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Organic Hydroxylamine Derivatives

VIII.* Structural Analogues of GABA of the Isoxazole Enol-Betaine Type. Synthesis of 5,6,7,8-Tetrahydro-4*H*-isoxazolo[3,4-*d*]azepin-3-ol Zwitterion and Some Derivatives

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The structural analogue of GABA, 5,6,7,8-tetrahydro-4*H*-isoxazolo[3,4-*d*]azepin-3-ol zwitterion (V), a new heterocyclic compound, and some derivatives have been synthesized using the reaction of hydroxylamine with enamines of β-ketoesters previously found to give isoxazolin-5-ones.[18] The pK_A values of the isoxazolin-5-ones described have been determined and the enol-betaine character of (V) and of the *N*-benzyl derivative (VI) has been established.

Some common structural features of GABA, muscimol, and compound (V) are compared.

Structure-activity correlations of conformationally restricted analogues of γ-aminobutyric acid (GABA), an inhibitory transmitter at certain synapses in the mammalian central nervous system,[1,2] are of importance in the investigations of the active conformations of GABA. Recent studies seem to indicate that extended conformations of GABA are important in the initial bindings of GABA to its transport carrier [3] as well as to the active sites of the GABA transaminase enzymes.[4] However, studies of the interactions between GABA analogues and the postsynaptic receptors have provided rather conflicting suggestions as to the active conformations of GABA. On these receptors GABA might be active in extended [5–8] and/or folded conformations.[9,10]

Muscimol (3-hydroxy-5-aminomethylisoxazole) has been demonstrated to be a GABA agonist of restricted conformation [5] and furthermore to be a non-competitive inhibitor of the GABA transport system.[3,11] Further information about the active conformations of GABA might be obtained from structure-activity investigations of pertinent aminoalkyl substituted 3-hydroxyisoxazoles. The zwitterionic character of these 3-hydroxyisoxazole derivatives is

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generally accepted and has been confirmed for muscimol and for the homologous compound, 3-hydroxy-5-(2-aminoethyl)isoxazole, by X-ray crystallographic structural analysis.[12,13]

The isoxazolin-5-one nucleus has pronounced acidic properties [14] and amphoteric properties have been shown for 4-(3-aminopropyl)-5-hydroxyisoxazole,[15]* a very unstable compound which is the hitherto only known 5-hydroxyisoxazole enol-betaine. These protolytic properties indicate that GABA agonists may well be found among 5-hydroxyisoxazole enol-betaines structurally related to muscimol. This paper presents the synthesis of 5,6,7,8-tetrahydro-4*H*-isoxazolo[3,4-*d*]azepin-3-ol zwitterion (V), which is a structural analogue of GABA. Two conformers of (V) (A and B in Fig. 1) seem to be almost equally favourable. The approximate *intra*-molecular distances between the exocyclic oxygen atoms and the azepine nitrogen atoms in A and B are 4.5 and 5.3 Å, respectively (Dreiding stereomodels) (*cf.* Ref. 12). The structural relationship between GABA, muscimol, and 5,6,7,8-tetrahydro-4*H*-isoxazolo[3,4-*d*]azepin-3-ol (V) including their amphoteric properties are shown in Fig. 1.

