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Organic Hydroxylamine Derivatives. XIII.* The Configurations of a Series of Stereoisomeric 3-Methoxy-5-acylisoxazole Ketoximes

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As part of the synthesis of a series of compounds structurally related to muscimol (3-hydroxy-5-aminomethylisoxazole zwitterion) the 3-methoxy-5-acylisoxazoles (Ia—c) were converted into the corresponding ketoximes. In each case a mixture of two compounds were formed, as shown by thin layer chromatography. The ^{1}H NMR spectra of the isolated products were consistent with mixtures of the stereoisomeric oximes (II) and (III).[1] The corresponding oximes were separated by column chromatography, and the constitutions were confirmed by UV, IR, and ^{1}H NMR spectroscopy, and elemental analyses.

A number of acylisoxazole ketoximes have previously been synthesized,[2,3] but the problems relating to the configurations of the products have in no case received any attention. Attempts to establish unambiguously the structures of (IIa—c) and (IIIa—c) by ^{1}H NMR spectroscopic methods,[4,5] including lanthanide induced [6] and aromatic solvent induced shift experiments,[5,7] were unsuccessful.

The configurations of the oximes were determined by Beckmann rearrangements (Scheme 1) using phosphorus pentachloride in ether, which is reported to favour stereospecific rearrangements.[8] The oximes (IIa-c) having the greater R_F values were rearranged to give the amides (IVa—c) indicating *Z*-configurations of these oximes. The amides (IVa—c) were identified by comparison with authentic amides prepared from the acid chloride (VI) and the amines (VIIa—c), respectively. Correspondingly the oximes (IIIa—c) having the smaller R_F values were rearranged to give the amides (Va—c). Thus the oximes (IIIa—c) possess *E*-configurations. The structure determinations of (Va—c) are based on UV, IR, and ^{1}H NMR spectroscopy and supported by elemental analyses. The UV spectroscopic data originating from the 3-methoxy-5-aminoisoxazole moieties are in agreement with those published for 3-hydroxy-5-aminoisoxazoles.[9,10] Thin layer chromatography indicated that no isomerizations of the oximes took place prior to the rearrangements, as only the expected amides could be detected in the reaction products.

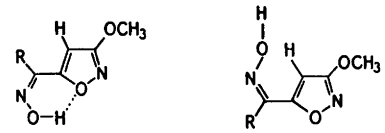

Fig. 1. Two possible conformations of *Z*-3-methoxy-5-(1-hydroxyiminoalkyl)isoxazoles.

Some spectroscopic data of the ketoximes (IIa—c) and (IIIa—c) and the amides (IVa—c) and (Va—c) are listed in Table 1.

The *Z*-isomers of some 2-acylfurane ketoximes have been proposed to form *intra*molecular hydrogen bonds as revealed by IR spectroscopic investigations of diluted solutions.[11] However, similar investigations seem to indicate that (IIb) as well as (IIIb) form hydrogen bonds in 0.04 % chloroform solutions and furthermore absorption bands at 3550 cm^{-1} appeared in the IR

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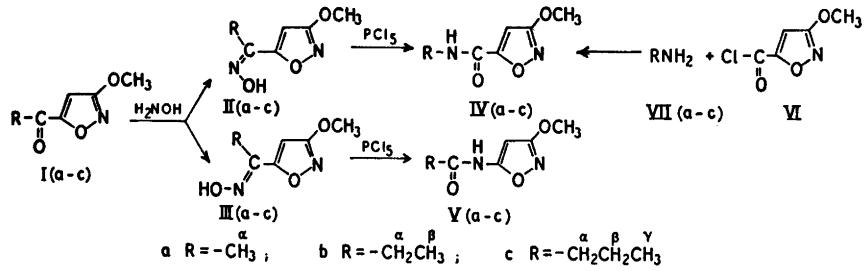
Table 1. UV, IR, and ^{1}H NMR data of the oximes (IIa–c) and (IIIa–c) and the amides (IVa–c) and (Va–c). The UV spectra were recorded in 99.9 % ethanol solutions. The IR spectra were recorded in the solid state (KBr). Unless otherwise stated the ^{1}H NMR spectra were recorded in deuteriochloroform solutions using TMS as an internal reference. The singlet, doublet, triplet, quartet, and multiplet patterns of the ^{1}H NMR spectra are designated s, d, t, q, and m, respectively.

