Synthesis of Some 4-Aminoalkyl-5-methyl-3-isoxazolols Structurally Related to Muscimol and \( \gamma \)-Aminobutyric Acid (GABA)

HANS HJEDS and POVL KROGSGAARD-LARSEN

Royal Danish School of Pharmacy, Department of Chemistry BC, DK-2100 Copenhagen Ø, Denmark

The synthesis of 4-(2-aminoethyl)-5-methyl-3-isoxazolol zwitterion (16a) and 4-(2-amino-propyl)-5-methyl-3-isoxazolol zwitterion (16b) which are structural analogues of 5-amino-methyl-3-isoxazolol (Muscimol) and of \( \gamma \)-aminobutyric acid (GABA) is described. The key reaction of the sequences leading to these compounds involves hydroxylamine treatment of the appropriately substituted five-membered cyclic enamides (13a and b). Furthermore the preparation of the \( \beta \)-alanine analogues 4-amino-methyl-5-methyl-3-isoxazolol zwitterion (19) and 4-(1-aminoethyl)-5-methyl-3-isoxazolol zwitterion (20) is described. The \( pK_a \) values of all four compounds have been determined.

As part of the investigations of the biological properties of conformationally restricted analogues of \( \gamma \)-aminobutyric acid (GABA) structurally related to muscimol (5-aminoethyl-3-isoxazolol)\(^{1,2}\) a series of bicyclic\(^{3,4}\) and 5-aminoalkylsubstituted\(^{5-7}\) 3-isoxazolols has been prepared. This paper presents the synthesis of some 3-isoxazololes with an aminoalkyl moiety in the 4-position.

As an approach to the synthesis of 4-(2-aminoethyl)-5-methyl-3-isoxazolol (16a), the method of preparation of 3-isoxazololes via ethylene acetals of \( \beta \)-oxoesters\(^{4,4,8}\) was extended to the preparation of 3-hydroxy-5-methylisoxazol-4-ylacetic acid (3). Reaction of the ethylene acetal 2 with hydroxylamine, however, gave 3 in a poor yield and since 5 could only be obtained in a 30% yield by treatment of 3 with diazomethane further transformations in the planned reaction sequence were considered of limited value.

The synthesis of the 3-methoxyisoxazole 5 via the diazoketone 7, which was readily obtained from the acid 6\(^{10}\) upon treatment with...
thionyl chloride followed by diazomethane, was then examined. A methanolic solution of the diazoketone 7 was irradiated with unfiltered UV-light to give 5 in a good yield. However, several experiments revealed the limit of the synthetic scale under the used conditions to be about 200 mg of 7. Attempts to rearrange the diazoketone 7 to 8 using silver thiosulfate according to the method of Wiberg and Hutton led to complex mixtures from which no compound was isolated.

Finally 16a, b was successfully prepared by the sequence outlined in Scheme 2. Ethyl acetoacetate was alkylated by the urethane 11a to give a mixture of two compounds. Column chromatography of the mixture gave the compound with the smaller $R_F$ value in a pure state, whereas the other compound during this procedure was partly transformed into the compound with the smaller $R_F$ value and could not be isolated in a pure state. Based on IR, UV, and $^1$H NMR spectroscopy and supported by chemical evidence the compound with the smaller $R_F$ value was shown to be the cyclic enamide 13a. On the basis of spectroscopic and TLC examinations the other compound was assigned the $\beta$-oxoester structure 12a. Treatment of the above-mentioned mixture of 12a and 13a in boiling toluene for 8 h using 4-toluenesulfonic acid as a catalyst completed the cyclization of 12a into 13a which was obtained in a good yield.

The cyclic enamide 13a was treated with hydroxylamine to give a reasonable yield of the isoxazole 14a. Investigation of the reaction mixture on TLC plates, however, revealed the presence of trace amounts of a compound which gave a violet spot on TLC using iron(III) chloride as a spraying reagent. The compound may be the corresponding 5-isoxazolone [3-methyl-4-(2-ethoxycarbonylaminomethyl)-5-isoxazolone] but several attempts to isolate the compound in a pure state were unsuccessful. The observed reaction course is remarkable as various $\beta$-oxoesters protected at the oxo group as benzyl-enamines, upon treatment with hydroxylamine exclusively yield 5-isoxazolones.

