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# Organic Hydroxylamine Derivatives. X.* Structural Analogues of γ-Aminobutyric Acid (GABA) of the Isoxazole Enol-betaine Type. Synthesis of 5,6,7,8-Tetrahydro-4*H*-isoxazolo[4,5-*d*]azepin-3-ol Zwitterion and 4,5,6,7-Tetrahydroisoxazolo[4,5-*c*]pyridin-3-ol Zwitterion

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The syntheses of the isoxazole enol-betaines 5,6,7,8-tetrahydro-4*H*-isoxazolo[4,5-*d*]azepin-3-ol zwitterion (VIII) and 4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridin-3-ol zwitterion (IX), both of which are new heterocyclic compounds, are described. The syntheses of (VIII) and (IX) are based on an acid catalyzed hydrolysis and subsequent cyclization of the ethylene ketals of the appropriate β-oxohydroxamic acids. The constitutions of (VIII) and (IX) are established by spectroscopic methods. The $pK_A$ values of (VIII) and (IX) have been determined to be $4.84 \pm 0.05$ and $9.20 \pm 0.02$, and $4.33 \pm 0.05$ and $9.06 \pm 0.04$, respectively. On the basis of Dreiding stereomodels the most probable conformers of (VIII) and (IX) are postulated.

Structure-activity correlations of conformationally restricted analogues of γ-aminobutyric acid (GABA) play a decisive part in the elucidations of the structural characteristics of the GABA receptors and of the active sites of the GABA transaminase enzymes.[1-5] As part of our investigations of the active conformations of GABA, syntheses and X-ray structure determinations of GABA analogues of the isoxazole enol-betaine type have been performed.[6-9] At present we are synthesizing a series of model compounds, which are conformationally restricted bicyclic isoxazole enol-betaines in which the *intra*-molecular distance between the zwitterionic centers is systematically changed. This paper presents the syntheses of two members of this series, namely 5,6,7,8-tetrahydro-4*H*-isoxazolo[4,5-*d*]azepin-3-ol zwitterion (VIII) and 4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridin-3-ol zwitterion (IX), which are structural analogues of GABA and β-alanine, respectively. Studies of Dreiding stereomodels seem to indicate that two conformers of (VIII) (A and B in Fig. 1) are almost equally favourable, whereas (IX) can adopt only one almost frozen conformation. The approximate *intra*-molecular distances between the charged oxygen atoms and the charged nitrogen atoms in the respective conformers of (VIII) and (IX) are shown in Fig. 1.

An X-ray diffraction analysis of (VIII) is in progress, and investigations of the biological properties of (VIII) and (IX) will be initiated in the near future.

The syntheses of the 3-hydroxyisoxazoles (VIa – c) were accomplished utilizing a reaction sequence analogous to that described by Jacquier *et al.*[10] for the preparation of 3-hydroxyisoxazoles using β-oxoesters as starting materials. The cyclic β-oxoesters (IIIb,c) were synthesized by reaction of compound (I) with ethyl and methyl chloroformate, respectively. The compounds (II) and (IIIb,c) were converted into the dioxolanes (IVa – c), which in turn were transformed into the corresponding hydroxamic acids (Va – c). Attempts to accomplish acid catalyzed hydrolyses and subsequent cyclizations of the

