^1H- and 100.6 MHz for ^{13}C-NMR) spectrometer; chemical shifts (δ) in ppm with reference to TMS; coupling constants (J) in Hz. MS: *Hewlett-Packard HP 5989A*.

*(4-Ethoxy-1,5-dihydro-2-oxo-2*H*-pyrrol-1-yl)acetic Acid* (**4d**). Glycine (50 g, 666 mmol) was suspended in H_2O (75 ml) at r.t., with vigorous stirring. This mixture was heated to 80°, and **3** (100 g, 519 mmol) was added to it in one portion. NaOH (117 ml of 10M (aq.), 1.17 mol) was added over 3 h. After additional 1 h, the mixture was cooled to 15°, and HCl (81 g, conc. aq.) was added over 15 min. The precipitated product was isolated by filtration, washed with brine (50 ml), and dried (40°/30 mbar) to give **4d** as a white amorphous solid (87.47 g containing 6.2% NaCl, 87% yield). An anal. sample was prepared by dissolving crude **4d** in 3M NaOH (aq.) and precipitating it out with conc. HCl (aq.), which, at pH 1, gave **4d** as white needles. M.p. 146–147°. IR (KBr): 2800–3200 (br.), 1740, 1725, 1635, 1605. ^1H-NMR ((D_6)DMSO): 12.70 (br. *s*, 1H); 5.14 (*s*, 1H); 4.03 (*q*, J = 7.1, 2H); 3.99 (*s*, 2H); 3.96 (*s*, 2H); 1.31 (*t*, J = 7.1, 3H). ^{13}C-NMR ((D_6)DMSO): 173.2; 171.7; 171.0; 93.7; 66.9; 50.4; 42.3; 13.9. EI-MS: 185

(15, M^+), 140 (65), 112 (40), 84 (55), 55 (80), 42 (100). Anal. calc. for $C_8H_{11}NO_4$ (185.18): C 51.89, H 5.99, N 7.56; found: C 51.58, H 6.21, N 7.64.

*(1,5-Dihydro-4-methoxy-2-oxo-2*H*-pyrrol-1-yl)acetic Acid* (**4b**). Prepared in a similar fashion to **4d** from **2** (67.2 g, 408 mmol) to give **4b** as a white amorphous solid (75.7 g containing 24.1% NaCl, 80% yield). An anal. sample was prepared by recrystallisation from i-PrOH: **4b**. White needles. M.p. 164–165°. IR (KBr): 3200–2800 (br.), 1740, 1725, 1655, 1615. ^{1}H-NMR ((D$_6$)DMSO): 12.70 (br. *s*, 1H); 5.17 (*s*, 1H); 3.99 (*s*, 2H); 3.92 (*s*, 2H); 3.78 (*s*, 3H). ^{13}C-NMR ((D$_6$)DMSO): 174.3; 171.5; 171.0; 93.7; 58.2; 50.3; 42.3. EI-MS: 171 (20, M^+), 126 (100), 112 (20), 98 (30), 69 (45), 42 (65). Anal. calc. for $C_7H_9NO_4$ (171.15): C 49.12, H 5.30, N 8.18; found: C 48.71, H 5.54, N 8.47.

*(1,5-Dihydro-4-methoxy-2-oxo-2*H*-pyrrol-1-yl)acetamide* (**4a**). *Ethyl (2,5-dihydro-4-methoxy-2-oxopyrrol-1-yl)acetate* (**4c**, 59.8 g, 294 mmol) was dissolved in MeOH (300 ml) at r.t., cooled to −20°, and liquid NH_3 (40.9 g, 2.4 mol) was added. The mixture was transferred into an autoclave, which was closed and warmed to 60°. After 6 h, the mixture was cooled to r.t. the autoclave opened, and the mixture concentrated *in vacuo* (to 50 ml) and left to stand at 4°, to give **4a** as thin white needles (48.6 g, 95%). M.p. 184–186°. IR (KBr): 3400, 3190, 1690, 1685, 1635, 1615. ^{1}H-NMR ((D$_6$)DMSO): 7.40 (br. *s*, 1H); 7.06 (br. *s*, 1H); 5.16 (*s*, 1H); 3.97 (*s*, 2H); 3.85 (*s*, 2H); 3.68 (*s*, 3H). Anal. calc. for $C_7H_{10}N_2O_3$ (170.17): C 49.41, H 5.92, H 16.46; found: C 49.69, H 5.98, N 16.53.

