

Muscimol Analogues. II. Synthesis of Some Bicyclic 3-Isoxazolol Zwitterions

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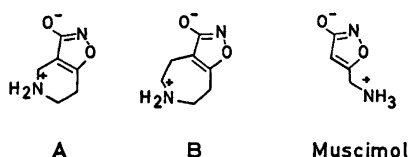
The syntheses of the 3-isoxazolol zwitterions 4,5,6,7-tetrahydroisoxazolo[5,4-*c*]pyridin-3-ol (*7a*), 5,6,7,8-tetrahydro-4*H*-isoxazolo[5,4-*c*]azepin-3-ol (*7b*), and 5,6,7,8-tetrahydro-4*H*-isoxazolo[4,5-*c*]azepin-3-ol (*7c*) are described. The starting materials were the cyclic β -oxoesters ethyl 1-methoxycarbonyl-3-oxopiperidine-4-carboxylate (*2a*), ethyl 1-methoxycarbonyl-3-oxoperhydroazepine-4-carboxylate (*2b*), and ethyl 1-methoxycarbonyl-4-oxoperhydroazepine-3-carboxylate (*2c*). The ethylene acetals of *2a-c* were treated with hydroxylamine, and deacetalization and cyclization of the intermediate β -oxohydroxamic acid ethylene acetals gave the respective 3-isoxazolol derivatives methyl 3-hydroxy-4,5,6,7-tetrahydroisoxazolo[5,4-*c*]pyridine-6-carboxylate (*5a*), methyl 3-hydroxy-4,5,6,8-tetrahydro-7*H*-isoxazolo[5,4-*c*]azepine-7-carboxylate (*5b*), and methyl 3-hydroxy-4,6,7,8-tetrahydro-5*H*-isoxazolo[4,5-*c*]azepine-5-carboxylate (*5c*), which were transformed into the zwitterions *7a-c*. The pK_A values of *7a-c* have been determined.

While muscimol (5-aminomethyl-3-isoxazolol) is a weak inhibitor of γ -aminobutyric acid (GABA) uptake,¹ the bicyclic muscimol analogue, 4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridin-3-ol (*A*) (Scheme 1), is a relatively potent inhibitor of GABA uptake.² The related compound 5,6,7,8-tetrahydro-4*H*-isoxazolo[4,5-*d*]azepin-3-ol (*B*) is inactive.² In order to study in further detail the relationship between struc-

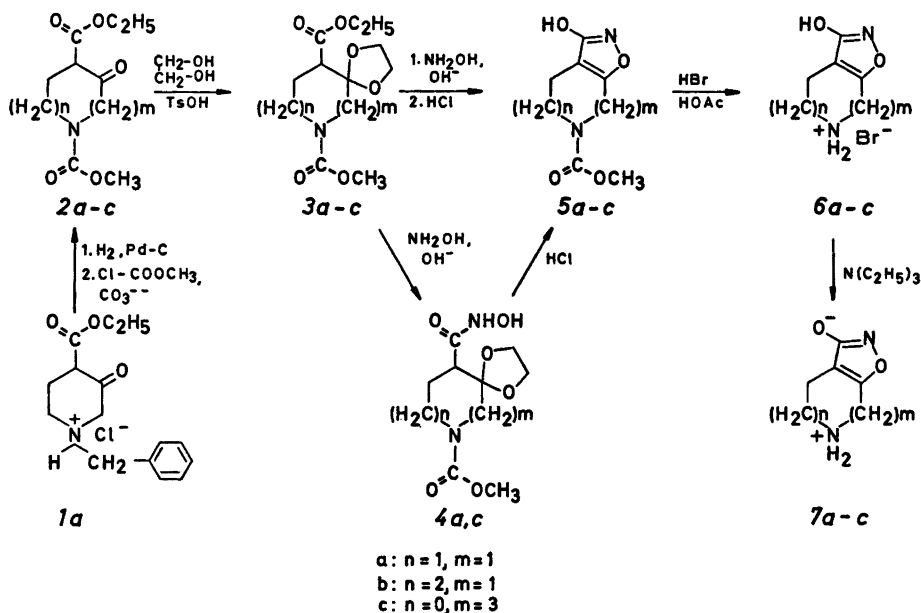
ture and biological activity of this type of muscimol analogues the related compounds *7a-c* have now been synthesized.