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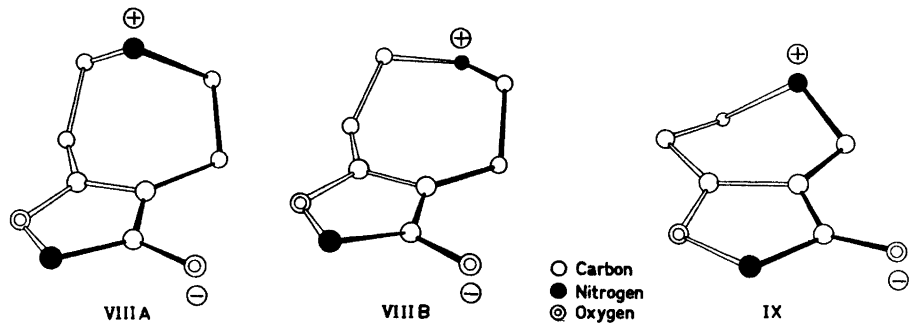
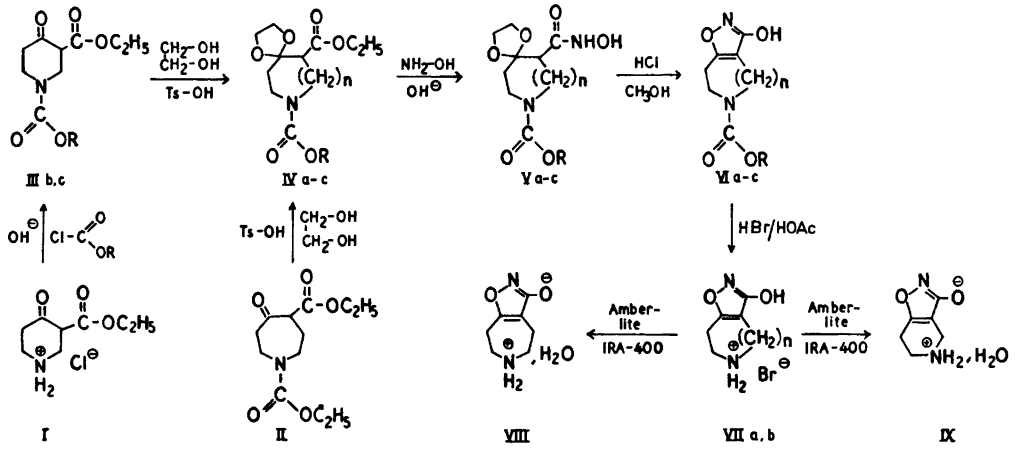



*Fig. 1.* Some structural characteristics of 5,6,7,8-tetrahydro-4*H*-isoxazolo[4,5-*d*]azepin-3-ol (VIII) and 4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridin-3-ol (IX). The structural similarities of VIII and IX to GABA and β-alanine, respectively, are indicated by heavy black lines. The $N^+$ to $O^-$ distances were estimated by measurements on Dreiding stereomodels: 4.5 Å (VIIIA), 5.3 Å (VIIIB), 4.4 Å (IX). $pK_A$-Values ($H_2O$): 4.84 ± 0.05, 9.20 ± 0.02 (17 °C; VIII); 4.33 ± 0.05, 9.06 ± 0.04 (20 °C; IX).

crude reaction products of the dioxolane hydroxamic acids (Va – c) to give the corresponding 3-hydroxyisoxazoles (VIa – c) according to the method described by Jacquier *et al.*[10] were rather unsuccessful. Thus in all cases complex reaction mixtures were obtained, from which no products were isolated. Isolation of the hydroxamic acids (Va – c) in a pure state using chromatography on silica gel columns and subsequent treatment of (Va – c) with hydrochloric acid, however, gave the 3-hydroxyisoxazoles (VIa – c) in moderate to good yields.

Cleavage of (VIa – c) to the corresponding hydrobromides (VIIa,b) was accomplished by treatment with 43 % solutions of hydrogen bromide in glacial acetic acid. The drastic reaction conditions including prolonged heating requisite for the cleavage of the ethoxycarbonyl group of (VIa,b) caused some decomposition of the compounds, especially of (VIb). The methoxycarbonyl group of (VIc), however, was easily cleaved by the above mentioned reagent to give (VIIb) in a pure state and in a high yield. The enol-betaines (VIII) and (IX) were




*Scheme 1.*

isolated from (VIIa,b), respectively, using a strongly basic ion exchange resin, and both compounds crystallized as monohydrates. The $pK_A$ values of (VIII) and (IX) are $4.84 \pm 0.05$ and $9.20 \pm 0.02$, and $4.33 \pm 0.05$ and $9.06 \pm 0.04$, respectively.

The structure determinations of (IIIb,c), (IVa–c), and (Va–c) are based on IR and $^1$H NMR spectroscopy and are supported by elemental analyses. Carbonyl absorption bands in the IR spectra of (IIIb,c) at 1660 cm$^{-1}$ supported by resonance signals in the $^1$H NMR spectra in tetrachloromethane solutions at $\delta$ *ca.* 12 and of intensities corresponding to 0.6 H and 0.8 H, respectively, reveal that the $\beta$-ketoesters (IIIb,c) are largely in the *intra*-molecular hydrogen bonded enol form. Structure elucidations of the 3-hydroxyisoxazoles (VIa–c) and (VIIa,b) were performed by IR, UV, and $^1$H NMR spectroscopy and were supported by elemental analyses. The spectroscopic data originating in the 3-hydroxyisoxazole moieties of (VIa–c) and (VIIa,b) are in accordance with the general findings described by Jacquier *et al.*[10]