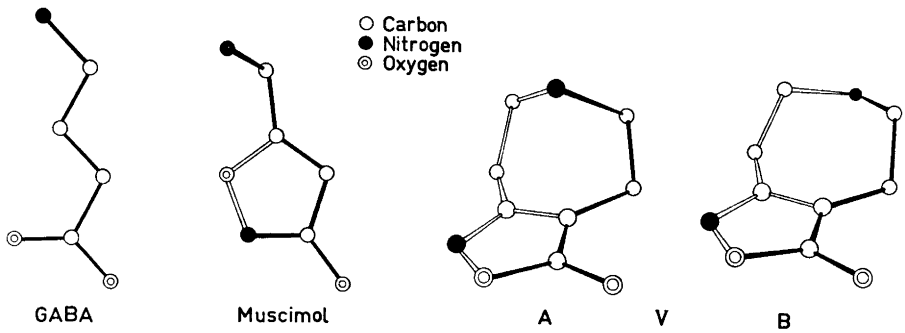
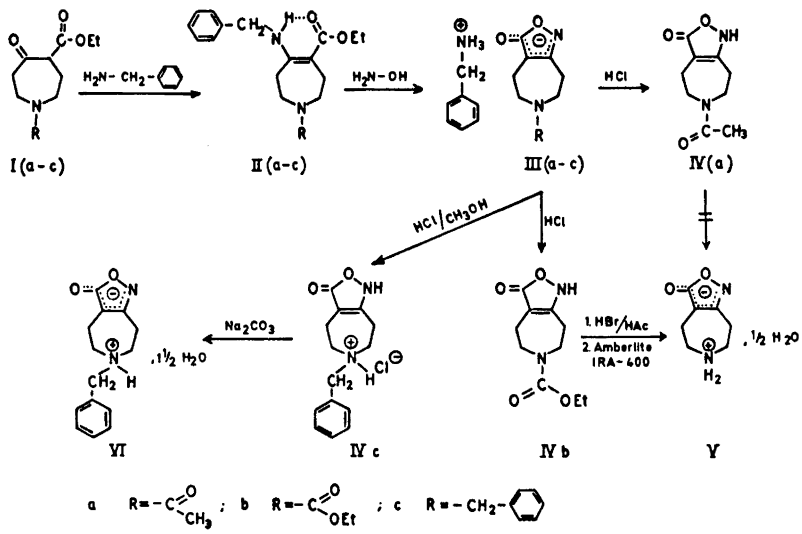


Fig. 1. Similarities of structures (heavy black lines) and amphoteric properties of GABA, muscimol, and two conformers of 5,6,7,8-tetrahydro-4*H*-isoxazolo[3,4-*d*]azepin-3-ol zwitterion (VA and VB). pK_A-values (H_2O): 4.03, 10.6 [16] (GABA); 4.78, 8.43 [17] (muscimol); 3.3, 9.6 (V).

The synthesis of compound (V) and derivatives as described below are based on the reaction of hydroxylamine with the *N*-benzylenamines (IIa – c) of the appropriate β-ketoesters (Ia–c) as shown in Scheme 1. This reaction was earlier shown [18] to give isoxazolin-5-ones *via* the corresponding benzylammonium salts. In Scheme 1 the isoxazolin-5-ones are depicted as the 3-isoxazolin-5-one tautomers, but in fact isoxazolin-5-ones usually are mixtures of at least this tautomer and the 2-isoxazolin-5-one tautomer.[14,19]

* In the literature this compound is named 4-(3-aminopropyl)-2-isoxazolin-5-one.



Scheme 1.

The β-ketoesters (Ia–c), prepared by ring expansion of the corresponding 4-piperidone derivatives with ethyl diazoacetate as described by Yamamoto *et al.*[20] and Moriya *et al.*,[21] were treated with benzylamine to give the enamines (IIa–c). The enamine structure of the compounds (IIa–c), each of which form an *intra*molecular hydrogen bond, were established by IR, UV, and ^{1}H NMR spectroscopy, and were in agreement with the previous findings for analogous compounds.[18] The enamines (IIa–c) were treated with hydroxylamine to give the benzylammonium salts (IIIa–c). The structure determinations of (IIIa–c) were based on IR, UV, and ^{1}H NMR spectroscopy and in the case of (IIIb–c) further supported by elemental analyses. Compound (IIIa) could not be obtained in a crystalline state. The spectroscopic data of (IIIa–c) were in accordance with the general findings for analogous products.[18]

Treatment of the benzylammonium salts (IIIa,b) with hydrochloric acid and of (IIIc) with methanolic hydrogen chloride afforded the isoxazolin-5-ones (IVa–c) in good yields. Conclusive evidence of the constitutions of these compounds were provided by elemental analyses and by IR, UV, and ^{1}H NMR spectroscopy. The spectroscopic data were in accordance with the general findings described by Jacquier *et al.*[19]

Attempts to prepare the enol-betaine (V) from the isoxazolin-5-one (IVa) were unsuccessful. Thus, reflux of (IVa) with 6 N hydrochloric acid for 4 h caused extensive decomposition of the molecule and no product was isolated. On the other hand after boiling under reflux of (IVa) with a 43 % solution of hydrogen bromide in glacial acetic acid for 3 h as well as with a 10 % solution of sodium methoxide in methanol for 4 h (IVa) was left almost completely unreacted. In another attempt to prepare (V) the isoxazolin-5-one