The reaction sequences for the preparation of *7a-c* are outlined in Scheme 2. The key steps in the reaction sequences are transformation of the β -oxoester ethylene acetals *3a-c* into the 3-isoxazolol derivatives *5a-c* via the corresponding hydroxamic acids. Only moderate yields of *5a-c* were obtained. The synthesis of *5a* required isolation of the hydroxamic acid *4a* in a pure state and subsequent heating of *4a* with concentrated hydrochloric acid, the latter reaction being accompanied by extensive degradation processes.

The depicted structures of the new compounds *2a* and *3-7* are based on the unequivocal structure determinations of the respective starting materials *1a*³ and *2b*,⁴ and confirmed spectroscopically and by elemental analyses. The spectroscopic data of the 4,5-disubstituted 3-oxygenated isoxazole moieties of *5a-c* and *6a-c* are in accordance with general findings.⁵ The spectroscopic and protolytic properties of *7a-c* are in agreement with those of other 3-isoxazolol zwitterions.⁶⁻¹¹ With the exceptions mentioned below the spectroscopic data of analogous compounds in Scheme 2 are very similar. The cyclic β -oxoester *2a* was shown by ¹H NMR and IR spectroscopy to be almost exclusively in the enol form, whereas this form of the related compound *2b* is hardly detectable by the same methods.⁴ The 3-isoxazolol derivative *5c* was obtained in two-crystal modifications with different IR spectra. In analogy with previous ¹H NMR spectroscopic findings for a series of cyclohepteno[1,2-*d*]isoxazole



Scheme 1.



Scheme 2.

derivatives¹¹ the resonance signals of the protons attached to C-4 in *5b*, *6b*, *5c*, and *6c* are observed at higher fields than those of the corresponding protons at C-8 in *5c*, *6c*, *5b*, and *6b*, respectively.

EXPERIMENTAL

Unless otherwise stated the determination of melting points, the recording of IR, UV, and ¹H NMR spectra, and the performance of microanalyses were accomplished as described in a previous paper.¹² Unless otherwise stated thin layer chromatography (TLC) and column chromatography (CC) was accomplished by using silica gel F₂₅₄ plates (Merck) and silica gel 0.05–0.200 mm (Merck), respectively. Columns were developed by stepwise gradient elution. An iron(III) chloride spraying reagent was used to visualize on TLC plates hydroxamic acids (purple colour) and 3-isoxazolol derivatives (yellow colour). Ammonium groups were visualized by spraying with a ninhydrin reagent (yellow colour). The pK_A values were determined as described in a previous paper.⁷

Ethyl 1-methoxycarbonyl-3-oxopiperidine-4-carboxylate (2a). A solution of *1a*³ (14.0 g; 47 mmol) in aqueous ethanol (300 ml; 50%) was hydrogenated (ca. 300 kPa) in a PARR hydrogenation apparatus by using a 10% Pd-C catalyst (1.4 g). The reaction mixture was filtered and evaporated to dryness *in vacuo*. To an ice cooled solution of the residue in water

(50 ml) was added with stirring an iced solution of potassium carbonate (19.4 g; 140 mmol) in water (20 ml) followed by addition of methyl chloroformate (11.3 g; 120 mmol). Stirring was continued at 0 °C for 30 min and at 25 °C for 30 min. The mixture was extracted with three 100 ml portions of ether. The combined and dried (Na₂SO₄) ether phases were evaporated *in vacuo* to give 10.0 g of crude product. Ball-tube distillation at 40–130 Pa (oven temperature 170 °C) gave *2a* (9.0 g; 84%) as a colourless oil, which slowly crystallized, m.p. 36–38 °C. Anal. C₁₆H₁₈N₂O₅: C, H, N. IR (film): 2980–2850 (several bands, m-s), 1700 (s), 1655 (s), 1620 (m) cm⁻¹. ¹H NMR (CCl₄): δ 12.3 (1 H, s), 4.13 (q, *J* 7 Hz) and 4.0–3.9 (m) (a total of 4 H), 3.62 (3 H, s), 3.43 (2 H, t, *J* 6 Hz), 2.4–2.1 (2 H, m), 1.30 (3 H, t, *J* 7 Hz).