*[4-(Benzyloxy)-1,5-dihydro-2-oxo-2*H*-pyrrol-1-yl]acetamide* (**4e**). Ester **4c** (73.8 g, 81% pure, 300 mmol) and MsOH (3.2 g, 33 mmol) were dissolved in $PhCH_2OH$ (165.5 g, 1.68 mol), at r.t., with stirring. The mixture was heated to 90–100° under reduced pressure (16–25 mbar). After 3 h, the soln. was transferred into an autoclave, cooled to −20°, and liquid NH_3 (35.7 g, 2.1 mol) was added. The autoclave was closed and heated to 55°, with stirring. After 8 h, the mixture was allowed to cool to r.t., the autoclave opened, and the mixture concentrated *in vacuo* to give **4e** as a brown oil. Crystallisation from H_2O and washing with acetone gave **4e** as a light brown amorphous solid (62.0 g, 83%). M.p. 174–175°. IR (KBr): 3400, 3185, 1690, 1635, 1615. ^{1}H-NMR ((D$_6$)DMSO): 7.46–7.35 (*m*, Ph, NH); 7.03 (br. *s*, NH); 5.26 (*s*, 1H); 5.07 (*s*, 2H); 4.02 (*s*, 2H); 3.86 (*s*, 2H). ^{13}C-NMR ((D$_6$)DMSO): 172.8; 171.5; 170.6; 135.4; 128.5; 128.1; 94.7; 72.4; 50.9; 43.4. Anal. calc. for $C_{13}H_{14}N_2O_3$ (246.27): C 63.40, H 5.73, N 11.38; found: C 63.31, H 5.88, N 11.25.

Ethyl (4-Methoxy-2-oxopyrrolidin-1-yl)acetate (**6c**). Compound **4c** (2.0 g, 10 mmol) was dissolved, and 5% Pd/C (200 mg) was suspended in EtOH (40 ml), at r.t. The mixture was placed under a H_2 atmosphere (10 bar), at r.t., with stirring. After 17 h, the suspension was filtered and the filtrate concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (20 ml), washed with H_2O (5 ml), dried (Na_2SO_4), and concentrated *in vacuo* to give **6c** as a colourless oil (1.9 g, 93%). IR (KBr): 2985, 2935, 1745, 1700. ^{1}H-NMR ($CDCl_3$): 4.21 (*d*, J = 17.6, 1H); 4.18 (*q*, J = 7.1, 1H); 4.10 (*m*, 1H); 3.91 (*d*, J = 17.6, 1H); 3.75 (*dd*, J = 10.3, 6.1, 1H); 3.44 (*dd*, J = 10.3, 2.6, 1H); 3.33 (*s*, 3H); 2.65 (*dd*, J = 17.3, 6.9, 1H); 2.45 (*dd*, J = 17.3, 3.1, 1H); 1.27 (*t*, J = 7.1, 3H). ^{13}C-NMR ($CDCl_3$): 171.1; 168.6; 73.2; 61.3; 56.3; 53.6; 43.8; 37.2; 14.2. EI-MS: 202 (4, $[M + 1]^+$), 169 (85), 128 (62), 96 (100), 58 (48), 41 (38).

