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Structural Analogues of γ-Aminobutyric Acid (GABA). Syntheses of a Series of Aminoalkanehydroxamic Acid Hydrochlorides

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The synthesis of six aminoalkanehydroxamic acids which are structural analogues of γ-aminobutyric acid (GABA) are described. The 4-aminobutyro-, 4-aminovalero-, and 3-hydroxy-4-aminobutyrohydroxamic acids (*5a,b*) and (*13*) have been prepared *via* the corresponding Cbz-aminoesters. The 2-hydroxy-4-aminobutyro-, 2-hydroxy-4-aminovalerohydroxamic acids (*19c,e*) were prepared *via* the corresponding isoxazolidines and the 2-hydroxy-5-aminovalerohydroxamic acid (*19d*) was prepared *via* the corresponding perhydro-1,2-oxazine.

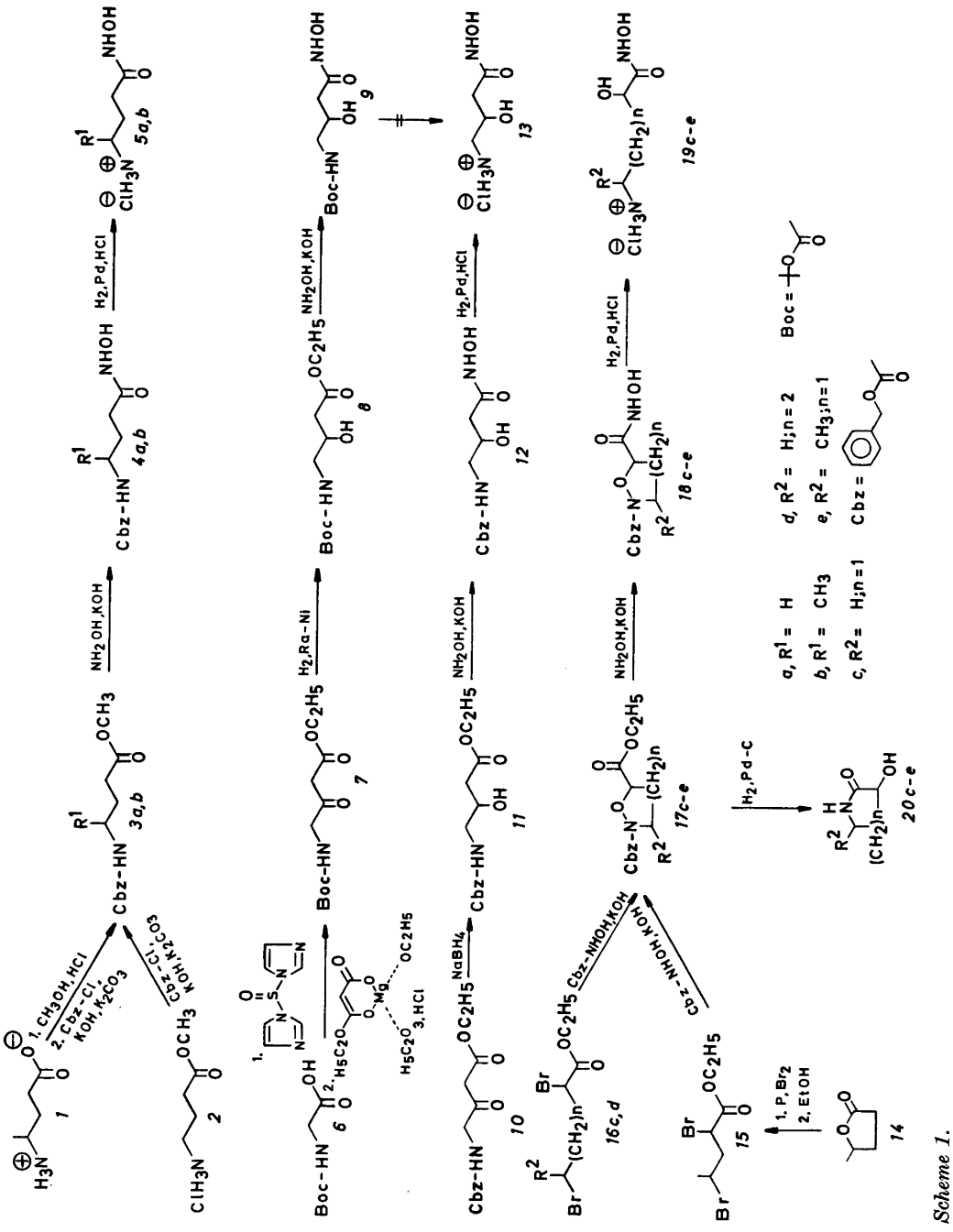
Stimulation of the central γ-aminobutyric acid (GABA) system indirectly accomplished by inhibition of the GABA-metabolizing enzyme, α-ketoglutarate-GABA transaminase (GABA-T), may be of pharmacological interest. Several compounds are reported,[1–6] which selectively inhibit GABA-T. As an attempt to make more specific GABA-T inhibitors available, a series of aminohydroxamic acids structurally related to GABA has been prepared.