In the sequence leading to the isoxazolol zwitterion 16b the starting material 2-nitropropan-1-ol (9) was low-pressure hydrogenated using a 10 % Pd-C catalyst to give 2-amino-1-propan-1-ol (10b). The desired compound 16b was obtained by a reaction sequence analogous to that described above including the cyclic enamide 13b. All attempts to obtain 16b in a crystalline state failed, and the compound could only be isolated as a glassy substance.

The synthesis of 4-aminomethyl-5-methyl-3-isoxazolol zwitterion (19) was achieved from 3-methoxy-4-aminomethyl-5-methylisoxazole hydrochloride (17a) prepared according to the directions of Bowden et al. 17a was readily cleaved by hydrogen bromide in glacial acetic
acids to give the 3-isoxazolyl 18a which by use of a strongly basic ion exchange resin gave the zwiterion 19. This compound has previously been prepared by Bowden et al. by hydrolytic cleavage of 4-trifluoroacetamidomethyl-5-methyl-3-isoxazolyl but was isolated as the 4-toluenesulfonate by these authors.16

A strong UV absorption at 281 nm and an absorption band at 1830 cm⁻¹ in the IR spectra indicated the presence of conjugation in the compounds 13a and b. This together with the ¹H NMR spectra and elemental analyses confirmed the cyclic enamide structure of these compounds.

The IR, UV, and ¹H NMR data obtained from the 3-oxygenated isoxazole moieties of 3, 5, 7, 14a,b, 15a,b, and from the 3-isoxazolone moiety of 4 are in accordance with the general findings described by Jacquier et al. The spectroscopic data of the zwiterions 16a, 19, and 20 are in accordance with those published for other isoxazole zwiterions.15 The IR absorption bands at 2100, 1620, and 1360 cm⁻¹ in the spectrum of 7 are in accordance with the results published for various diazocarbonyl compounds by Yates et al.14 Some IR, UV, and ¹H NMR data of the starting materials 6 and 17a,b are given in the experimental part as no spectroscopic data of these compounds are available in the literature.

The pKₐ values of 16a,b, 19, and 20 are given in the experimental part. The pKₐ values of the compounds are in accordance with those published for other isoxazole zwiterions.15-17

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. Thin layer and column chromatographic procedures were accomplished using silica gel GF₄₅ plates (Merck) and silica gel, 0.05-0.20 mm (Merck), respectively. pH values were measured on a Radiometer pH meter 26. The pKₐ values were determined according to the method described by Albert and Serjeant15 as described in a previous paper.

Diethyl acetoacetate acetal (2). A solution of 54.0 g (0.25 mol) of diethyl acetoacetate (I),15 26.0 g (0.40 mol) of ethylene glycol, and 1 g of 4-toluenesulfonic acid in 500 ml of benzene was refluxed for ca. 40 h using a Dean-Stark water separator. The solution was washed with two 200 ml portions of water, dried (K₂CO₃), and distilled to give 40.9 g (62 %) of 2 as a colourless oil, b.p. 155-158°C/7 mmHg. An analytical sample was further purified by column chromatography using CH₂Cl₂ as an eluent. (Found C 55.30; H 7.84. Calc. for C₁₁H₂₆O₄: C 55.37; H 7.75.) IR data (neat) cm⁻¹: 1735(s); 1H NMR data (CDCl₃): δ 4.13 and 4.07 [2 × q (J = 7 Hz in both cases), 4H, 2 × CH₃-CH₂-O]; 3.95 (s, 4H, O-CH₂-CH₂-O); 3.3-3.5 (m, 1H, CH-CH₃); 2.9-2.2 (m, 2H, CH-CH₂); 1.38 (s, 3H, CH₃-C); 1.27 and 1.23 [2 × t (J = 7 Hz in both cases), 6H, 2 × CH₃-CH₂-O].