Ethyl 1-methoxycarbonyl-3-oxopiperidine-4-carboxylate ethylene acetal (3a). A mixture of *2a* (9.0 g; 39 mmol), ethylene glycol (100 ml), 4-toluenesulfonic acid (0.7 g), and benzene (500 ml) was refluxed for 6 d using a Dean-Stark water separator. The mixture was washed with aqueous sodium carbonate (300 ml; 1 M), water (300 ml), and saturated aqueous sodium chloride (300 ml). The organic phase was dried (K₂CO₃) and evaporated *in vacuo* to give 8.6 g of an oil. CC [silica gel (Woelm 0.063–0.1 mm); 350 g; eluents: methylene chloride to which ethyl acetate (20–35%) was added] followed by ball-tube distillation at 40 Pa (oven temperature 170 °C) gave *3a* (7.0 g; 65%) as a colourless oil. Anal. C₁₈H₂₀N₂O₆: C, H, N. IR (film): 2970 (s), 2900 (s), 1730 (s)

cm^{-1} . ^1H NMR (CCl_4): δ 4.05 (q, J 7 Hz) and 3.92 (s) (a total of 6 H), 3.60 (s) and 3.7–3.0 (m) (a total of 7 H), 2.8–2.5 (1 H, t), 2.2–1.6 (2 H, m), 1.23 (3 H, t, J 7 Hz).

1-Methoxycarbonyl-3-oxopiperidine-4-carboxylic acid ethylene acetal (4a). To a stirred and iced solution of potassium hydroxide (7.3 g; 130 mmol) in methanol (30 ml) was added hydroxylammonium chloride (6.9 g; 100 mmol). After stirring at 0 °C for a further 30 min a solution of **3a** (6.8 g; 25 mmol) in methanol (20 ml) was added, and the mixture was left at 8 °C for 8 d. Upon addition of glacial acetic acid (15 ml) and filtration the filtrate was evaporated *in vacuo* to give a treacly mass. CC [silica gel (Woelm 0.063–0.1 mm)]: 250 g; eluents: ethyl acetate to which methanol (15–26 %) and formic acid (1 %) was added] afforded **4a** (1.9 g; 29 %) as a crystalline and TLC-pure substance [R_F : 0.23; eluent: ethyl acetate–methanol–formic acid (90:9:1)]. An analytical sample was recrystallized (ethanol–benzene) to give **4a** as colourless crystals, m.p. 150.0–152.0 °C. Anal. $\text{C}_{10}\text{H}_{16}\text{N}_2\text{O}_6$: C, H, N. IR (KBr): 3700–3350 (m), 3280 (m), 3210 (s), 3055 (w), 3000–2870 (several bands, w-m), 1690 (s), 1640 (s), 1550 (w) cm^{-1} . ^1H NMR [CDCl_3 –DMSO- d_6 (1:1)]: δ 10.5–10.1 (1 H, m), 4.9–4.3 (1 H, m), 3.93 (s), 3.60 (s), and 4.1–3.1 (m) (a total of 11 H), 2.8–2.6 (1 H, m), 2.2–1.8 (2 H, m).

Methyl 3-hydroxy-4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridine-6-carboxylate (5a). A solution of **4a** (750 mg; 2.9 mmol) in concentrated hydrochloric acid (13 ml) was heated to 70 °C for 10 min. The mixture was evaporated *in vacuo* to give a black oil. CC [silica gel (Woelm 0.063–0.1 mm)]: 60 g; eluents: benzene to which ethyl acetate (40–70 %) and formic acid (1 %) was added] gave crystalline and TLC-pure **5a** (244 mg; 43 %) [R_F : 0.27; eluent: benzene–ethyl acetate–formic acid (50:50:1)]. An analytical sample was recrystallized (benzene–cyclohexane) to give pure **5a** as colourless crystals, m.p. 136.0–138.0 °C. Anal. $\text{C}_8\text{H}_{10}\text{N}_2\text{O}_4$: C, H, N. IR (KBr): 3700–3300 (m), 3300–2500 (several bands, w-m), 1655 (s), 1525 (m), 1490 (s) cm^{-1} . UV [methanol (log ϵ): 212 (3.64) nm. ^1H NMR (CDCl_3): δ 10.6 (1 H, s), 4.43 (2 H, s), 3.70 (s) and 3.8–3.5 (t) (a total of 5 H), 2.6–2.3 (2 H, t).