The hydroxamic acids *5a,b* and *19c–e* have been tested as inhibitors of the activity *in vitro* of GABA-T isolated from rat brains. 4-Aminobutyrohydroxamic acid *5a* was a weak inhibitor, whereas *5b* and *19c-e* were potent inhibitors of the enzyme. The concentrations of these inhibitors required for 50 % inhibition of enzyme activity were 0.2–0.3 mM, the degree of inhibition being dependent on the time of preincubation with the enzyme preparation. The mechanism of the action of the hydroxamic acids *5b* and *19c–e* as inhibitors of GABA-T activity is being studied.

Preparation of γ-aminohydroxamic acids from the corresponding esters does not seem to be an attractive route, since amino esters containing a free amino group in the γ or δ position spontaneously lactamize.[7,8] Consequently the syntheses of γ- and δ-aminohydroxamic acids must involve a protection of the amino group of the amino esters before treatment with hydroxylamine. The benzyloxycarbonyl group was used as it could be removed selectively as outlined in Scheme 1.

The protected amino esters *3a* and *3b* were obtained by treatment of the corresponding amino ester hydrochlorides with benzyloxycarbonyl chloride. Treatment of *3a* and *3b* with hydroxylamine gave the corresponding hydroxamic acids *4a* and *4b*, which by low pressure hydrogenolysis in the presence of equivalent amounts of 0.1 M HCl were converted to the aminohydroxamic acids *5a* and *5b*.

N-tert-Butyloxycarbonylglycine (*6*) was converted[9] into the β-ketoester *7*. Raney-nickel hydrogenation of *7* gave the β-hydroxyester *8*, which was treated with hydroxylamine to afford the hydroxamic acid *9*. All attempts to remove the *tert*-butyloxycarbonyl group of *9* without hydrolyzing the hydroxamic acid group failed. The aminohydroxamic acid hydrochloride *13* was finally prepared from the β-ketoester *10*, which could be converted into the β-hydroxyester *11* by selective hydrogenation with sodium borohydride. Treatment with hydroxylamine gave the hydroxamic acid *12*, which upon low pressure hydrogenolysis yielded the aminohydroxamic acid hydrochloride *13*.



Scheme 1.

Ethyl 2,4-dibromovalerate (*15*) was prepared [10] from 4-valerolactone (*14*). As established by ^{1}H NMR spectroscopy *15* was a 1:1 mixture of the two diastereomeric forms, which could not be separated on a preparative scale. The isoxazolidines *17c,e* and the perhydro 1,2-oxazine *17d* were prepared [10] from the corresponding dibromoesters *15*, *16c*, and *16d* by treatment with *N*-benzyloxycarbonyl hydroxylamine. The structures of the isox-

azolidines *17c,e* and the perhydro-1,2-oxazine *17d* were confirmed by spectroscopic methods elemental analyses and hydrogenation [8] to the corresponding lactams *20c-e*.

The hydroxamic acids *18c-e* were prepared under mild conditions since the ethyl esters *17c-e* are sensitive to hydrolysis. By repeated column chromatographic (CC) procedures the isoxazolidine hydroxamic acid *18e* was separated in two diastereomeric forms. *18c–e* were converted into the corresponding aminohydroxamic acid hydrochlorides *19c–e* using a method similar to that described for *5a,b*. The relative configurations of the two diastereomeric forms of *19e* as established by X-ray crystallographic methods of the corresponding amino acid [11] obtained by acid hydrolysis of *19e* are given in the experimental part.