(IVb) was refluxed with a 15 % solution of potassium hydroxide in methanol for 24 h after which time the starting material (IVb) could be recovered from the reaction mixture in 90 % yield. Finally (IVb) was cleaved by treatment with a 43 % solution of hydrogen bromide in glacial acetic acid and 5,6,7,8-tetrahydro-4*H*-isoxazolo[3,4-*d*]azepin-3-ol zwitterion (V) was isolated from the reaction mixture in moderate yield using a strongly basic ion exchange resin. The compound was shown to crystallize as a hemihydrate.

The enol-betaine (VI) was isolated from an aqueous solution of the isoxazolin-5-one hydrochloride (IVc) after adjustment of pH of the solution to 6.5. The compound crystallized with 1.5 mol of water.

IR and UV spectroscopic data of the compounds (II)–(VI), which are all new, and pK_A values of the acidic or amphoteric compounds (IV)–(VI) are listed in Table 1. In the IR spectra of the compounds (V) and (VI) carbonyl group signals were absent, and the aromatic character of the isoxazole nucleus of the compounds (V) and (VI) as well as of (IIIa–c) manifests itself as absorp-

Table 1. IR and UV data and pertinent pK_A values of the compounds (II) – (VI).

	IR data [a]	UV data [b]		pK_A values [c]	
	(cm^{-1})	λ_{max}(nm)	$\varepsilon \times 10^{-3}$	I	II
IIa	3250(m), 1650(s), 1630(s), 1595(s)	304	13.3		
IIb	3240(m), 1695(s), 1645(s), 1600(s)	304	14.4		
IIc [d]	3240(m), 1642(s), 1600(s)	304	13		
IIIa [d,e]	3600 – 2300(s), 2150(w), 1680(m), 1640 – 1610(s), 1500 – 1470(s)	261	6.6		
IIIb [e]	3200 – 2300(s), 2180(w), 1690(s), 1620(s), 1490 – 1460(s)	260	6.68		
IIIc [e]	3300 – 2300(s), 2160(w), 1630 – 1610(s), 1510 – 1460(s)	261	5.95		
IVa	3300 – 2600(s), 1720(s), 1640 – 1610(s)	263	8.51	4.3	
IVa [f]	3500 – 2600(m), 1790(m), 1730(s), 1640(s), 1600(m)				
IVb	3300 – 2600(m), 1725(s), 1665(s), 1630(s)	263	8.26	4.7	
IVb [f]	3500 – 2600(m), 1790(m), 1720(s), 1665(s), 1625(s)				
IVc	3200 – 2300(s), 1725(s), 1640(s), 1610(m)	259	7.26	3.3	8.
V	3600 – 2200(m), 2150(w), 1650 – 1610(s), 1520 – 1470(s)	255	9.00	3.3	9.6
IV	3600 – 2000(m), 1650 – 1610(s), 1520 – 1470(s)	254	8.00	3.3	8.3

[a] Unless otherwise stated the IR spectra were recorded in the solid state (KBr). [b] Unless otherwise stated the UV spectra were recorded in ethanol solutions. [c] pK_A values were determined by electrometrical titration in water at 25°C according to the method described by Albert and Serjeant.[23] [d] The IR spectrum was recorded using the film technique. [e] The UV spectra were recorded in tetrahydrofuran solutions. [f] The IR spectra were recorded in chloroform solutions (*cf.* Ref. 19).

tion bands in the 1520 – 1460 and 1650 – 1600 cm^{-1} regions.[22] Broad absorptions in the IR spectra of (V) and (VI) over the range 3600 – 2000 cm^{-1} and in the case of compound (V) an absorption band at 2150 cm^{-1} suggest ammonium salt character of the molecules. These observations compared with the acidic properties of the isoxazolin-5-one nucleus confirm the proposed zwitterionic character of the compounds (V) and (VI). The UV maxima of the enol-betaines (V) and (VI) were observed at wavelengths of 255 and 254 nm, respectively, in agreement with that observed (255 nm) for the zwitterionic compound 4-(3-aminopropyl)-5-hydroxyisoxazole by Quin and Pinion.[15]

EXPERIMENTAL

Unless otherwise stated the determinations 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.[18] The singlet, doublet, triplet, quartet, and multiplet patterns of the ^1H NMR spectra are designed s, d, t, q, and m, respectively. pH Values were measured on a Radiometer pH meter 26.