The aromatic character of the isoxazole nucleus of (VIII) and (IX) is evident from the IR absorption bands in the 1520–1460, 1630–1600, and 1680–1650 cm$^{-1}$ regions.[11] Absorptions over the range 3600–1900 cm$^{-1}$ and at 2140 and 2250 cm$^{-1}$, respectively, suggest ammonium salt character of (VIII) and (IX). The UV maxima of (VIII) and (IX) at 216 and 215 nm, respectively, are in agreement with those observed (210 and 211 nm, respectively) for 3-hydroxy-5-(2-aminoethyl)isoxazole,[8] and 3-hydroxy-5-(3-aminopropyl)isoxazole,[12] the structures of which have been established by X-ray diffraction analyses.[8,12] The above mentioned

*Table 1.* Some IR and UV data of the compounds (III)-(IX).

| | IR data[a] (cm$^{-1}$) | UV data[b] $\lambda_{max}$(nm) | $\varepsilon \times 10^{-3}$ |
|---|---|---|---|
| IIIb[c] | 3600–3100(w), 1760(m), 1700(s), 1600(s), 1620(m) | | |
| IIIc[c] | 3600–3100(w), 1730(m), 1710(s), 1660(s), 1620(m) | | |
| IVa[c] | 1730(s), 1690(s) | | |
| IVb[c] | 1730(s), 1700(s) | | |
| IVc[c] | 1730(s), 1710(s) | | |
| Va[d] | 3700–3000(m), 1685(s), 1675(s) | | |
| Vb[d] | 3600–3000(m), 1690(s), 1675(s) | | |
| Vc[d] | 3600–3000(m), 1695(s), 1690(s) | | |
| VIa | 3600–2100(s), 1695(s), 1650(m), 1540(s) | 213 | 5.86 |
| VIb | 3600–2100(s), 1705(s), 1675(m), 1550(m), 1535(m) | 211 | 6.55 |
| VIc | 3600–2100(s), 1705(s), 1675(m), 1550(m), 1535(m) | 212 | 6.23 |
| VIIa | 3700–3300(m), 3300–2300(m), 1665(m), 1590(m), 1530(s) | 211 | 6.23 |
| VIIb | 3700–3300(s), 3300–2300(s), 1670(s), 1630(m), 1610(m), 1540(s) | 210 | 5.77 |
| VIII | 3700–1800(s), 2140(w), 1660(s), 1630(m), 1500–1420(s) | 216 | 4.65 |
| IX | 3700–1800(s), 2250(m), 1675(s), 1615(m), 1510–1430(s) | 215 | 5.31 |

[a] Unless otherwise stated the IR spectra were recorded in the solid state (KBr). [b] The UV spectra were recorded in ethanol solutions. [c] The IR spectra were recorded using the film technique. [d] The IR spectra were recorded in chloroform solutions.

observations combined provide conclusive evidence of the proposed constitutions of (VIII) and (IX).

Some spectroscopic data of the new compounds (IIIb,c), (IVa–c), (Va–c), (VIa–c), (VIIa,b), (VIII), and (IX) are listed in Table 1.

## EXPERIMENTAL

Unless otherwise stated the determination of melting points, the recording of IR, UV, and $^1$H NMR spectra, the designation of the patterns of the $^1$H NMR spectra, and the performance of microanalyses were accomplished as described in a previous paper.[13] pH values were measured on a Radiometer pH meter 26, and the $pK_A$ values were determined according to the method of Albert and Serjeant [14] as described in a previous paper.[8] Thin layer and column chromatographic procedures were accomplished using silica gel $GF_{254}$ plates (Merck) and silica gel, 0.05–0.20 mm (Merck), respectively.