EXPERIMENTAL

The determination of melting points, the recording of IR- and ^{1}H NMR spectra (when D_2O is used as solvent, sodium 3-(trimethylsilyl)propanesulfonate is used as internal reference), and the microanalyses were performed as described in a previous paper.[12] TLC and CC were accomplished using silica gel GF_{254} plates (Merck) and silica gel 0.05–0.20 mm (Merck), respectively. The silica gel used for CC of the hydroxamic acids *4a*, *18c-e*, and *9* was purified according to the method of Seiler and Rothweiler.[13] The pK_A values were determined according to the method of Albert and Serjeant.[14]

Methyl N-*benzyloxycarbonyl-4-aminobutyrate* (3a). An ice-cooled solution of 5.0 g (90 mmol) of KOH and 20.0 g (140 mmol) of K_2CO_3 in 150 ml of water was added to a solution, cooled to −5 °C, of 15.0 g (100 mmol) of *2* [15] in 50 ml of water. To the solution was rapidly added 30.0 g (190 mmol) of benzyloxycarbonyl chloride with stirring, which was continued at −5 °C for 1 h and at 25 °C for 1 h. The reaction mixture was extracted with five 150 ml portions of methylene chloride. The combined methylene chloride phases were dried (Na_2SO_4) and evaporated *in vacuo* to give an oil, which was submitted to CC (eluent: benzene–ethyl acetate 3:1 to which increasing amounts of ethyl acetate were added). Yield 13.7 g (55 %). Anal. $C_{13}H_{17}NO_4$: C, H, N. IR (film): 3340 (m), 3030 (w), 2950 (m), 1720 (s), 1530 (m) cm^{-1}. ^{1}H NMR (CCl_4): δ 7.17 (5 H, s), 5.27 (1 H, broad signal), 4.87 (2 H, s), 3.47 (3 H, s), 3.05 (2 H, q, J 6.0 Hz), 2.4–1.4 (4 H, m).

Methyl N-*benzyloxycarbonyl-4-aminovalerate* (3b). To a solution of 5.2 g (45 mmol) of *1* [16] in 100 ml of methanol was added 5 g of HCl. The solution was refluxed for 24 h. The esterification was followed by TLC (eluent: butanol–glacial acetic acid–water 4:1:1, spraying agent ninhydrin). The reaction mixture was evaporated *in vacuo* to give a viscous oil which was treated as described for the preparation of *3a* using 2.3 g (41 mmol) of KOH, 4.0 g (63 mmol) of K_2CO_3, and 9.2 g (54 mmol) of benzyloxycarbonyl chloride. Yield 5.4 g (45 %). An analytical sample was recrystallized from cyclohexane, m.p. 66.7–67.7 °C. Anal. $C_{14}H_{19}NO_4$: C, H, N. IR (KBr): 3300 (s), 3070 (w), 2975 (m), 1735 (s), 1705 (s), 1680 (s), 1555 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.33 (5 H, s), 5.2–4.3 (3 H, broad signal containing a singlet), 3.9–3.4 (4 H, broad signal containing a singlet), 2.37 (2 H, t, J 8.0 Hz), 1.9–1.5 (2 H, m), 1.15 (3 H, d, J 6.0 Hz).

N-*Benzyloxycarbonyl-4-aminobutyrohydroxamic acid* (4a). To an ice-cooled solution of 10.0 g (40 mmol) of *3a* in 30 ml of methanol was added an ice-cooled solution of 11.0 g (160 mmol) of NH_2OH, HCl and 13.4 g (200 mmol) of KOH in 150 ml of methanol. After standing for 5 days at 8 °C 17 ml (280 mmol) of glacial acetic acid were added to the reaction mixture. After filtration and evaporation *in vacuo* the reaction mixture was submitted to CC (eluent: benzene–ethyl acetate–methanol–formic acid 60:30:10:1 to which increasing amounts of methanol were added). Yield 5.0 g (50 %), m.p. 104.0–106.0 °C (decomp.). Anal. $C_{12}H_{16}N_2O_4$: C, H, N. IR (KBr): 3320 (s), 3050 (broad signal, m), 2800 (broad signal, m), 1690 (s), 1660 (s), 1620 (m), 1550 (s) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 10.57 (0.6 H, broad signal), 8.77 (0.6 H, broad signal), 7.33 (5 H, s), 4.97 (2 H, s), 3.37 (1.8 H, broad signal), 3.33–2.77 (2 H, m), 2.17–1.33 (4 H, m).