3-Hydroxy-5-methylisoxazol-4-ylacetic acid (3). To a solution of 15.2 g (0.22 mol) of hydroxylamine hydrochloride in 400 ml of methanol was added 41.4 g (0.30 mol) of potassium carbonate. After stirring for 15 min 52.0 g (0.20 mol) of 2 was added and the suspension was refluxed for 12 h. The filtered reaction mixture was evaporated in vacuo to give an oil which was dissolved in 250 ml of water.
The aqueous solution was extracted with three 100 ml portions of methylene chloride which were discarded. To the aqueous phase was added 250 ml of concentrated hydrochloric acid and the solution was boiled for 1 h. The solution was extracted continuously for 2 h by ether-methylene chloride 4:1 to give 11.1 g of an oily product which was submitted to column chromatography (silica gel: 500 g; eluent: benzene-ethyl acetate-formic acid 10:20:0.3 to which increasing amounts of ethyl acetate were added) to yield 1.60 g (6.2 %) of yellowish crystals. An analytical sample was recrystallized from ethyl acetate to give colourless crystals, m.p. 150 - 152°C. (Found: C 45.85; H 4.52; N 8.80. Calc. for C24H20NO3: C 45.86; H 4.49; N 8.97. λmax(CH3OH): 211 nm (ε = 5.92 x 104). IR (KBr) cm⁻¹: 3600 - 2200 (ν1); 1698 (ν2); 1650 - 1592 (s, several bands). 1H NMR (CDCl3): δ 9.68 (s, 2 H, OH and COOH); 3.35 (s, 3 H, OC - CH3). 2.27 (s, 3 H, CH3 - C =).

Methyl 2,5-dimethyl-3-oxoisoxazolin-4-ylacetate (4) and methyl 3-methoxy-5-methylisoxazol-4-ylacetate (5). To a solution of 750 mg (4.8 mmol) of 3-hydroxy-5-methylisoxazol-4-ylacetic acid (3) in 50 ml of ether was added with stirring a solution of ca. 0.5 g (ca. 15 mmol) of diazomethane (prepared from 4.30 g (20 mmol) of N-methyl-N-nitroso-p-toluene-sulfonamide)¹⁷ in 40 ml of ether. Stirring was continued for 2 h and the remaining diazomethane was destroyed by addition of excess of formic acid. The solution was evaporated to dryness in vacuo to give 950 mg of a colourless oil which was submitted to column chromatography (silica gel: 30 g; eluent: ether-petroleum ether 1:1). Distillation of the fractions containing 4 in a "Kugelrohr" at 1 mm Hg (oven temp. 160°C) gave 432 mg (49 %) of a colourless oil (Found: C 51.10; H 6.17; N 7.39. Calc. for C21H24NO4: C 51.88; H 5.99; N 7.56. λmax(CH3OH): 233 nm (ε = 7.4 x 104). IR (neat) cm⁻¹: 3600 - 2700 (ν1); 1740 (ν2); 1660 (ν3). 1H NMR (CDCl3): δ 3.69 (s, 2 H, -COOH); 3.47 (s, 3 H, N - CH3); 3.27 (s, 2 H, - C - CH3); 2.22 (s, 3 H, - C = CH3). Distillation of the fractions containing 5 in a "Kugelrohr" at 1 mm Hg (oven temp. 125°C) gave 273 mg (30 %) of a colourless oil which was submitted to colourless crystals, m.p. 41.5 - 42.5°C. (Found: C 51.80; H 6.07; N 7.58. Calc. for C21H24NO4: C 51.88; H 5.99; N 7.56. λmax(CH3OH): 211 nm (ε = 6.02 x 10⁴). IR (KBr) cm⁻¹: 3700 - 3200 (m); 3050 - 2800 (m); 1730 (s); 1655 (m); 1530 (s); 1450 (s). 1H NMR (CDCl3): δ 3.53 (s, 3 H, = C - CH3); 3.57 (s, 3 H, - COOCH3); 3.15 (s, 2 H, = C - CH3). 3-Methoxy-5-methylisoxazol-4-carboxylic acid (6), prepared as described by Bowden et al.¹⁸ to give crystals, m.p. 195 - 196°C (Ref. 10: 195 - 197°C). λmax(CH3OH): 215 nm (ε = 7.42 x 10⁴). IR (KBr) cm⁻¹: 3600 - 2300 (m); 1680 (s); 1620 (s); 1530 (s); 1490 (s). 1H NMR (CDCl3): δ 13.5 - 11 (broad band, 1 H, - COOH); 3.86 (s, 3 H, = OCH3); 2.53 (s, 3 H, = C - CH3). 3-Methoxy-4-diazoacetyl-5-methylisoxazole (7). A solution of 1.57 g (10 mmol) of 3-methoxy-5-methylisoxazol-4-carboxylic acid (6) in 12 g (100 mmol) of thionyl chloride was refluxed for 40 min. Excess of thionyl chloride was removed in vacuo and the residual oil was dissolved in 25 ml of dry ether. The ethereal solution was added dropwise with stirring to a phosphorus hydride dried solution of ca. 1 g (ca. 24 mmol) of diazomethane (prepared from 7.17 g (33 mmol) of N-methyl-N-nitroso-p-toluene-sulfonamide)¹⁷ in 75 ml of ether. Stirring was continued for 3 h and after addition of an excess of formic acid in order to destroy the remaining diazomethane the solution was evaporated to dryness in vacuo to give 1.79 g of crude product as yellow crystals. Recrystallization from ether-petroleum ether afforded 900 mg (50 %) of yellow crystals, m.p. 107.5 - 108.5°C. (Found: C 46.35; H 4.02; N 23.10. Calc. for C21H18N2O4: C 46.41; H 3.90; N 23.20. λmax(CH3OH): < 210 nm; 246 nm (ε = 9.07 x 10⁴); 291 nm (ε = 16.1 x 10⁴). IR (neat) cm⁻¹: 3700 - 3200 (w); 3120 (w); 2950 (w); 2110 (s); 1620 (s); 1595 (s); 1520 (m); 1470 (m); 1360 (s). 1H NMR (CDCl3): δ 5.97 (s, 1 H, CH - CH2); 4.02 (s, 3 H, = C - OCH3); 2.62 (s, 3 H, CH3 - C =). Methyl 3-methoxy-5-methylisoxazol-4-ylacetate (5). A solution of 200 mg (0.11 mmol) of 7 in 50 ml of methanol was irradiated in a quartz-tube with unfiltered UV-light (Philips HPK 125 W, BA 15 D, Typ 57203B/00) for 2 h at ca. 10°C. The solution was filtered and evaporated to dryness in vacuo and the residue was submitted to column chromatography (silica gel: 20 g; eluent: methylene chloride-ethyl acetate 3:1) to give 157 mg of crude product. Recrystallization from ether-petroleum ether (−70°C) gave colourless crystals 87 mg (45 %) of which the IR-spectrum was identical with that of 5 prepared as described above.