*Diethyl 4-oxoperhydroazepine-1,5-dicarboxylate ethylene ketal (IVa).* (IVa) was synthesized according to the general reaction for the preparation of β-oxoester ethylene ketals described by Jacquier *et al.*[10] using 11.7 g (46 mmol) of (II),[15] 14.0 g (230 mmol) of ethylene glycol, 0.6 g of 4-toluenesulfonic acid, and 400 ml of benzene. After reaction for 76 h the reaction mixture was worked up to give 12.6 g of crude product, which was subjected to column chromatography (silica gel: 200 g; eluent: methylene chloride to which increasing amounts of ethyl acetate were added). Obtained was 8.62 g of product, which after distillation gave 7.56 g (55 %) of (IVa) as a colourless oil, b.p. 152–154 °C/0.2 mmHg. (Found: C 55.75; H 7.72; N 4.59. Calc. for $C_{14}H_{23}NO_6$: C 55.80; H 7.69; N 4.65). $^1$H NMR data ($CCl_4$): δ 4.05 [two coincident q ($J$ = 7 Hz), 4 H, 2 × O–C*H*$_2$–CH$_3$]; 3.87 (s, 4 H, O–C*H*$_2$–C*H*$_2$–O); 3.8–3.1 (m, 4 H, CH$_2$–C*H*$_2$–N–C*H*$_2$–CH$_2$); 2.8–2.5 (perturbed t, 1 H, C–C*H*–CH$_2$); 2.5–1.5 (m, 4 H, CH$_2$–C*H*$_2$–C and CH$_2$–C*H*$_2$–CH); 1.25 [two coincident t ($J$ = 7 Hz), 6 H, 2 × O–CH$_2$–C*H*$_3$].

*1-Ethoxycarbonyl-4-oxoperhydroazepine-5-carbohydroxamic acid ethylene ketal (Va).* To a stirred solution of 4.5 g (*ca.* 65 mmol) of potassium hydroxide in methanol (45 ml) was added 3.6 g (52 mmol) of hydroxylamine hydrochloride. The mixture was stirred for further 90 min and after cooling in an ice bath a solution of 4.02 g (13 mmol) of (IVa) in methanol (12 ml) was added, and the mixture was allowed to stand at 8 °C for 18 d. Upon addition of 5 ml of glacial acetic acid the mixture was filtered and the filtrate was evaporated *in vacuo* to give a thick mass which was worked up utilizing column chromatography [silica gel: 130 g; eluent: ethyl acetate-methanol-formic acid (90:10:1)]. Obtained was 1.76 g (46 %) of (Va) as a reddish, glassy compound. (Found: C 49.78; H 7.11; N 9.65. Calc. for $C_{12}H_{20}N_2O_6$: C 49.99; H 6.99; N 9.72). $^1$H NMR data ($CDCl_3$): δ 9.4–7.7 (broad signal, 2 H, CO–N*H*–O*H*); 4.08 [q ($J$ = 7 Hz), 2 H, O–C*H*$_2$–CH$_3$]; 3.92 (s, 4 H, O–C*H*$_2$–C*H*$_2$–O); 3.8–3.1 (m, 4 H, CH$_2$–C*H*$_2$–N–C*H*$_2$–CH$_2$); 2.9–2.4 (m, 1 H, C–C*H*–CH$_2$); 2.4–1.6 (m, 4 H, CH$_2$–C*H*$_2$–C and CH$_2$–C*H*$_2$–CH); 1.23 [t ($J$ = 7 Hz), 3 H, O–CH$_2$–C*H*$_3$].

*Ethyl 3-hydroxy-5,6,7,8-tetrahydro-4H-isoxazolo[4,5-d]azepine-6-carboxylate (VIa).* To a solution of 1.84 g (6.4 mmol) of (Va) in methanol (5 ml) was added 3 ml of concentrated hydrochloric acid. After heating to 70 °C for 5 min the solution was evaporated *in vacuo* to give an oil which was subjected to column chromatography [silica gel: 120 g; eluent: methylene chloride-ethyl acetate-formic acid (85:15:1) to which increasing amounts of ethyl acetate were added]. Obtained was 1.36 g (94 %) of (VIa) in a crystalline state. An analytical sample was recrystallized (benzene-cyclohexane) to give colourless crystals, m.p. 95.5–97.5 °C. (Found: C 53.15; H 6.25; N 12.35. Calc. for $C_{10}H_{14}N_2O_4$: C 53.09; H 6.24; N 12.38). $^1$H NMR data ($CCl_4$): δ 9.5–8.8 (broad signal, 1 H, O*H*); 4.13 [q ($J$ = 7 Hz), 2 H, O–C*H*$_2$–CH$_3$]; 3.8–3.4 (m, 4 H, CH$_2$–C*H*$_2$–N–C*H*$_2$–CH$_2$); 3.05–2.65 [t, 2 H, CH$_2$–C*H*$_2$–C(O)=C]; 2.65–2.35 [t, 2 H, CH$_2$–C*H*$_2$–C(C)=C]; 1.25 [t ($J$ = 7 Hz), 3 H, O–CH$_2$–C*H*$_3$].