N-*Benzyloxycarbonyl-4-aminovalerohydroxamic acid* (4b). *4b* was prepared as described above for *4a* using 10.6 g (40 mmol) of *3b*, 2.8 g (40 mmol) of NH_2OH, HCl, and 5.4 g (80 mmol) of KOH. The evaporated reaction mixture was mixed with 75 ml of water and extracted twice with 100 ml of ethyl acetate. The combined organic phases were dried (Na_2SO_4), evaporated *in vacuo* and crystallized from benzene–ethanol to give 5.7 g (54 %), m.p. 124.3–125.3 °C (decomp.). Anal. $C_{13}H_{18}N_2O_4$: C, H, N. IR (KBr): 3600–2600 (broad signal, m), 3335 (s), 2965 (m), 1685 (s), 1655 (m), 1620 (s), 1535 (s) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 10.45 (1 H, s), 8.80 (1 H, s), 7.31 (5 H, s), 4.94 (2 H, s), 3.78–3.08 (2 H, broad signal containing a singlet), 2.15–1.20 (4 H, m), 1.01 (3 H, d, J 6.0 Hz).

4-Aminobutyrohydroxamic acid hydrochloride (5a). To a solution of 2.0 g (8 mmol) of *4a* in 120 ml of methanol was added 8 mmol of 0.1 M HCl and the mixture was hydrogenated (101 kPa) in a PARR hydrogenation apparatus using 250 mg of Pd black as a catalyst. After 1 h the reaction mixture was filtered and

evaporated *in vacuo* to give 900 mg of crude product. Recrystallization from ethanol gave 564 mg (50 %), m.p. 112.8 – 113.8 °C (decomp.). Anal. $C_4H_{11}ClN_2O_2$: C, H, Cl, N. IR (KBr): 3350 – 2900 (s, several broad bands), 2800 (m), 1640 (s), 1600 (m), 1520 (m), 1500 (m) cm^{-1}. pK_A values (H_2O, 21 °C): 9.4 ± 0.9, 10.5 ± 0.2. ^1H NMR (D_2O): δ 4.73 (*ca.* 6 H, s), 3.00 (2 H, t, *J* 7.0 Hz), 2.4 – 1.7 (4 H, m).

4-Aminovalerohydroxamic acid hydrochloride (5b). *5b* was prepared as described above for *5a* using 3.5 g (13.2 mmol) of *4b*, 13.2 mmol of 0.1 M HCl and 0.5 g of Pd black catalyst. Yield 2.5 g of a hygroscopic glassy substance, which by TLC (butanol – acetic acid – water 4:1:1) only gave one spot (R_F value 0.06) when visualized with ninhydrin, $FeCl_3$, and iodine vapour, respectively. (Found: C 34.30; H 8.19; N 13.60; Cl 19.05. Calc. for $C_5H_{13}ClN_2O_2$: C 35.62; H 7.77; N 16.61; Cl 21.02). IR (film): 3500 – 2700 (s, several broad bands), 1655 (s), 1515 (m), 1445 (m), 1390 (m) cm^{-1}. ^1H NMR (D_2O): δ 4.67 (*ca.* 8 H, s), 3.47 – 3.19 (1 H, m), 2.67 – 1.65 (4 H, m), 1.30 (3 H, d, *J* 6.5 Hz).

Ethyl N-tert-*butyloxycarbonyl-3-oxo-4-aminobutyrate (7).* To a solution of 36.0 g (200 mmol) of *6* in 100 ml of THF was added a solution of 36.4 g (200 mmol) of *N,N'*-thionyldiimidazole [9] in 500 ml of THF. The reaction mixture was concentrated *in vacuo* to 300 ml. This solution was added to a stirred solution of 73.2 g (300 mmol) of malonic acid monoethylester diethoxy magnesium enolate [9] in 550 ml of THF. After the addition was completed, the reaction mixture was stirred for 2 h followed by addition of 950 ml 0.1 M HCl (pH ~3), and additional stirring for 1 h. The layers were separated, and the aqueous phase was extracted with five 100 ml portions of ether. The combined organic phases were extracted with five 100 ml portions of 1 % aqueous $NaHCO_3$, with two 100 ml portions of water, dried ($MgSO_4$) and evaporated *in vacuo* to give 37.7 g of an oil. The oil was submitted to CC (eluent: benzene – ethyl acetate 86:14 to which increasing amounts of ethyl acetate were added). Yield 29.6 g (60 %). (Found: C 53.50; H 7.53; N 6.28. Calc. for $C_{11}H_{19}NO_5$: C 53.86; H 7.81; N 5.71). IR (film): 3385 (m), 2980 (m), 2940 (w), 1745 (s), 1720 (s), 1515 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.25 (1 H, broad signal), 4.38 – 3.87 (4 H, m), 3.48 (2 H, s), 1.51 – 1.05 (12 H, m).