(4-Methoxy-2-oxopyrrolidin-1-yl)acetamide (**6a**). Prepared in a similar fashion to **6c** from **4a** (10.0 g, 59 mmol) to give **6a** as a light brown amorphous solid. Recrystallization from toluene (900 ml) gave **6a** as white needles (8.1 g, 80%). M.p. 113–114°. IR (KBr): 3350, 3180, 2940, 1680, 1670, 1630. ^{1}H-NMR ((D$_6$)DMSO): 7.32 (br. *s*, 1H), 7.06 (br. *s*, 1H); 4.03 (*m*, 1H); 3.87 (*d*, J = 16.5, 1H); 3.65 (*d*, J = 16.5, 1H); 3.63 (*dd*, J = 10.5, 6.0, 1H); 3.33 (*dd*, J = 10.5, 2.5, 1H); 3.22 (*s*, 3H); 2.58 (*dd*, J = 17.1, 6.9, 1H); 2.21 (*dd*, J = 17.1, 2.1, 1H). ^{13}C-NMR ((D$_6$)DMSO): 172.2; 169.5; 72.8; 55.5; 53.1; 44.5; 37.0. EI-MS: 173 (2, $[M + 1]^+$), 140 (85), 123 (55), 96 (100), 86 (32), 68 (30), 53 (70), 41 (56). Anal. calc. for $C_7H_{12}N_2O_3$ (172.18): C 48.83, H 7.02, N 16.27; found: C 48.80, H 7.17, N 16.29.

Ethyl (4-Hydroxy-2-oxopyrrolidin-1-yl)acetate (**1c**). Dry sodium iodide (4.50 g, 30 mmol) and $MeSiCl_3$ (4.50 g, 30 mmol) were dissolved in dry MeCN (60 ml) at r.t. To this soln. was added a soln. of **6c** (5.0 g, 25 mmol) in dry MeCN (15 ml), with stirring, and the mixture heated to reflux. After 9 h, further NaI (0.45 g, 3 mmol) and $MeSiCl_3$ (0.45 g, 3 mmol) were added. After further 2 h, the mixture was allowed to cool to r.t. and then concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ (200 ml), washed with $Na_2S_2O_3$ (aq., 10 ml of a 40% soln.), dried (Na_2SO_4), and concentrated *in vacuo* to give crude **1c** as a brown oil. Chromatography, eluting with AcOEt, gave **1c** as a light brown oil (2.7 g, 57% yield). IR (KBr): 3380 (br.), 2980, 2935, 1745, 1675. ^{1}H-NMR ($CDCl_3$): 4.50 (*m*, 1H); 4.31 (br. *s*, 1H); 4.19 (*q*, J = 7.2, 2H); 4.18 (*d*, J = 17.5, 1H); 3.93 (*d*, J = 17.5, 1H); 3.77 (*dd*, J = 10.4, 5.6, 1H); 3.34 (*dd*, J = 10.4, 1.9, 1H); 2.69 (*dd*, J = 17.4, 6.5, 1H); 2.38 (*dd*, J = 17.4, 2.5, 1H); 1.28 (*t*, J = 7.2, 3H). ^{13}C-NMR ($CDCl_3$): 174.2; 168.8; 64.3; 61.5; 57.0; 44.0; 40.6; 14.1. EI-MS: 186 (1, $[M - 1]^+$), 169 (50), 114 (100), 96 (90).

*Ethyl (4-Acetoxy-1,5-dihydro-2-oxo-2*H*-pyrrol-1-yl)acetate* (**8**). Compound **4c** (59.8 g, 300 mmol) was dissolved in AcOH (240 ml), at r.t., with stirring. The mixture was warmed to 40° and HCl(g) was bubbled through the soln. After 5 h, the HCl(g) addition was stopped. After further 16 h, the mixture was concentrated *in vacuo*, without

the temp. rising above 60°, to give a yellow oil (58.8 g). This oil was dissolved in CH_2Cl_2 (360 ml) with stirring, at −10°, and Ac_2O (32.6 g, 319 mmol) was added. Et_3N (36.79 g, 364 mmol) was added dropwise over 30 min in such a manner that the temp. did not rise above −5°. After 45 min, the mixture was allowed to warm to 0° and washed with HCl (aq.) (2 × 100 ml of 0.01M) and Na_2SO_4 (sat., 50 ml). The org. phase was dried ($MgSO_4$) and concentrated *in vacuo* to give crude **8** (55 g). Crystallisation (AcOEt/hexane) gave **8** (41.6 g, 62%) as light brown needles. M.p. 50–51°. ^{1}H-NMR ($CDCl_3$): 6.02 (*t*, *J* = 1.0, 1 H); 4.25 (*d*, *J* = 1.0, 2 H); 4.21 (*s*, 2 H); 4.20 (*q*, *J* = 7.5, 2 H); 2.28 (*s*, 3 H); 1.29 (*t*, *J* = 7.5, 3 H). EI-MS: 227 (5, M^+), 185 (20), 112 (100), 84 (30), 43 (85).