3-Hydroxy-4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridinium bromide (6a). A solution of **5a** (309 mg; 1.6 mmol) in a solution of hydrogen bromide in glacial acetic acid (3 ml; 43 %) was refluxed for 15 min. Upon evaporation to dryness *in vacuo* the residue was treated with the same reagent (3 ml) for further 15 min. Evaporation of the reaction mixture to dryness *in vacuo* and recrystallization (methanol–ether) of the residue gave **6a** (193 mg; 56 %) as faintly reddish crystals, m.p. 162–163 °C (decomp.). Anal. $\text{C}_8\text{H}_9\text{BrN}_2\text{O}_3$: C, H, Br, N. IR (KBr): 3700–3300 (m), 3070 (s), 3000–2300 (several bands, m-s), 1670 (m), 1580 (m), 1525 (s),

1505 (w) cm^{-1} . UV (methanol): < 210 nm. ^1H NMR [D_2O (sodium 3-(trimethylsilyl)propanesulfonate was used as an internal standard)]: δ 4.77 (ca. 5 H, s), 4.43 (2 H, t, J 1 Hz), 3.7–3.4 (2 H, q, J 6 and 7 Hz), 3.0–2.7 (2 H, t).

4,5,6,7-Tetrahydroisoxazolo[5,4-c]pyridin-3-ol zwitterion (7a). To a solution of **6a** (77 mg; 0.35 mmol) in water (0.6 ml) was added a solution of triethylamine (39 mg; 0.39 mmol) in ethanol (0.6 ml). The mixture was left at 25 °C for 2 h. **7a** (42 mg; 86 %) was isolated as colourless crystals, m.p. 242–244 °C (decomp.). Anal. $\text{C}_8\text{H}_9\text{N}_2\text{O}_3$: C, H, N. IR (KBr): 3700–2900 (s), 2900–1900 (several bands, m-s), 1670 (s), 1625 (m) cm^{-1} . UV [methanol (log ϵ): 212 (3.64) nm. $\text{p}K_A$ values (H_2O , 25 °C): 4.44 \pm 0.03, 8.48 \pm 0.04.

Ethyl 1-methoxycarbonyl-3-oxoperhydroazepine-4-carboxylate ethylene acetal (3b). **3b** was synthesized as described above for **3a** by using **2b** (4.1 g; 17 mmol) and ethylene glycol (20 ml). After reaction for 6 d the reaction mixture was worked up to give 6.0 g of crude product. CC [silica gel: 300 g; eluents: benzene to which ether (30–50 %) was added] followed by ball-tube distillation at 40 Pa (oven temperature 180 °C) gave **3b** (3.2 g; 66 %) as a colourless oil. Anal. $\text{C}_{13}\text{H}_{21}\text{NO}_6$: C, H, N. IR (film): 2980–2890 (several bands, m), 1730 (s), 1705 (s) cm^{-1} . ^1H NMR (CCl_4): δ 4.02 (q, J 7 Hz) and 3.9–3.8 (m) (a total of 6 H), 3.60 (s) and 3.6–3.2 (m) (a total of 7 H), 2.7–2.5 (1 H, m), 2.0–1.6 (4 H, m), 1.23 (3 H, t, J 7 Hz).

Methyl 3-hydroxy-4,5,6,8-tetrahydro-7H-isoxazolo[5,4-c]azepine-7-carboxylate (5b). **3b** (1.29 g; 4.5 mmol) was treated with hydroxylamine for 9 d as described above for **4a** by using potassium hydroxide (1.29 g; ca. 23 mmol), hydroxylammonium chloride (1.25 g; 18 mmol), and methanol (8 ml). After addition of methanol (10 ml) and glacial acetic acid (2 ml) the mixture was filtered and the filtrate evaporated *in vacuo*. A solution of the residue in methanol–concentrated hydrochloric acid (2:1) (12 ml) was heated to 70 °C for 5 min and evaporated *in vacuo* to give an oil. CC [silica gel: 60 g; eluents: benzene to which ethyl acetate (30–45 %) and formic acid (1 %) was added] gave **5b** (227 mg; 24 %) as TLC-pure crystals [R_F : 0.35; eluent: benzene–ethyl acetate–formic acid (50:50:1)]. An analytical sample was recrystallized (benzene) to give pure **5b** as colourless crystals, m.p. 162.0–162.5 °C. Anal. $\text{C}_8\text{H}_{12}\text{N}_2\text{O}_4$: C, H, N. IR (KBr): 3700–3300 (m), 3200–2500 (several bands, w-m), 1695 (s), 1655 (m), 1540 (s), 1475 (s) cm^{-1} . UV [methanol (log ϵ): 214 (3.79) nm. ^1H NMR (CDCl_3): δ 11.0 (1 H, s), 4.50 (2 H, s), 3.65 (s), and 3.7–3.4 (m) (a total of 5 H), 2.6–2.2 (2 H, t), 2.0–1.6 (2 H, m).