Ethyl N-*benzyloxycarbonyl-3-hydroxy-4-aminobutyrate (11).* A solution of 15.0 g (54 mmol) of *10*[17] in 500 ml of ethanol was cooled on ice and an ice-cooled solution of 1.56 g (41 mmol) of $NaBH_4$ in 270 ml of ethanol was added. After 30 m the reaction mixture was evaporated *in vacuo*, dissolved in 500 ml of ether and extracted with 300 ml of 1 M $NaHSO_4$, 300 ml of 1 m $NaHCO_3$, and 300 ml of water. The organic phase was dried ($MgSO_4$) and evaporated *in vacuo* to give 8.9 g of an oil which was submitted to CC (eluent: toluene – ethyl acetate (2:1) to which increasing amounts of ethyl acetate were added). Yield 6.7 g (44 %). Anal. $C_{14}H_{19}NO_5$: C, H, N. IR (film): 3365 (s), 3070 (w), 3035 (w), 2985 (m), 1720 (s), 1535 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.31 (5 H, s), 5.55 – 5.15 (1 H, broad signal), 5.05 (2 H, s), 4.31 – 3.89 (3 H, m), 3.68 – 3.44 (1 H, broad signal), 3.38 – 3.05 (2 H, m), 2.43 (2 H, d, *J* 6.0 Hz), 1.24 (3 H, t, *J* 6.0 Hz).

N-*Benzyloxycarbonyl-3-hydroxy-4-aminobutyrohydroxamic acid (12).* *12* was prepared as described above for *4b* using 5.6 g (20 mmol) of *11*, 1.4 g (20 mmol) of NH_2OH, HCl and 2.7 g of KOH. Recrystallization (benzene) gave 2.0 g (37 %) (84 % based on non-recovered starting material), m.p. 122.2 – 123.1 °C (decomp.). Anal. $C_{12}H_{16}N_2O_5$: C, H, N. IR (KBr): 3455 (s), 3370 (s), 3215 (s), 3045 (m), 2965 (w), 1670 (s), 1630 (s), 1540 (s) cm^{-1}. ^1H NMR (DMSO-d_6): δ 7.44 – 6.75 (8 H, broad signal containing a singlet at 7.33), 5.04 – 4.48 (3 H, broad signal containing a singlet at 4.96), 4.10 – 3.41 (2 H, m), 2.97 (2 H, t, *J* 6.0 Hz), 2.01 (2 H, d, *J* 5.5 Hz).

3-Hydroxy-4-aminobutyrohydroxamic acid hydrochloride (13). *13* was prepared as described above for *5a* using 1.9 g (7 mmol) of *12*, 7 mmol of 0.1 M HCl, and 0.2 g of Pd black catalyst. Yield 1.0 g of a hygroscopic glassy substance, which by TLC (butanol – acetic acid – water 4:1:1) only gave one spot (R_F value 0.14) when developing with ninhydrin, $FeCl_3$, and iodine vapour, respectively. (Found: C 28.00; H 7.10; N 15.41; Cl 20.15. Calc. for $C_4H_{11}N_2O_3Cl$: C 28.16, H 6.50, N 16.42, Cl 20.78). IR (film): 3650 – 2400 (s, broad band), 1660 (s), 1510 (m), 1450 (w) cm^{-1}. ^1H NMR (D_2O): δ 4.39 – 3.93 (1 H, m), 3.15 – 2.78 (2 H, m), 2.48 (2 H, d, *J* 6.0 Hz).

Ethyl 2,4-dibromovalerate (15). *15* was synthesized from 100.0 g (1 mol) of *14*, 12.0 g (39 mmol) of red phosphorus, 328.0 g (2 mol) of bromine, and 370.0 g (8 mol) of ethanol by a method analogous to that described [10] for the preparation of *16c*. Obtained was 202.0 g (70 %), b.p. 122 – 124 °C/1.73 kPa. Anal. $C_7H_{12}O_2Br_2$: C, H, Br. IR (film): 2985 (m), 2920 (w), 2865 (w), 1735 (s), 1445 (m), 1380 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.64 – 3.70 (4 H, m), 2.64 – 2.15 (2 H, m), 1.76 and 1.72 (3 H, a double d, *J* 6.5 Hz), 1.31 (3 H, t, *J* 7.5 Hz).