Diethyl 2-methyl-2-pyrrolin-1,3-dicarboxylate (18a). To a suspension of 21.9 g (0.5 mol) of a 55 % dispersion of sodium hydride in mineral oil and 250 ml of DMA was added with stirring 65.0 g (0.5 mol) of ethyl acetoacetate. When the hydrogen evolution had ceased, 15 g of sodium iodide (dried at 140°C for 24 h) and 83.5 g (0.55 mol of 11a) was added and the stirred solution was heated to 80°C for 4 h. After cooling to room temperature 750 ml of water and 125 ml of hydrochloric acid (4 M) was added and the solution was extracted with three 200 ml portions of methylene chloride. The pooled organic phases were washed with 200 ml of water, dried (MgSO4), and evaporated in vacuo to give an oil which was distilled at 144 - 146°C/0.5 mmHg to give a colourless oil which solidified upon standing. TLC showed the distillate to consist of two compounds (spraying reagent DNP) of which the less polar compound was shown to be 18a whereas the other compound according to the spectro-
Scopio investigations is assumed to be the corresponding 
β-oxoester 12a. IR (neat) cm⁻¹: 3700–3100(m); 3050–2800(m); 1740–1690(s, 
several bands); 1530(m). To complete the 
cyclization the mixture was dissolved in 
400 ml of toluene and after addition of 1 g of 
\(p\)-toluene sulfonic acid the solution was refluxed for 
ca. 8 h using a Dean-Stark water separator, 
dried (K₂CO₃), and evaporated in vacuo to 
give an oil. Distillation at 126–135 °C/0.5 
mmHg gave 73.7 g (66 %) of 13a as a colourless oil 
which solidified upon standing. 0.5 g of 13a 
was purified by column chromatography (silica 
gel: 25 g; eluent: benzene-ethyl acetate 4:1) 
to give crystals of 13a. Recrystallization from 
methanol yielded colourless crystals, m.p. 
56–57 °C. (Found: C 58.25; H 7.34; N 6.11. 
Calc. for \(C₈H₁₅N₂O₄\): C 58.13; H 7.54; N 6.18). 
\(\lambda_{max}(C₅H₅OH): 281 \text{ nm (ε = 19.5 × 10⁴)} \text{ IR data (KBr): cm}^{-1}: 3600–3100(m); 3050–2800(s); 
1740–1720(s); 1690(s); 1530(s). \text{ H NMR (CDCl₃): δ 4.15 and 4.12 [2 × q} \text{ (J = 7 Hz in both 
cases); 4.2 H; 2 × CH₂-C=CH₂]; 4.0–3.5 (m, 
2 H, CH₂-C=CH₂); 2.54 (s, 3 H, CH₃-C=CH₂); 1.27 
and 1.25 [2 × t (J = 7 Hz in both cases), 
6 H, 2 × O-C=CH₂].