*3-Hydroxy-5,6,7,8-tetrahydro-4H-isoxazolo[4,5-d]azepinium bromide (VIIa).* A solution of 1.40 g (6.2 mmol) of (VIa) in 8 ml of glacial acetic acid containing 43 % of hydrogen bromide was refluxed for a total of 2 h (bath temperature: 100 °C). After reflux for 30 and 60 min, respectively, further amounts of 8 ml of glacial acetic acid containing 43 % of hydrogen bromide were added. After cooling to 25 °C the mixture was evaporated to dryness *in vacuo*. The crystalline residue was recrystallized (methanol-ether) to give 1.13 g (78 %) of (VIIa) as colourless crystals, m.p. 253 °C (decomp.). (Found: C 35.73; H 4.68; N 11.97; Br 34.07. Calc. for $C_7H_{11}BrN_2O_2$: C 35.75; H 4.73; N 11.91; Br 34.01). $^1$H NMR data [$D_2O$ (sodium 3-(trimethylsilyl)propanesulfonate was used as an internal standard)]: δ 4.74 (s. *ca.* 4 H, DO*H*); 3.7–3.3 (m, 4 H, CH$_2$–C*H*$_2$–NH$_2^+$–C*H*$_2$–CH$_2$); 3.3–3.0 [m, 2 H, CH$_2$–C*H*$_2$–C(O)=C]; 3.0–2.6 [m, 2 H, CH$_2$–C*H*$_2$–C(C)=C].

*5,6,7,8-Tetrahydro-4H-isoxazolo[4,5-d]azepin-3-ol zwitterion (VIII).* A solution of 792 mg (3.4 mmol) of (VIIa) in water (10 ml) was passed through a column containing an ion exchange resin [Amberlite IRA 400, (OH), 100 ml] using acetic acid (1 M) as an eluent. Crude product (605 mg) was obtained. Recrystallization (water-ethanol) gave 334 mg (58 %) of (VIII) as colourless crystals, m.p. 211 °C (decomp.). (Found: C 48.75; H 7.01; N 16.37. Calc. for $C_7H_{10}N_2O_2.1H_2O$: C 48.83; H 7.03; N 16.27). [Found after drying of (VIII) over $P_2O_5$ (48 h;

125 °C; 0.05 mmHg): C 54.40; H 6.69; N 18.22. Calc. for $C_7H_{10}N_2O_3$: C 54.53; H 6.54; N 18.17]. $^1$H NMR data [$D_2O$-$CF_3COOD$ (19:1) (sodium 3-(trimethylsilyl)propanesulfonate was used as an internal standard)]: $\delta$ 4.95 (s, *ca.* 5 H, DO*H*); 3.6–3.3 (m, 4 H, $CH_2-CH_2-NH_2^+-CH_2-CH_2$); 3.3–2.6 (m, 4 H, $CH_2-CH_2-C=C-CH_2-CH_2$).

*Diethyl 4-oxopiperidine-1,5-dicarboxylate (IIIb).* To an ice-cooled solution of 12.3 g (59 mmol) of (I) (Fluka) in water (40 ml), an ice-cooled solution of 3.9 g (*ca.* 55 mmol) of potassium hydroxide and 11.0 g (80 mmol) of potassium carbonate in water (75 ml) was added with stirring, and immediately thereafter 12.9 g (118 mmol) of ethyl chloroformate was added over a period of 15 s. Stirring was continued at 0 °C for 1 h and finally at 25 °C for further 1 h. The reaction mixture was extracted with four 75 ml portions of ether and the combined ether phases were dried and evaporated to give 11.4 g of a red oil. Distillation gave 9.9 g (69 %) of (IIIb) as a colourless oil, b.p. 133–138 °C/0.7 mmHg. (Found: C 54.50; H 6.94; N 5.77. Calc. for $C_{11}H_{17}NO_5$: C 54.31; H 7.04; N 5.76). $^1$H NMR data ($CCl_4$): $\delta$ 12.0 (s, 0.6 H, enol O*H*); 4.4–3.2 (m, consisting of several partially overlapping patterns of resonance signals, total 8.3 H); 2.7–2.2 [m, 2 H, $CH_2-CH_2-C=O$(oxo form) and $CH_2-CH_2-C=C$(enol form)]; 1.5–1.1 (m, consisting of several overlapping t, total 6 H, $O-CH_2-CH_3$).