2-Benzyloxycarbonyl-5-ethoxycarbonylisoxazolidine (17c). To a solution of 38.4 g (140 mmol) of *16c*[10] in 80 ml of ethanol was added a mixture of 25.0 g (150 mmol) of *N*-benzyloxycarbonylhydroxylamine [18] dissolved in 120 ml of ethanol and 20.0 g (300 mmol) of KOH dissolved in 280 ml of ethanol. The reaction mixture was refluxed for 1 h. After cooling to room temperature the reaction mixture was filtered and evaporated *in vacuo* to give a crude oil. The oil was dissolved in 1000 ml of benzene and extracted with two 250 ml portions of 0.1 M NaOH followed by 250 ml of water. The organic phase was dried (Na_2SO_4) and

evaporated *in vacuo* to give an oil, which was submitted to CC (eluent: benzene – ethyl acetate 9:1 to which increasing amounts of ethyl acetate were added). Yield 9.3 g (24 %). An analytical sample was purified by ball-tube distillation at 133 Pa (oven temperature 210 °C). Anal. $C_{14}H_{17}NO_5$: C, H, N. IR (film): 3085 (w), 3050 (w), 3000 (m), 2920 (w), 1745 (s), 1510 (m), 1460 (m), 1400 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.30 (5 H, s), 5.11 (2 H, s), 4.69 (1 H, t, J 7.0 Hz), 4.28 – 3.53 (4 H, m), 2.41 (2 H, q, J 7.5 Hz), 1.20 (3 H, t, J 7.5 Hz).

2-Benzyloxycarbonyl-6-ethoxycarbonylperhydro-1,2-oxazine (17d). *17d* was prepared as described above for *17c* using 13.4 g (47 mmol) of *16d*,[19] 8.7 g (52 mmol) of *N*-benzyloxycarbonylhydroxylamine, and 6.0 g (90 mmol) of KOH. Obtained was 7.7 g (56 %) of an oil. An analytical sample was purified by ball-tube distillation at 40 Pa (oven temperature 195 °C) to give an oil. Anal. $C_{15}H_{19}NO_5$: C, H, N. IR (film): 3065 (w), 3040 (w), 2950 (m), 1735 (s), 1710 (s), 1505 (m), 1450 (m), 1410 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.34 (5 H, s), 5.14 (2 H, s), 4.58 – 3.08 (5 H, m), 2.16 – 1.43 (4 H, m), 1.25 (3 H, t, J 7.0 Hz).

2-Benzyloxycarbonyl-3-methyl-5-ethoxycarbonylisoxazolidine (17e). *17e* was prepared as described above for *17c* using 50.0 g (170 mmol) of *15*, 31.2 g (190 mmol) of *N*-benzyloxycarbonylhydroxylamine, and 21.3 g (320 mmol) of KOH. Yield 14 g (28 %). An analytical sample was purified by ball-tube distillation at 133 Pa (oven temperature 198 °C). Anal. $C_{15}H_{19}NO_5$: C, H, N. IR (film): 3050 (w), 3025 (w), 2970 (m), 2920 (w), 1730 (s), 1700 (s), 1495 (m), 1475 (m), 1450 (m), 1385 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.29 (5 H, s), 5.11 (2 H, s), 4.67 – 3.76 (4 H, m), 2.90 – 1.71 (2 H, m) 1.46 – 1.00 (6 H, m).

2-Benzyloxycarbonyl-5-hydroxyaminocarbonylisoxazolidine (18c). To an ice-cooled solution of 5.6 g (20 mmol) of *17c* in 40 ml of methanol was added an ice-cooled solution of 2.8 g (40 mmol) of NH_2OH, HCl in 50 mmol of 1 M methanolic KOH. After stirring for 2 h at 0 °C 5 ml (83 mmol) of glacial acetic acid was added to the reaction mixture which was filtered and evaporated *in vacuo* to an oil, which was submitted to CC (eluent: ethyl acetate – formic acid 99:1). Yield 2.5 g (47 %). IR (film): 3240 (broad signal, s), 3060 (w), 3035 (w), 2950 (w), 2900 (w), 1710 (s), 1675 (s), 1500 (m), 1450 (m), 1390 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 9.95 – 7.60 (2 H, broad signal), 7.30 (5 H, s), 5.10 (2 H, s), 4.63 (1 H, t, J 7.5 Hz), 4.05 – 3.00 (2 H, m), 2.83 – 2.10 (2 H, m).

2-Benzyloxycarbonyl-5-hydroxyaminocarbonylperhydro-1,2-oxazine (18d). *18d* was prepared as described above for *18c* using 7.2 g (25 mmol) of *17d* and 3.5 g (50 mmol) of NH_2OH, HCl and 63 mmol of 1 M methanolic KOH. CC using benzene – ethyl acetate – methanol – formic acid (60:30:10:1) to which increasing amounts of methanol were added gave 5.2 g (74 %). IR (film): 3500 – 2550 (several broad signals, s), 1725 – 1655 (several bands, s), 1500 (m), 1450 (m), 1410 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 9.39 – 8.33 (2 H, broad signal), 7.31 (5 H, s), 5.11 (2 H, s), 4.58 – 4.20 (1 H, m), 3.78 – 3.18 (2 H, m), 2.22 – 1.41 (4 H, m).