Ethyl (4-Acetoxy-2-oxopyrrolidin-1-yl)acetate (**9**). Compound **8** (10.0 g, 44 mmol) was dissolved, and 5% Pd/C/$BaSO_4$ (500 mg) was suspended in AcOEt (100 ml), at r.t. with stirring. The mixture was placed under a H_2 atmosphere (10 bar). After 18 h, the mixture was filtered and then concentrated *in vacuo* to give **9** as a light brown oil (10.0 g, 91% pure by GC, 92%). IR (KBr): 2985, 2940, 1745, 1700. ^{1}H-NMR ($CDCl_3$): 5.33 (*m*, 1 H); 4.20 (*q*, *J* = 7.1, 2 H); 4.17 (*d*, *J* = 17.6, 1 H); 3.98 (*d*, *J* = 17.6, 1 H); 3.91 (*dd*, *J* = 11.2, 6.1, 1 H); 3.46 (*dd*, *J* = 11.2, 2.0, 1 H); 2.83 (*dd*, *J* = 17.9, 7.2, 1 H); 2.50 (*dd*, *J* = 17.9, 2.4, 1 H); 2.08 (*s*, 3 H); 1.28 (*t*, *J* = 7.1, 3 H). ^{13}C-NMR ($CDCl_3$): 172.7, 170.6, 168.4, 67.0, 61.5, 54.0, 43.8, 37.2, 20.9, 14.2. EI-MS 230 (1, $[M + 1]^+$), 169 (45), 123 (10), 96 (100), 43 (45).

Oxiracetam (**1a**) *from* **4d** *Using a $NaBH_4$ Reduction.* Compound **4d** (60.0 g, 239 mmol) was dissolved and 5% Pd/C (2.4 g) was suspended in DMA (210 ml), with stirring, at r.t. The mixture was placed under a H_2 atmosphere (5 bar). After 3 h, Pd/C was removed by filtration. The yellow filtrate was added dropwise over 2 h to a soln. of $NaBH_4$ (3.8 g, 138 mmol) in DMA (30 ml), with stirring, at 15°, under an Ar atmosphere. After a further h, MeOH (84.0 ml) was added to the mixture followed by HCOOH (5.6 ml; gas evolution). After 15 min, the $B(OMe)_3$ and excess MeOH were removed *in vacuo*. The precipitated NaCl was removed by filtration and the filtrate concentrated *in vacuo*. The residue was dissolved in H_2O (150 ml), with stirring. After 2 h, the insoluble material was removed by filtration. The filtrate was continuously extracted with CH_2Cl_2, until the DMA content was less than 100 ppm. The aq. phase was passed through a cation-exchange column (120 g of *Dowex 50WX8*) and an anion-exchange column (120 g of *Amberlite IRA 68*), washing with H_2O (300 ml). The aq. soln. was concentrated *in vacuo* to give **1a** as a white amorphous solid. Washing with EtOH and drying gave **1a** as a white amorphous solid (28.9 g, 98.5% pure by HPLC, 75%). M.p. 168–169° ([1a]: 167–170°). The ^{1}H-NMR and IR spectra are in agreement with published data [1a].

(2,4-Dioxopyrrolidin-1-yl)acetamide·Hydrochloride (**5a**·HCl). Compound **4a** (20.0 g, 118 mmol) was dissolved in AcOH (240 ml) at r.t., with stirring. HCl(g) was bubbled through the soln. at 30°. After 2 h, the HCl(g) addition was stopped and the mixture was allowed to cool to r.t. The precipitated product was isolated by filtration and washed with CH_2Cl_2 (2 × 70 ml). Drying (50°/10 mbar) gave **5a**·HCl as a white amorphous solid (21.8 g, 96%). M.p. 190–191°. This material was used without any purification in the next step.