*Ethyl 1-acetyl-4-benzylamino-2,3,6,7-tetrahydro-1*H*-azepine-5-carboxylate (IIa).* A mixture of 8.4 g (37 mmol) of (Ia),[20] 4.4 g (41 mmol) of benzylamine, and 18 g of molecular sieve, Union Carbide 3A, was refluxed in 75 ml of benzene for 5 h. The mixture was filtered and concentrated *in vacuo* to give 8.5 g (73 %) of pale yellow crystals. Recrystallization (cyclohexane) of an analytical sample afforded colourless crystals, m.p. 106.0 – 108.5°C. (Found: C 68.50; H 7.73; N 8.94. Calc. for $C_{18}H_{24}N_2O_3$: C 68.33; H 7.65; N 8.85). ^1H NMR data (CCl_4) δ: 9.7 [broadened t ($J = 6$ cps), 1 H, CH_2-NH-C]; 7.25 (slightly broadened s, 5 H, C_6H_5); 4.36 [d ($J = 6$ cps), 2 H, $C-CH_2-NH$]; 4.06 [q ($J = 7$ cps), 2 H, $O-CH_2-CH_3$]; 3.7 – 3.1 (m, 4 H, $CH_2-CH_2-N-CH_2-CH_2$); 2.8 – 2.3 (m, 4 H, $CH_2-CH_2-C=C-CH_2-CH_2$); 2.00 [s, 3 H, $CH_3-C=O$); 1.21 (t ($J = 7$ cps), 3 H, CH_3-CH_2].

*Benzylammonium salt of 6-acetyl-5,6,7,8-tetrahydro-4*H*-isoxazolo[3,4-*d*]azepin-3-ol (IIIa).* 368 mg (16 mmol) of sodium were allowed to react with methanol (50 ml) and to this solution were added 1.10 g (16 mmol) of hydroxylammonium chloride. After stirring for 5 min 4.5 g (15 mmol) of (IIa) were added and the mixture was refluxed for 2 h. After cooling to room temperature 25 ml of tetrahydrofuran (THF) were added. The mixture was stirred for 5 min, filtered, and evaporated to dryness *in vacuo* to give 4.2 g (97 %) of a glassy compound which on TLC plates [silica gel GF_{254} (Merck), chloroform – methanol – formic acid (66:33:1), ninhydrin] gave two spots corresponding to benzylamine and the isoxazolin-5-one (IVa). ^1H NMR data (DMSO-d_6) δ: 7.6 – 7.2 (m, 5 H, C_6H_5); 7.1 – 6.4 (broadened signal, 3 H, $CH_2-NH_3^+$); 3.98 (slightly broadened s, 2 H, $C-CH_2-NH_3^+$); 3.7 – 3.2 (m, 4 H, $CH_2-CH_2-N-CH_2-CH_2$); 2.7 – 2.0 (m, 4 H, $CH_2-CH_2-C=C-CH_2-CH_2$); 2.03 (s, 3 H, $CH_3-C=O$).

*6-Acetyl-1,3,4,5,7,8-hexahydro-3-oxo-6*H*-isoxazolo[3,4-*d*]azepine (IVa).* 3.4 g (11 mmol) of crude benzylammonium salt (IIIa) were dissolved in 10 ml of water. Upon addition of 5 g of sodium carbonate the mixture was continuously extracted with ether for 1.5 h. The ether phase was discarded, and upon addition of 8 ml of concentrated hydrochloric acid the aqueous phase was continuously extracted with ether – methylene chloride (4:1) for 48 h. The extract was dried, filtered, and evaporated. Recrystallization (methanol) of the residue afforded 1.4 g (64 %) of (IVa) as colourless crystals, m.p. 162.5 – 164.5°C (decomp.). (Found: C 55.10; H 6.28; N 14.35. Calc. for $C_9H_{12}N_2O_3$: C 55.09; H 6.17; N 14.28). ^1H NMR data (DMSO-d_6) δ: 3.8 – 3.3 (m, 4 H, $CH_2-CH_2-N-CH_2-CH_2$); 2.8 – 2.1 (m, 4 H, $CH_2-CH_2-C=C-CH_2-CH_2$); 2.06 (s, 3 H, $CH_3-C=O$). Several ^1H NMR spectra of (IVa) were recorded in DMSO-d_6 solution, but in no case could the resonance signal of the acidic proton of (IVa) be detected.