4-(2-Ethoxycarbonylaminomethyl)-5-methyl-3- 
isoxazolol (14a). To a solution of 2.1 g (30 mmol) 
of hydroxylamine hydrochloride in 50 ml of 
water was added a solution of 6.3 g (ca. 
90 mmol) of potassium hydroxide in 50 ml of 
each solution mixture was placed at 5 °C for 8 days. 
Additionally, ether was added to the resulting 
material and stirred. 
The mixture was left at room temperature 
for 1 h and was subsequently extracted 
continuously for 1 h with ether-methylene chloride 
4:1. The extract was dried (MgSO₄) and 
volatile in vacuo to give 1.45 g of crude product 
with ca. 71 % yield. 

90 min. After reflux for 60 min an additional 
amount of 3 ml of glacial acetic acid containing 
43 % of hydrogen bromide was added. After 
cooling to room temperature the solution was 
evaporated to dryness in vacuo to give brownish 
crystals. Recrystallization from methanol-ether 
gave 343 mg (77 %) of colourless crystals, m.p. 
205–208 °C (decomp.). (Found: C 32.45; 
H 5.01; Br 35.58; N 12.63. 
Calc. for \(C₃H₅BrN₂O₂\): C 32.31; H 4.97; Br 35.82; N 12.56). 
\(\lambda_{max}(CH₃OH): < 210 \text{ nm (IR (KBr): cm}^{-1}: 
3600–2200(s); 1600(s); 1575(m); 1540–1520(s, 
several bands); 1500(s); 1370(w). 
\text{ H NMR (DMSO-d₆): δ 8.3–7.6 (broad signal, 
3 H, \(\text{NH}₂^+\)); 3.2–2.3 (broad signal, 4 H, 
CH₂-C=CH₂-NH₂); 2.25 (s, 3 H, CH₃-C=CH₂). 
The OH-proton could not be detected. 

4-(2-Aminoethyl)-5-methyl-3-isoxazolol 
zwiterion (16a). A solution of 1.80 g (8.1 mmol) 
of 15a in water (12 ml) was passed through 
across a column containing an ion exchange resin 
(amberlite IRA 400 (OH), 40 ml) using acetic 
acid (1 M) as an eluent. Recrystallization from 
water-ethanol gave 339 mg (30 %) of 
colourless crystals, m.p. 159.5–161.5 °C 
(decomp.). (Found: C 50.58; H 7.21; N 19.98. 
Calc. for \(C₇H₆N₂O₂\): C 50.69; H 7.09; N 19.71). 
\(\lambda_{max}(CH₃OH): 213 \text{ nm (ε = 5.83 × 10⁴)} \text{ IR (KBr): cm}^{-1}: 3600–2200(s); 2090(w); 1655(s); 1570–1550(s, 
several bands); 1500–1480(s, several 
bands). \text{ pKₐ-Values (H₂O, 17 °C): 5.12 ± 0.05, 
10.42 ± 0.06. \text{ H NMR (D₂O [sodium 3-(tri- 
methylsilyl)propanesulphonate was used as an 
internal standard]): δ 4.79 (s, ca. 4 H, DOH); 
3.10 [t (J = 6 Hz), 2 H, CH₂-NH₂]; 2.55 
[t (J = 6 Hz), 2 H, CH₂-C=CH₂]; 2.15 
(s, 3 H, CH₃-C=CH₂). 

2-Aminopropan-1-ol (10b) was prepared 
before low pressure (3 atm.) hydrogenation of 
an ethanolic solution of 2-nitropropan-1-ol (9) 
in a PARR hydrogenation apparatus using 
500 mg of a 10 % Pd-C catalyst and 500 ml of 
ethanol per 0.5 mol of starting material. 
Yield 70 %, b.p. 71–74 °C/11 mmHg. (Ref. 
76–78 °C/15 mmHg). 