*Ethyl 1-methoxycarbonyl-4-oxopiperidine-5-carboxylate (IIIc).* (IIIc) was prepared as described above for (IIIb) using 12.3 g (59 mmol) of (I) and 11.2 g (118 mmol) of methyl chloroformate, which gave 10.2 g of crude product as a red oil. Distillation gave 9.20 g (68 %) of (IIIc) as a colourless oil, b.p. 131–133 °C/0.3 mmHg. (Found: C 52.45; H 6.58; N 6.09. Calc. for $C_{10}H_{15}NO_5$: C 52.39; H 6.60; N 6.11). $^1$H NMR data ($CCl_4$): $\delta$ 12.1 (s, 0.8 H, enol O*H*); 4.4–4.0 (two overlapping q, $O-CH_2-CH_3$) and 4.1–3.9 [m, $N-CH_2-CH$ (oxo form) and $N-CH_2-C=C$ (enol form)], total 4 H; 3.9–3.3 [m, $N-CH_2-CH_2$ (oxo and enol form)], 3.67 (s, $O-CH_3$), and 3.65 (s, $O-CH_3$), total 5 H; 2.6–2.1 [m, 2 H, $CH_2-CH_2-C=O$ (oxo form) and $CH_2-CH_2-C=C$ (enol form)]; 1.5–1.1 (two overlapping t, 3 H, $O-CH_2-CH_3$).

*Diethyl 4-oxopiperidine-1,5-dicarboxylate ethylene ketal (IVb).* (IVb) was synthesized as described above for (IVa) using 11.4 g (47 mmol) of (IIIb) and 14.9 g (240 mmol) of ethylene glycol. After reaction for 81 h the reaction mixture was worked up to give 12.2 g of crude product as an oil, which without previous purification by column chromatography was distilled to give 9.20 g (68 %) of (IVb) as a colourless oil, b.p. 152–156 °C/0.2 mmHg. (Found: C 54.20; H 7.21; N 4.75. Calc. for $C_{13}H_{21}NO_6$: C 54.34; H 7.37; N 4.88). $^1$H NMR data ($CCl_4$): $\delta$ 4.04 [q ($J$=7 Hz), $O-CH_2-CH_3$], 4.00 [q ($J$=7 Hz), $O-CH_2-CH_3$], and 3.88 (s, $O-CH_2-CH_2-O$), total 8 H; 3.8–3.1 (m, 4 H, $CH_2-CH_2-N-CH_2-CH$); 2.6–2.3 (perturbed t, 1 H, $C-CH-CH_2$); 2.3–1.3 (m, 2 H, $CH_2-CH_2-C$); 1.24 [t ($J$=7 Hz), $O-CH_2-CH_3$] and 1.21 [t ($J$=7 Hz), $O-CH_2-CH_3$], total 6 H.

*Ethyl 1-methoxycarbonyl-4-oxopiperidine-5-carboxylate ethylene ketal (IVc).* (IVc) was synthesized as described above for (IVa) using 9.21 g (40 mmol) of (IIIc) and 12.4 g (200 mmol) of ethylene glycol. After reaction for 69 h the reaction mixture was worked up to give 9.8 g of crude product as an oil, which without previous purification by column chromatography was distilled to give 6.60 g (60 %) of (IVc) as a colourless oil, b.p. 160–162 °C/0.4 mmHg. (Found: C 52.80; H 7.08; N 5.23. Calc. for $C_{12}H_{19}NO_6$: C 52.74; H 7.01; N 5.13). $^1$H NMR data ($CCl_4$): $\delta$ 4.05 [q ($J$=7 Hz), $O-CH_2-CH_3$] and 3.91 (s, $O-CH_2-CH_2-O$), total 6 H; 3.8–3.3 (m, $CH_2-CH_2-N-CH_2-CH$) and 3.60 (s, $O-CH_3$), total 7 H; 2.6–2.4 (perturbed t, 1 H, $C-CH-CH_2$); 2.3–1.3 (m, 2 H, $CH_2-CH_2-C$); 1.25 [t ($J$=7 Hz), 3 H, $O-CH_2-CH_3$].