*Diethyl 4-benzylamino-2,3,6,7-tetrahydro-1*H*-azepine-1,5-dicarboxylate (IIb).* (IIb) was synthesized as described above for (IIa) using 8.6 g (33 mmol) of (Ib)[21] and 3.9 g (36 mmol) of benzylamine to give 11.0 g (95 %) of crude product as a pale yellow oil. An analytical sample was subjected to column chromatography on silica gel (0.05 – 0.20 mm,

Merck), eluent: benzene – ethyl acetate (2:1). The purified enamine (IIb) was crystallized (petroleum ether) to give colourless needles, m.p. 36.5 – 39.0°C. (Found: C 65.75; H 7.64; N 8.07. Calc. for $C_{19}H_{26}N_2O_4$: C 65.87; H 7.57; N 8.09). ^{1}H NMR data (CCl_4) δ: 9.8 [broadened t ($J = 6$ cps), 1 H, CH_2-NH-C]; 7.20 (slightly broadened s, 5 H, C_6H_5); 4.38 [d ($J = 6$ cps), 2 H, $C-CH_2-NH$]; 4.02 and 3.95 [2 × q ($J = 7$ cps in both cases), 4 H, $2 \times O-CH_2-CH_3$]; 3.5 – 3.1 (m, 4 H, $CH_2-CH_2-N-CH_2-CH_2$); 2.7 – 2.3 (m, 4 H, $CH_2-CH_2-C=C-CH_2-CH_2$); 1.23 and 1.16 [2 × t ($J = 7$ cps in both cases), 6 H, $2 \times CH_3-CH_2$].

*Benzylammonium salt of ethyl 5,6,7,8-tetrahydro-4*H*-isoxazolo[3,4-*d*]azepin-3-ol-6-carboxylate (IIIb).* (IIIb) was prepared as described above for (IIIa) using 5.0 g (15 mmol) of (IIb) and 1.10 g (16 mmol) of hydroxylammonium chloride to give 5.8 g of a crystalline product. An analytical sample was recrystallized twice (THF) to give (IIIb) as colourless crystals, m.p. 152 – 156°C (decomp.). (Found: C 61.30; H 7.08; N 12.80. Calc. for $C_{17}H_{23}N_3O_4$: C 61.22; H 6.99; N 12.60). ^{1}H NMR data (DMSO-d_6) δ: 8.3 – 7.5 (broadened signal, 3 H, $CH_2-NH_3^+$); 7.4 (slightly broadened s, 5 H, C_6H_5); 3.94 [q ($J = 7$ cps), 2 H, $O-CH_2-CH_3$]; 3.94 (slightly broadened s, 2 H, $C-CH_2-NH_3^+$); 3.6 – 3.1 (m, 4 H, $CH_2-CH_2-N-CH_2-CH_2$); 2.4 – 1.9 (m, 4 H, $CH_2-CH_2-C=C-CH_2-CH_2$); 1.15 [t ($J = 7$ cps), 3 H, CH_3-CH_2].