1-Chloro-2-ethoxy carbonylaminopropane (11b) 
was prepared via 1-hydroxy-2-(ethoxycarbonyl- 
amino)propane as described by Najer et al.,
using 10b as starting material.

Diethyl 2,5-dimethyl-2-pyrroline-1,3-dicarboxy- 
late (15b). To a suspension of 17.9 g (0.41 mol) 
of a 55 % dispersion of sodium hydroxide in 
methanol, and 200 ml of DMA was added 
with stirring 63.0 g (0.41 mol) of ethyl aceto- 
acetate. When the hydrogen evolution had 
ceased, 61.5 g (0.41 mol) of sodium iodide 
(dried at 140 °C for 24 h) and 66.2 g (0.45 mol) 
of 11b was added and the solution was stirred 
for 3 h at 100 °C. After cooling to room 
temperature the crude product was isolated 
as described for 13a. Treatment with p-toluene- 
sulfonic acid in toluene under reflux for 24 
h and isolation as described for 13a gave 33.7 
g of crude product as a brownish oil which was
used without further purification for the preparation of 16b. An analytical sample of the crude product was purified by column chromatography (silica gel: 25 g; eluent: methylene chloride) to give a colourless oil which was distilled in a "Kugelrohr" at 0.5 mm Hg (oven temperature 160 °C) to give pure 13b as an oil. (Found: C 59.65; H 7.85; N 5.72. Calc. for C8H15NO2: C 59.73; H 7.94; N 5.81. \( \lambda_{\text{max}} \) (CH2OH): 281 nm (\( \varepsilon = 1.7 \times 10^2 \)) (IR (neat) cm\(^{-1}\): 3700 – 3100 (w), 3050 – 2800 (s), 1725 (s), 1690 (s), 1630 (s). \(^1\)H NMR (CDCl3): \( \delta \) 4.07 and 4.00 [2 x (J = 7 Hz in both cases), 4 H, 2 x O - CH2 - CH2]; 4.5 – 3.8 (m, 1 H, N - CH - CH2); 3.2 – 1.9 (m, 2 H, H = C - CH2 – CH2); 2.44 (t, 3 H, CH2 – C –); 1.8 – 1.0 (m, 9 H, CH2 – CH and 2 x O - CH2 – CH2).

4-(2-Ethoxycarbonylaminopropyl)-5-methyl-3-isoazolol (14b) was prepared as described above for 14a. 7.53 g (30 mmol) of crude 12b gave 4.55 g of crude product which was submitted to column chromatography (silica gel: 200 g; eluent: methylene chloride-ethyl acetate-formic acid (60:40:1)) to give 2.9 g of product. Recrystallization from ethyl acetate-benzene gave 280 mg (14 %) of colourless crystals, m.p. 170 – 170.5 °C. (Found: C 52.50; H 6.97; N 12.11. Calc. for C14H26N2O2: C 52.62; H 7.07; N 12.27. \( \lambda_{\text{max}} \) (CH2OH): 216 nm (\( \varepsilon = 6.70 \times 10^2 \)). IR (KBr) cm\(^{-1}\): 3340 (m); 3200 – 2200 (m); 1680 (s); 1660 (m); 1560 – 1520 (s, several bands). \(^1\)H NMR (CDCl3 – DMSO-d6, 5:3): 3.7 – 6.5 (broad s, ca. 1 H, CH2); 6.5 – 6.0 (broadened signal, 1 H, NH); 3.95 [J = 7 Hz, 2 H, O - CH2 – CH2]; 4.2 – 3.3 (m, 1 H, – CH2 – NH); 2.35 [d (J = 7 Hz), 2 H, = C - CH2 – CH2]; 2.20 (s, 3 H, CH2 – C –); 1.18 and 1.05 [2 x t (J = 7 Hz in both cases), 6 H, 2 x O - CH2 – CH2].