2-Benzyloxycarbonyl-3-methyl-5-hydroxyaminocarbonylisoxazolidine (18e). *18e* was prepared as described above for *18d* using 5.9 g (20 mmol) of *17e* and 2.8 g (40 mmol) of NH_2OH, HCl and 50 mmol of 1 M methanolic KOH. Yield 5.5 g (98 %). The product was a mixture of two compounds as shown by TLC (methylene chloride – methanol – formic acid 95:5:0.5), compound A has $R_F = 0.23$, and B has $R_F = 0.17$. After CC three times (eluent: methylene chloride – methanol – formic acid 95:5:0.5) 1.0 g of pure A as crystals and 0.9 g of B as an oil were obtained.

Compound A: m.p. 85.3 – 87.3 °C (decomp.). Anal. $C_{13}H_{16}N_2O_5$: C, H, N. IR (KBr): 3400 – 3100 (several broad signals, m), 3035 (w), 2980 (w), 1710 (s), 1675 (s), 1500 (w), 1460 (m), 1450 (m) cm^{-1}. ^1H NMR (DMSO-d_6): δ 10.78 (1 H, s), 9.13 (1 H, s), 7.33 (5 H, s), 5.00 (2 H, s), 4.58 – 3.97 (2 H, m), 2.76 – 1.66 (2 H, m), 1.18 (3 H, d, J 7.0 Hz).

Compound B: IR (film): 3235 (broad signal, m), 3040 (w), 2985 (w), 1710 (s), 1680 (s), 1500 (w), 1460 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.30 (2 H, broad signal), 7.33 (5 H, s), 5.10 (2 H, s), 4.37 – 3.85 (2 H, m), 2.93 – 1.73 (2 H, m), 1.23 (3 H, d, J 6.5 Hz).

2-Hydroxy-4-aminobutyrohydroxamic acid hydrochloride (19c). *19c* was prepared as described above for *5a* using 1.8 g (6.8 mmol) of *18c*, 6.8 mmol of 0.1 M HCl, and 100 mg of Pd black catalyst. After 2 h the reaction mixture was evaporated *in vacuo* and crystallized from methanol – ether to give 900 mg (77 %) of crystals, m.p. 144.5 – 145.5 °C (decomp.). Anal $C_4H_{11}ClN_2O_3$: C, H, Cl, N. IR (KBr): 3340 (s. broad signal), 3125 (s, broad signal), 2935 (w), 1645 (s), 1500 (m) cm^{-1}. pK_A values (H_2O, 25 °C): 8.5 ± 0.1, 10.42 ± 0.05. ^1H NMR (D_2O): δ 4.73 (*ca.* 6 H, s), 4.45 – 4.10 (1 H, m), 3.13 (2 H, t, J 7.0 Hz), 2.30 – 1.78 (2 H, m).

2-Hydroxy-5-aminovalerohydroxamic acid hydrochloride (19d). *19d* was prepared as described above for *5a* using 1.0 g (3.6 mmol) of *18d*, 3.6 mmol of 0.1 M HCl, and 100 mg of Pd black catalyst. After 6 h the reaction mixture was evaporated *in vacuo* and crystallized from methanol – ether to give 400 mg (60 %) crystals, m.p. 116.0 – 117.0 °C (decomp.). Anal. $C_5H_{13}N_2O_3Cl$: C, H, Cl, N. IR (KBr): 3385 (s), 3285 (s), 3075 (s, broad signal), 2925 (m), 2850 (m), 1640 (s), 1570 (m), 1500 (s) cm^{-1}. pK_A values (H_2O, 25 °C): 8.57 ± 0.01, 10.56 ± 0.05. ^1H NMR (D_2O): δ 4.66 (6 H, s), 4.29 – 3.91 (1 H, m), 3.31 – 2.64 (2 H, m), 2.29 – 1.36 (4 H, m).