*1-Ethoxycarbonyl-4-oxopiperidine-5-carbohydroxamic acid ethylene ketal (Vb).* (Vb) was synthesized as described above for (Va) using 4.00 (14 mmol) of (IVb), 4.9 g (*ca.* 70 mmol) of potassium hydroxide, and 3.9 g (56 mmol) of hydroxylamine hydrochloride. After standing at 8 °C for 6 d the reaction mixture was worked up as described above for (Va) to give 2.42 g (63 %) of (Vb) in a crystalline state. An analytical sample was recrystallized (ethanol-benzene) to give (Vb) as colourless crystals, m.p. 134.5–136.5 °C. (Found: C 48.40; H 6.72; N 10.32. Calc. for $C_{11}H_{18}N_2O_6$: C 48.17; H 6.62; N 10.21). $^1$H NMR data [$CCl_4$-$CDCl_3$ (2:1)]: $\delta$ 9.2–8.4 (broad signal, 2 H, $CO-NH-OH$); 4.09 [q ($J$=7 Hz), $O-CH_2-CH_3$], 3.98 (s, $O-CH_2-CH_2-O$), and 4.4–3.0 (m, $CH_2-CH_2-N-CH_2-CH$), total 10 H; 2.8–2.3 (m, 1 H, $C-CH-CH_2$); 2.3–1.3 (m, 2 H, $CH_2-CH_2-C$); 1.30 [t ($J$=7 Hz), 3 H, $O-CH_2-CH_3$].

*1-Methoxycarbonyl-4-oxopiperidine-5-carbohydroxamic acid ethylene ketal (Vc).* (Vc) was synthesized as described above for (Va) using 7.72 g (28 mmol) of (IVc), 9.8 g (*ca.* 140 mmol) of potassium hydroxide, 7.8 g (112 mmol) of hydroxylamine hydrochloride, and 90 ml of methanol. After standing at 8 °C for 6 d the reaction mixture was worked up as described above for (Va) using 10 ml of glacial acetic acid and 160 g of silica gel to give 3.50 g (48 %) of (Vc) in a crystalline state. An analytical sample was recrystallized (ethanol-benzene) to give (Vc) as colourless crystals, m.p. 162–165 °C (decomp.). (Found: C 46.45; H 6.16; N 10.63. Calc. for $C_{10}H_{16}N_2O_6$: C 46.15; H 6.20; N 10.77). $^1$H NMR data ($CDCl_3$): $\delta$ 9.5–8.5 (broad signal, 2 H, $CO-NH-OH$); 3.97 (s, $O-CH_2-CH_2-O$), 3.66 (s, $O-CH_3$), and 4.2–2.9 (m, $CH_2-CH_2-N-CH_2-CH$), total 11 H; 2.8–2.3 (m, 1 H, $C-CH-CH_2$); 2.1–1.1 (m, 3 H, $CH_2-CH_2-C$).

*Ethyl 3-hydroxy-4,5,6,7-tetrahydroisoxazolo-[4,5-c]pyridine-5-carboxylate (VIb).* (VIb) was

synthesized and isolated from the reaction mixture as described above for (VIa) using 2.30 g (8.4 mmol) of (Vb). (VIb) (1.33 g, 75 %) was obtained in a crystalline state. An analytical sample was recrystallized (benzene-cyclohexane) to give colourless crystals, m.p. 118.0 – 120.5 °C. (Found: C 50.85; H 5.67; N 13.13. Calc. for $C_9H_{12}N_2O_4$: C 50.94; H 5.70; N 13.20). $^1$H NMR data ($CDCl_3$): $\delta$ 10.60 (s, 1 H, O*H*); 4.4 – 4.1 (m, N – C*H*$_2$ – C = C) and 4.12 [q ($J$ = 7 Hz), O – C*H*$_2$ – CH$_3$], total 4 H; 3.9 – 3.5 (t, 2 H, N – C*H*$_2$ – CH$_2$); 2.8 – 2.5 (t, 2 H, CH$_2$ – C*H*$_2$ – C = C); 1.27 [t ($J$ = 7 Hz), 3 H, O – CH$_2$ – C*H*$_3$].