4-(2-Aminopropyl)-5-methyl-3-isooazolol hydrobromide (15b). A solution of 250 mg (1.1 mmol) of 14b was treated with glacial acetic acid containing 43 % of hydrogen bromide as described for the preparation of the compound 15a to give an oil which crystallized from methanol-ether to give 210 mg (85 %) of 15b as colourless crystals, m.p. 198 – 199 °C (decomp.). (Found: C 55.25; H 5.78; Br 33.70; N 11.82. Calc. for C14H26BrN2O2: C 35.46; H 5.52; Br 33.71; N 11.82. \( \lambda_{\text{max}} \) (CH2OH): 211 nm (\( \varepsilon = 5.88 \times 10^3 \)). IR (KBr) cm\(^{-1}\): 3600 – 3300 (w), 3300 – 3200 (s); 2060 – 1900 (w); 1660 (m); 1585 (m); 1530 (s); 1450 (s). \(^1\)H NMR (D2O [sodium 3-(trimethylsilyl)propanesulfonate was used as an internal standard]): 4.73 (s, 4 H, DOH); 4.1 – 3.6 (broad signal, 2 H, CH2 – NH2); 2.5 – 2.0 (broad signal, 3 H, CH3 – C –).

3-Methoxy-4-(1-aminoethyl)-5-methylisooazolol hydrochloride (17b) was prepared as described by Bowden et al.18 to give crystals, m.p. 199.5 – 200.5 °C (decomp.). (Ref: 10: m.p. 203 °C). \( \lambda_{\text{max}} \) (CH2OH): 212 nm (\( \varepsilon = 4.57 \times 10^4 \)). IR (KBr) cm\(^{-1}\): 3600 – 3300 (w), 3300 – 2400 (e), 2500 – 1900 (w), 1640 – 1600 (m), 1560 (s); 1470 (s). \(^1\)H NMR (DMSO-d6): \( \delta \) 9.0 – 8.1 (broadened s, 3 H, NH2); 3.87 [s, 3 H, OCH3]; 4.5 – 4.0 (m, 1 H, CH2 – CH2 – NH2); 2.40 [s, 3 H, = C – CH2 –].

4-(1-Aminoethyl)-5-methyl-3-isooazolol hydrobromide (18b) was prepared as described above for 15a using 500 mg (2.6 mmol) of 17b as starting material. The crude oily product was crystallized from methanol-ether to give 423 mg (75 %) of colourless crystals, m.p. 193 – 195 °C (decomp.). (Found: C 32.25; H 5.03; Br 36.05; N 12.71. Calc. for C14H19BrN2O2: C 32.30; H 4.97; Br 35.82; N 12.56. \( \lambda_{\text{max}} \) (CH2OH): 211 nm (\( \varepsilon = 5.10 \times 10^4 \)). IR (KBr).
cm$^{-1}$: 3600 – 3300 (m); 3300 – 2300 (s); 1660 – 1640 (s); 1540 (s); 1495 (s). 1H NMR (DMSO-d$_6$): δ 8.7 – 7.3 (broad signal, 3 H, NH$_{3}^{+}$); 4.5 – 3.7 (m, 1 H, CH$_3$ – CH – NH$_{3}^{+}$); 2.33 (s, 3 H, CH$_3$ – C═); 1.47 (d [J = 6 Hz], 3 H, CH$_3$ – CH). The OH proton could not be detected.

4-(1-Aminoethyl)-5-methyl-3-isoxazoloxzwitterion (20). To a solution of 39 mg (0.17 mmol) of 18b in 2 ml of ethanol was added 50 μl (5 mmol) of triethylamine at 40°C, and the reaction mixture was kept at room temperature to complete crystallization. 19 mg (80%) of colourless crystals were obtained. Recrystallization from water-ethanol-ether gave crystals, m.p. 204.5 – 205°C (decomp.). (Found: C 50.40; H 7.77; N 19.92. Calc. for C$_8$H$_{18}$N$_2$O$_4$: C 50.69; H 7.09; N 19.71. λ$_{max}$(CH$_3$OH): < 210 nm. IR (KBr) cm$^{-1}$: 3600 – 3300 (m); 3300 – 2300 (m); 2200 (m); 1640 (m); 1520 – 1490 (s). pK$_A$ Values (H$_2$O, 20°C): 4.74 ± 0.03, 9.73 ± 0.03. 1H NMR (D$_2$O [sodium 3-(trimethylsilyl)propanesulfonate was used as an internal standard]): δ 4.75 (s, 3 H, DOH); 4.28 (q [J = 7 Hz], 1 H, CH$_3$ – CH); 2.23 (s, 3 H, CH$_3$ – C═); 1.58 (d [J = 7 Hz], 3 H, CH$_3$ – CH).

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