(2RS,4RS)-2-Hydroxy-4-aminovalerohydroxamic acid hydrochloride (19e). *19e* was prepared as described above for *5a* using 0.8 g

(2.9 mmol) of *18eB*, 2.9 mmol of 0.1 M HCl and 50 mg of Pd black. Recrystallization from ethanol gave 350 mg (65 %), m.p. 139.0–141.0 °C (decomp.). Anal. $C_5H_{13}ClN_2O_3$: C, H, Cl, N. IR (KBr): 3400–2865 (several broad bands, s), 1655 (s), 1515 (m), 1500 (m), 1390 (m) cm^{-1}. pK_A values (H_2O, 25 °C): 10.0 ± 1.2, 10.3 ± 0.2. ^1H NMR (D_2O): δ 4.74 (*ca.* 6 H, s), 4.48–4.08 (1 H, m), 3.78–3.20 (1 H, m), 2.13–1.70 (2 H, m), 1.35 (3 H, d, J 6.5 Hz).

(2RS,4SR)-2-Hydroxy-4-aminovalerohydroxamic acid hydrochloride (19e). 19e was prepared as described above for *5a* using 1.0 g of Pd black. Recrystallization from ethanol gave 450 mg (68 %), m.p. 121.0–122.0 °C (decomp.). Anal. $C_5H_{13}ClN_2O_3$: C, H, Cl, N. IR (KBr): 3600–2765 (several broad bands, s), 1665 (s), 1505 (m), 1390 (m) cm^{-1}. pK_A values (H_2O, 25 °C): 8.6 ± 0.4, 10.2 ± 0.1. ^1H NMR (D_2O): 4.74 (*ca.* 6 H, s), 4.58–4.23 (1 H, m), 3.77–3.18 (1 H, m), 2.19–1.88 (2 H, m) 1.35 (3 H, d, J 6.5 Hz).

3-Hydroxypyrrolidone-(2) (20c). A solution of 250 mg (0.9 mmol) of *17c* in 50 ml of ethanol was hydrogenated (355 kPa) in a PARR hydrogenation apparatus using 50 mg of a Pd/C 10 % catalyst. After 2 h the reaction mixture was filtered, evaporated *in vacuo* and purified by ball-tube distillation at 200 Pa (oven temperature 200 °C) to give 66 mg (65 %) of an oil, which crystallized upon standing, m.p. 81.5–83.5 °C. Anal. $C_4H_7NO_2$: C, H, N. IR (KBr): 3350 (s, broad signal) 2975 (w), 2870 (w), 1685 (s), 1495 (w), 1290 (m) cm^{-1}. ^1H NMR ($CDCl_3$-DMSO-d_6, 3:2): δ 7.80–7.35 (1 H, broad signal), 5.60–5.05 (1 H, broad signal), 4.15 (1 H, t, J 8.5 Hz), 3.45–3.05 (2 H, m), 2.45–1.65 (2 H, m). (Lit. (10) m.p. 82–84 °C. IR (KBr): 1690 cm^{-1}).

3-Hydroxypiperidone-(2) (20d). 20d was prepared as described above for *20c* using 500 mg (1.7 mmol) of *17d* and 50 mg of a Pd/C 10 % catalyst. Recrystallization from ethyl acetate gave 150 mg (77 %), m.p. 135.0–137.0 °C. Anal. $C_5H_9NO_2$: C, H, N. IR (KBr): 3300 (s, broad signal), 2950 (m), 2860 (w), 1655 (s), 1500 (m), 1425 (m), 1320 (m) cm^{-1}. ^1H NMR ($CDCl_3$-DMSO-d_6, 3:2): δ 7.75–7.15 (1 H, broad signal), 4.75 (1 H, s), 4.15–3.75 (1 H, m), 3.40–3.00 (2 H, m), 2.15–1.35 (4 H, m). (Lit. (20) m.p. 133–135 °C).

3-Hydroxy-5-methylpyrrolidone-(2) (20e). 20e was prepared as described above for *20c* using 250 mg (0.9 mmol) of *17e* and 50 mg of Pd/C 10 % catalyst. Yield 77 mg (74 %), m.p. 115.0–117.0 °C. Anal. $C_5H_9NO_2$: C, H, N. IR (KBr): 3320 (s, broad signal), 2960 (w), 2870 (w), 1690 (s), 1450 (w), 1385 (w), 1345 (m), 1290 (m) cm^{-1}. ^1H NMR ($CDCl_3$-DMSO-d_6, 3:2): δ 7.75–7.40 (1 H, broad signal), 5.55–5.05 (1 H, broad signal), 4.35–3.95 (1 H, m), 3.85–3.10 (2 H, m), 2.30–1.40 (1 H, m), 1.15 and 1.05 (3 H, a double d, J 6.5 Hz).

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