*Ethyl 1,3,4,5,7,8-hexahydro-3-oxo-6*H*-isoxazolo[3,4-*d*]azepine-6-carboxylate (IVb).* (IVb) was synthesized as described above for (IVa) using 5.6 g (17 mmol) of crude (IIIb). Continuous extraction of the acidified aqueous phase with ether-methylene chloride (4:1) for 1.5 h afforded 3.8 g of crude (IVb), which was recrystallized (THF – ether) to give 2.3 g (58 %) of (IVb) as colourless crystals, m.p. 112.0 – 113.0°C (decomp.). (Found: C 53.45; H 6.33; N 12.55. Calc. for $C_{10}H_{14}N_2O_4$: C 53.09; H 6.24; N 12.38). ^{1}H NMR data [$CCl_4 - CDCl_3$ (1:1)] δ: 9.8 – 9.4 (broadened signal, 1 H, N*H*); 4.14 [q ($J = 7$ cps), 2 H, $O-CH_2-CH_3$]; 3.8 – 3.3 (m, 4 H, $CH_2-CH_2-N-CH_2-CH_2$); 3.0 – 2.2 (m, 4 H, $CH_2-CH_2-C=C-CH_2-CH_2$); 1.27 [t ($J = 7$ cps), 3 H, CH_3-CH_2].

*5,6,7,8-Tetrahydro-4*H*-isoxazolo[3,4-*d*]azepin-3-ol zwitterion (V).* 3.7 g (17 mmol) of (IVb) were dissolved in 35 ml of glacial acetic acid containing 43 % of hydrogen bromide at 25°C. The solution was heated in an oil bath for 30 min during which time the temperature rose to 90°C. A further amount of 35 ml of glacial acetic acid containing hydrogen bromide (43 %) was carefully added and the solution was refluxed (bath temperature: 90 – 100°C) for 1.5 h. After cooling to 25°C a black oil separated. Upon addition of water (20 ml) the solution was evaporated *in vacuo*. The crystalline residue was dissolved in water (15 ml), refluxed with activated charcoal (2 g) for 2 min, cooled to 25°C, filtered, and evaporated to dryness *in vacuo*. The brown crystalline residue was dissolved in water (10 ml) and passed through a column containing an ion exchange resin [Amberlite IRA 400, (OH), 150 ml] using acetic acid (1 N) as an eluent. Obtained were 2.3 g of crude (V), which crystallized extremely slowly. Extraction twice with 25 ml portions of boiling methanol left 1.6 g (60 %) of (V) as a faint greyish crystalline powder. An analytical sample was recrystallized (ethanol – water) to give (V) as colourless needles, m.p. 215 – 217°C (decomp.). (Found: C 51.50; H 6.79; N 17.10. Calc. for $C_7H_{10}N_2O_2$. 0.5 H_2O: C 51.52; H 6.80; N 17.17). [Found after drying of (V) over P_2O_5 (60 h; 125°C; 0.1 mmHg): C 54.50; H 6.59; N 18.15. Calc. for $C_7H_{10}N_2O_2$: C 54.53; H 6.54; N 18.17]. ^{1}H NMR data [D_2O (acetonitrile was used as an internal standard)] δ: 4.71 (s, 3 H, DO*H*); 3.5 – 3.2 (m, 4 H, $CH_2-CH_2-NH_2^+-CH_2-CH_2$); 3.1 – 2.5 (m, 4 H, $CH_2-CH_2-C=C-CH_2-CH_2$).

*Ethyl 1-benzyl-4-benzylamino-2,3,6,7-tetrahydro-1*H*-azepine-5-carboxylate (IIc).* (IIc) was synthesized as described above for (IIa) using 5.5 g (20 mmol) of (Ic) [21] and 2.4 g (22 mmol) of benzylamine to give 6.0 g (82 %) of crude product as a pale yellow oil. An analytical sample was rapidly passed down a short column of silica gel (0.05 – 0.20 mm, Merck) using methylene chloride – ethyl acetate (2:1) as an eluent. The isolated enamine (IIc) was obtained as a yellowish oil. As demonstrated by IR and ^{1}H NMR spectroscopy (IIc) contained small amounts of impurities, which could not be removed by repeated chromatographic procedures. ^{1}H NMR data (CCl_4) δ: 9.8 [broadened t ($J = 6$ cps), 1 H, CH_2-NH-C]; 7.10 and 7.14 (2 × s, 10 H, $2 \times C_6H_5$); 4.32 [d ($J = 6$ cps), 2 H, $C-CH_2-NH$]; 3.98 [q ($J = 7$ cps), *ca.* 3 H, $O-CH_2-CH_3$]; 3.36 (s, 2 H, $C-CH_2-N$); 2.7 – 2.0 (m, 8 H, $CH_2-CH_2-N-CH_2-CH_2$ and $CH_2-CH_2-C=C-CH_2-CH_2$); 1.20 [t ($J = 7$ cps), *ca.* 4 H, CH_3-CH_2].