3-Hydroxy-5,6,7,8-tetrahydro-4H-isoxazolo[5,4-c]azepinium bromide (6b). **6b** was synthesized as described above for **6a** by using **5b** (400 mg; 1.9 mmol) and two 6 ml portions of

reagent. Recrystallization of crude **6b** (methanol-ether) gave pure **6b** (366 mg; 83 %) as faintly yellowish crystals, m.p. 222 °C (decomp.). Anal. $C_7H_{11}BrN_2O_2$: C, H, Br, N. IR (KBr): 3700–3300 (w), 3200–2200 (several bands, m-s), 1670 (m), 1535 (s) cm^{-1} . UV [methanol (log ϵ): 212 (3.81) nm. 1H NMR [D_2O (sodium 3-(trimethylsilyl)propanesulfonate was used as an internal standard]): δ 4.70 (ca. 4 H, s), 4.40 (2 H, s), 3.7–3.5 (2 H, t), 2.7–2.3 (2 H, m), 2.3–1.8 (2 H, m).

5,6,7,8-Tetrahydro-4H-isoxazolo[5,4-c]azepin-3-ol zwitterion monohydrate (7b). **7b** was prepared as described above for **7a** by using **6b** (83 mg; 0.35 mmol). The mixture was left at 5 °C for 3 d. **7b** (41 mg; 68 %) was isolated as colourless crystals, m.p. 200–201 °C (decomp.). Anal. $C_7H_{10}N_2O_2 \cdot H_2O$: C, H, N. Anal. $C_7H_{10}N_2O_2$ (after heating of **7b** to 120 °C for 20 h): C, H, N. IR (KBr): 3700–3200 (s), 3100–1900 (several bands, m-s), 1660 (m), 1620 (s) cm^{-1} . UV [methanol (log ϵ): 215 (3.74) nm. pK_A values (H_2O , 26 °C): 4.56 ± 0.03 , 8.56 ± 0.06 .

Ethyl 1-methoxycarbonyl-4-oxoperhydroazepine-3-carboxylate ethylene acetal (3c). **3c** was synthesized as described above for **3a** by using **2c** (4.7 g; 19 mmol) and ethylene glycol (7 ml). After reaction for 2 d the reaction mixture was worked up to give 6.2 g of crude product. Ball-tube distillation at 70 Pa (oven temperature 170 °C) gave **3c** (4.6 g; 83 %) as a colourless oil. Anal. $C_{13}H_{21}NO_6$: C, H, N. IR (film): 2980–2890 (several bands, m), 1730 (s), 1700 (s) cm^{-1} . 1H NMR (CCl_4): δ 3.98 (q, J 7 Hz) and 3.82 (s) (a total of 6 H), 3.55 (s) and 3.6–3.2 (m) (a total of 7 H), 2.9–2.6 (1 H, m), 1.9–1.4 (4 H, m), 1.23 (3 H, t, J 7 Hz).

1-Methoxycarbonyl-4-oxoperhydroazepine-3-carboxylic acid ethylene acetal (4c). **4c** was synthesized as described above for **4a** by using **3c** (2.5 g; 9 mmol), potassium hydroxide (2.5 g; ca. 45 mmol), hydroxylammonium chloride (2.5 g; 36 mmol), and methanol (16 ml). After reaction for 10 d glacial acetic acid (6 ml) was added. The mixture was filtered, and evaporation *in vacuo* of the filtrate gave a treacly mass. CC [silica gel (Woelm 0.063–0.1 mm): 320 g; eluents: ethyl acetate to which methanol (10–21 %) and formic acid (1 %) was added] gave crude crystalline **4c**. After recrystallization (ethanol-benzene) **4c** (510 mg; 21 %) was obtained as colourless crystals, m.p. 178.5–180.0 °C. Anal. $C_{11}H_{18}N_2O_6$: C, H, N. IR (KBr): 3700–3450 (m), 3290 (m), 3160 (m), 3000–2880 (several bands, m), 1705 (s), 1635 (s), 1530 (m) cm^{-1} . 1H NMR [$CDCl_3$ – $DMSO-d_6$ (2:1)]: δ 10.2 (1 H, s), 8.9–8.5 (1 H, m), 3.85 (s), 3.60 (s), and 4.0–3.1 (m) (a total of 11 H), 2.6–2.4 (1 H, m), 2.0–1.5 (4 H, m).