Oxiracetam (**1a**) *from Hydrogenation of* **5a**·*HCl.* The salt **5a**·HCl (5.0 g, 26 mmol) was dissolved, and 5% Ru/C (250 mg) was suspended in H_2O (50 ml), with vigorous stirring at r.t., in an autoclave. The mixture was placed under a H_2 atmosphere (25 bar). After 20 h, the pressure was released and the catalyst removed by filtration. The filtrate was concentrated *in vacuo* to give a brown amorphous solid (5.0 g). This crude product (4.37 g) was dissolved in H_2O and passed through an anion-exchange column (10 g of *Amberlite IRA 60*). Concentration *in vacuo* gave a white amorphous solid mixture (3.31 g) of **1a** (48.2% by HPLC, 45%) and **1b** (26.4% by HPLC, 24%).

Butyl (4-Hydroxy-2-oxopyrrolidin-1-yl)acetate (**1d**). Acid **4d** (46.2 g, 249.5 mmol) was suspended in HCl (aq.) (500 ml of 1M), at r.t., with stirring. The mixture was warmed to 50°, **4d** dissolving completely at 40°. After 2 h, the soln. was cooled to 5°, and NaOH (aq.) (45.1 g of 10M) was added dropwise to adjust the pH to pH 1. This soln. was transferred into an autoclave, and 5% Ru/C (2.5 g) was added. The mixture was placed under a H_2 atmosphere (10 bar), at r.t., and stirred. After 24 h, the catalyst was removed by filtration and the soln. concentrated *in vacuo* to give a thick brown oil. This was dissolved in BuOH (500 ml) and, with vigorous stirring, BuOH/H_2O (300 ml) was distilled off at normal pressure. The residue was filtered to remove the precipitated NaCl and then concentrated *in vacuo* to give crude **1d** (64.4 g, 73.4% pure by HPLC, 88%) as a brown oil. A wiped film distillation (210°/1.5 mm Hg) gave **1d** (52.2 g), which was dissolved in H_2O (210 ml) and continually extracted with toluene for 3 h. The aq. phase was then continually extracted with CH_2Cl_2 for 17 h. The CH_2Cl_2 extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give **1d** as a colourless oil (40.8 g, 76% yield). IR (KBr): 3400–3200 (br.), 2960, 1745, 1675. ^{1}H-NMR ($CDCl_3$): 4.45–4.55 (*m*, 2 H); 4.18 (*d*, *J* = 17.6, 1 H); 4.14 (*t*, *J* = 6.7, 2 H); 3.95 (*d*, *J* = 17.6, 1 H); 3.77 (*dd*, *J* = 10.4, 5.4, 1 H); 3.35 (*dd*, *J* = 10.4, 1.4, 1 H); 2.67 (*dd*, *J* = 17.3, 6.3, 1 H); 2.39 (*dd*, *J* = 17.3, 1.5, 1 H); 1.63 (*m*, 2 H); 1.37 (*m*, 2 H); 0.94 (*t*, *J* = 7.4, 3 H). ^{13}C-NMR ($CDCl_3$): 174.3, 169.0, 65.4, 64.3, 57.0, 44.0, 40.6, 30.5, 19.1, 13.7. EI-MS: 197 (25, $[M - 18]^+$), 114 (100), 96 (90).

Oxiracetam (**1a**) *from Ammonolysis of* **1d**. Ester **1d** (53.4 g, 248 mmol) was dissolved in EtOH/NH_3 (217 g of a 15% NH_3 in EtOH soln.), at r.t., with stirring. The mixture was placed in an autoclave and heated to 50°. After 14 h, the mixture was cooled to r.t. and the autoclave opened. Precipitated **1a** was isolated by filtration and, after drying, gave **1a** as a white amorphous solid (36.29 g, 98.7% pure by HPLC, 93% yield). Recrystallisation of this crude **1a** (34.55 g from above) from H_2O gave **1a** as white prisms (23.05 g, 99.6% pure by HPLC, 65%). M.p. 168–169° ([1a]: 167–170°).

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