*Benzylammonium salt of 6-benzyl-5,6,7,8-tetrahydro-4*H*-isoxazolo[3,4-*d*]azepin-3-ol (IIIc).* (IIIc) was prepared as described above for (IIIa) using 6.0 g (17 mmol) of crude

(IIc) and 1.24 g (18 mmol) of hydroxylammonium chloride to give 5.4 g (94 %) of crystalline crude product. An analytical sample was recrystallized (THF) to give colourless needles, m.p. 137.5 – 140.0°C (decomp.). (Found: C 71.65; H 7.23; N 11.88. Calc. for $C_{21}H_{25}N_3O_2$: C 71.77; H 7.17; N 11.96). ^{1}H NMR data (DMSO-d_6) δ: 7.36 and 7.26 (two slightly perturbed s, 10 H, $2 \times C_6H_5$); 5.8 – 5.1 (broad signal, 3 H, $CH_2-NH_3^+$); 3.91 (s, 2 H, $C-CH_2-NH_3^+$); 3.65 (s, 2 H, $C-CH_2-N$); 2.8 – 1.9 (m, 8 H, $CH_2-CH_2-N-CH_2-CH_2$ and $CH_2-CH_2-C=C-CH_2-CH_2$).

*6-Benzyl-1,3,4,5,7,8-hexahydro-3-oxo-6*H*-isoxazolo[3,4-*d*]azepine hydrochloride (IVc).* To a solution of 2.9 g (8.3 mmol) of crude (IIIc) in methanol (24 ml) were added with cooling and stirring a methanolic solution of hydrogen chloride, prepared from methanol (20 ml) and acetyl chloride (5 ml). Ether (16 ml) was added and the salt (IVc) was allowed to crystallize at 5°C for 70 h to give 910 mg (39 %) of (IVc) as a white crystalline powder. An analytical sample was recrystallized (methanol) to give colourless crystals, m.p. 186 – 190°C (decomp.). (Found: C 59.90; H 6.21; N 10.12. Calc. for $C_{14}H_{17}ClN_2O_2$: C 59.87; H 6.12; N 9.98). ^{1}H NMR data (DMSO-d_6) δ: 7.9 – 7.3 (m, 5 H, C_6H_5); 4.48 (s, 2 H, $C-CH_2-NH^+$); 3.6 – 2.4 (m, 8 H, $CH_2-CH_2-NH^+-CH_2-CH_2$ and $CH_2-CH_2-C=C-CH_2-CH_2$). The acidic protons of (IVc) were not detectable in the spectrum.

*6-Benzyl-5,6,7,8-tetrahydro-4*H*-isoxazolo[3,4-*d*]azepin-3-ol zwitterion (VI).* In a solution of 420 mg (1.5 mmol) of (IVc) in water (4.5 ml) the pH was brought to *ca.* 6.5 with 2 N sodium carbonate at 65°C, and the enol-betaine (VI) was allowed to crystallize at 5°C for 18 h to give 350 mg (86 %) as colourless plates, m.p. 138.5 – 141.0°C (decomp.). (Found: C 61.80; H 7.09; N 10.38. Calc. for $C_{14}H_{16}N_2O_2 \cdot 1.5\ H_2O$: C 61.97; H 7.06; N 10.33). [Found after drying of (VI) over P_2O_5 (20 h; 60°C; 0.1 mmHg): C 68.90; H 6.93; N 11.57. Calc. for $C_{14}H_{16}N_2O_2$: C 68.83; H 6.60; N 11.47]. ^{1}H NMR data (DMSO-d_6) δ: 7.36 (slightly broadened s, 5 H, C_6H_5); 5.38 (broadened s, 4 H, NH^+ and 1.5 H_2O); 3.86 (slightly broadened s, 2 H, $C-CH_2-NH^+$); 3.0 – 2.1 (m, 8 H, $CH_2-CH_2-NH^+-CH_2-CH_2$ and $CH_2-CH_2-C=C-CH_2-CH_2$).

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