Methyl 3-hydroxy-4,6,7,8-tetrahydro-5H-isoxazolo[4,5-c]azepine-5-carboxylate (5c). **Method a**. **5c** was synthesized as described above for **5b** by using **3c** (2.5 g; 9 mmol), potassium hydroxide (2.5 g; ca. 45 mmol), hydroxylammonium

chloride (2.5 g; 36 mmol), glacial acetic acid (4 ml), and methanol-concentrated hydrochloric acid (2:1) (20 ml). Purification of a crude reaction product by CC [silica gel: 60 g; eluents: benzene to which ethyl acetate (30–40 %) and formic acid (1 %) was added] followed by recrystallization (benzene) of slightly impure **5c** gave **5c** (442 mg; 24 %) as colourless crystals, m.p. 141.5–142.5 °C. Anal. $C_9H_{12}N_2O_4$: C, H, N. IR (KBr): 3600–3300 (w), 3200–2400 (several bands, w-m), 1710 (s), 1650 (m), 1550 (s), 1525 (m), 1480 (s), 1305 (s), 1250 (s), 1115 (s), 965 (s) cm^{-1} . UV [methanol (log ϵ): 213 (3.80) nm. 1H NMR ($CDCl_3$): δ 11.2 (1 H, s), 4.23 (2 H, s), 3.63 (s) and 3.7–3.4 (m) (a total of 5 H), 2.9–2.6 (2 H, t), 2.1–1.6 (2 H, m). In another experiment a modification of **5c** with m.p. 144.5–146.0 °C was obtained. IR (KBr): 3700–3300 (w), 3300–3000 (m), 2980–2400 (several bands, w-m), 1665 (s), 1650 (s), 1520 (s), 1485 (s), 1440 (s), 1410 (s), 1270 (s), 1255 (s), 955 (s) cm^{-1} .

Method b. A solution of **4c** (436 mg; 1.6 mmol) in methanol-concentrated hydrochloric acid (2:1) (10 ml) was heated to 70 °C for 5 min. The solution was evaporated *in vacuo* to give an oil. Upon addition of a saturated aqueous solution of sodium chloride (5 ml) the mixture was extracted with three 20 ml portions of chloroform. The combined and dried (Na_2SO_4) organic phases were evaporated *in vacuo* to give TLC-pure **5c** (331 mg) [R_F : 0.32; eluent: benzene-ethyl acetate-formic acid (50:50:1)]. Recrystallization (benzene) gave **5c** (280 mg; 83 %) as colourless crystals, m.p. 144.5–145.5 °C. The IR spectrum was identical with that of the modification of **5c** with m.p. 144.5–146.0 °C prepared according to method a.

3-Hydroxy-5,6,7,8-tetrahydro-4H-isoxazolo[4,5-c]azepinium bromide (6c). **6c** was synthesized as described above for **6a** by using **5c** (381 mg; 1.8 mmol) and two 5 ml portions of reagent. Recrystallization of crude **6c** (methanol-ether) gave **6c** (320 mg; 76 %) as colourless crystals, m.p. 213 °C (decomp.). Anal. $C_7H_{11}BrN_2O_2$: C, H, Br, N. IR (KBr): 3700–3300 (w), 3200–2100 (several bands, w-s), 1665 (s), 1600 (s), 1540 (s), 1515 (w) cm^{-1} . UV [methanol (log ϵ): 211 (3.82) nm. 1H NMR [D_2O (sodium 3-(trimethylsilyl)propanesulfonate was used as an internal standard]): δ 4.70 (ca. 4 H, s), 4.04 (2 H, s), 3.7–3.5 (2 H, t), 3.1–2.8 (2 H, t), 2.3–1.9 (2 H, m).

5,6,7,8-Tetrahydro-4H-isoxazolo[4,5-c]azepin-3-ol zwitterion (7c). **7c** was prepared as described above for **7a** by using **6c** (83 mg; 0.35 mmol). Upon addition of ether (0.1 ml) the mixture was left at 25 °C for 4 d. **7c** (45 mg; 83 %) was isolated as colourless crystals, m.p. 257–258 °C (decomp.). Anal. $C_7H_{10}N_2O_2$: C, H, N. IR (KBr): 3700–3300 (m), 3050 (m), 2940–2000 (several bands, m-s), 1665 (s), 1600 (m), 1550 (s), 1510 (m) cm^{-1} . UV [methanol (log ϵ): 212 (3.88) nm. pK_A values (H_2O , 26 °C): 4.50 ± 0.05 , 9.76 ± 0.05 .

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