*Methyl 3-hydroxy-4,5,6,7-tetrahydroisoxazolo-[4,5-c]pyridine-5-carboxylate (VIc).* (VIc) was synthesized as described above for (VIa) using 3.20 g (12.3 mmol) of (Vc), 15 ml of methanol, and 8 ml of concentrated hydrochloric acid. The reaction mixture was evaporated *in vacuo* to give an oil, which was dissolved in chloroform (30 ml). The chloroform solution was washed with a saturated solution of sodium chloride, dried, and evaporated *in vacuo* to give 2.28 g of crude (VIc). Recrystallization (benzene-cyclohexane) gave 1.16 g (48 %) of (VIc) as colourless crystals, m.p. 155.0 – 156.5 °C. (Found: C 48.50; H 5.07; N 14.08. Calc. for $C_8H_{10}N_2O_4$: C 48.48; H 5.09; N 14.14). $^1$H NMR data ($CDCl_3$): $\delta$ 10.50 (s, 1 H, O*H*); 4.4 – 4.2 (m, 2 H, N – C*H*$_2$ – C = C); 3.9 – 3.6 (t, N – C*H*$_2$ – CH$_2$) and 3.69 (s, O – C*H*$_3$), total 5 H; 2.9 – 2.5 (t, 2 H, CH$_2$ – C*H*$_2$ – C = C).

*3-Hydroxy-4,5,6,7-tetrahydroisoxazolo[4,5-c]-pyridinium bromide (VIIb). Method a.* (VIIb) was synthesized as described above for (VIIa) using 1.15 g (5.4 mmol) of (VIb). The crude product was recrystallized (methanol-ether) to give 781 mg (65 %) of (VIIb) as colourless crystals, m.p. 168 – 170 °C (decomp.). (Found: C 32.46; H 4.18; N 12.67; Br 36.28. Calc. for $C_6H_9BrN_2O_2$: C 32.60; H 4.10; N 12.67; Br 36.14). $^1$H NMR data [$D_2O$ (sodium 3-(trimethylsilyl)propanesulfonate was used as an internal standard)]: $\delta$ 4.68 (s, *ca.* 5 H, DO*H*); 4.2 – 4.0 (m, 2 H, $NH_2^+$ – C*H*$_2$ – C = C); 3.7 – 3.4 (t, 2 H, $NH_2^+$ – C*H*$_2$ – CH$_2$); 3.2 – 2.8 (t, 2 H, CH$_2$ – C*H*$_2$ – C = C).

*Method b.* A solution of 1.15 g (5.8 mmol) of (VIc) in 10 ml of glacial acetic acid containing 43 % of hydrogen bromide was heated for 25 min (bath temperature: 100 °C). Evaporation of the reaction mixture to dryness *in vacuo* and recrystallization (methanol-ether) of the residue afforded 1.13 g (88 %) of (VIIb) as colourless crystals, m.p. 169 – 171 °C (decomp.). The IR spectrum was identical with that of the product of method a.

*4,5,6,7-Tetrahydroisoxazolo[4,5-c]pyridin-3-ol zwitterion (IX).* (IX) was prepared as described above for (VIII) using 581 mg (2.6 mmol) of (VIIb) and 65 ml of ion exchange resin. (IX) (205 mg, 49 %) was obtained as colourless crystals, m.p. 254 – 256 °C (decomp.) (water-ethanol). (Found: C 45.50; H 6.38; N 17.82. Calc. for $C_6H_8N_2O_2.1H_2O$: C 45.56; H 6.37; N 17.71). [Found after drying of (IX) over $P_2O_5$ (48 h; 125 °C; 0.05 mmHg): C 51.65; H 5.88; N 20.03. Calc. for $C_6H_8N_2O_2$: C 51.42; H 5.75; N 19.99]. $^1$H NMR data [$D_2O$-$CF_3COOD$ (19:1) (sodium 3-(trimethylsilyl)propanesulfonate was used as an internal standard)]: $\delta$ 4.88 (s, *ca.* 6 H, DO*H*); 4.2 – 4.0 (m, 2 H, $NH_2^+$ – C*H*$_2$ – C = C); 3.7 – 3.4 (t, 2 H, $NH_2^+$ – C*H*$_2$ – CH$_2$); 3.2 – 2.8 (t, 2 H, CH$_2$ – C*H*$_2$ – C = C).

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