Compound	UV data λ_{max} (nm)	$\varepsilon \times 10^{-4}$	IR data (cm^{-1})	^{1}H NMR data (δ-values) Alkyl protons α	β	γ	C=C*H*-C	C*H*$_3$-O	O*H*	N*H*
IIa[a]	248	1.23	3400–3100(s), 1605(s), 1540–1500(s)	2.25s			6.75s	3.95s		
IIIa[a]	250	1.29	3400–3120(s), 1640(m), 1595(s), 1540–1500(s)	2.20s			6.07s	3.96s		
IVa[b]	226	1.21	3260(s), 3140(m), 1660(s), 1610(s)	2.76d			6.74s	3.93s		9.1–8.6
Va[c]	241	1.25	3020(s), 1680(s), 1640(m), 1580(s)	2.22s			5.92s	3.90s		10.3–10.0
IIb	249	1.18	3400–3100(s), 1605(s), 1540–1500(s)	2.70q	1.23t		6.81s	4.00s	9.8	
IIIb	251	1.29	3400–3100(s), 1640(m), 1595(s), 1540–1500(s)	2.70q	1.18t		6.08s	3.98s	8.7	
IVb	226	1.24	3320(s), 3140(m), 1660(s), 1600(m)	3.7–3.2m	1.25t		6.48s	3.98s		6.9–6.3
Vb	241	1.31	3260(s), 1690(s), 1620(s), 1540–1500(s)	2.43q	1.21t		5.98s	3.91s		8.6
IIc[a,d]	250	1.15	3400–3100(s), 1640(w), 1605(s), 1540–1500(s)	2.55t	1.9–1.4m	0.95t	6.60s	3.95s		
IIIc	252	1.41	3400–3100(s), 1640(m), 1595(s), 1540–1500(s)	2.67t	1.9–1.3m	0.98t	6.07s	3.97s	9.3	
IVc	228	1.11	3270(s), 3120(m), 1660(s), 1600(s)	3.6–3.1m	1.9–1.4m	1.1–0.8t	6.45s	3.96s		6.9–6.4
Vc	244	1.37	3210(s), 1680(s), 1620(s), 1580–1500(s)	2.6–2.2m	2.0–1.5m	1.2–0.8t	6.05s	3.98s		9.1–8.8

[a] The OH signal could not be detected in the ^{1}H NMR spectrum. [b] The ^{1}H NMR spectrum was recorded in hexadeuteriodimethyl sulfoxide. [c] The ^{1}H NMR spectrum was recorded in deuteriochloroform-hexadeuterioacetone (4:1). [d] The ^{1}H NMR spectrum was recorded in tetrachloromethane.



Scheme 1.

spectrum of (IIb) as a result of increasing dilution.

The distinctly greater R_F values of the *Z*-forms compared with those of the corresponding *E*-forms, and the pronounced deshielding of the isoxazole protons in the ^{1}H NMR spectra of the *Z*-isomers (see Table 1) may be explained by assuming an *intra*molecular hydrogen bonded *s-trans* conformation of the bond system C=C–C=N (Fig. 1, A). The latter effect, however, is not inconsistent with an *s-cis* conformation of the *Z*-isomers (Fig. 1, B). In this conformation the hydroxyimino group has approached the isoxazole proton, and thus the observed deshielding might arise from the NOH anisotropy.[4,5] Similar deshieldings of the corresponding furane protons in a series of *Z*-2-furanaldoximes are explained by assuming the *s-cis* conformations.[12,13] Also the very small difference between the chemical shift of the isoxazole proton of (IIb) recorded in deuteriochloroform and that recorded in hexadeuteriobenzene (0.08 ppm) indicates, that the hydroxyl oxygen is situated near this proton.[12]

EXPERIMENTAL

Unless otherwise stated the determinations of melting points, the recording of IR, UV, and ^{1}H NMR spectra, and the performance of microanalyses were accomplished as described in a previous paper.[14] Thin layer and column chromatographic procedures were accomplished using silica gel GF_{254} plates and silica gel, 0.05–0.20 mm (Merck), respectively.

Z-3-Methoxy-5-(1-hydroxyiminoethyl)isoxazole (IIa) and E-3-methoxy-5-(1-hydroxyiminoethyl)-isoxazole (IIIa). A mixture of (IIa) and (IIIa) was prepared as previously described,[1] using 1.41 g (10 mmol) of (Ia), 1.50 g (11 mmol) of sodium acetate trihydrate, and 0.77 g (11 mmol) of hydroxylammonium chloride. The mixture was concentrated to 10 ml *in vacuo*, and extracted with two 20 ml portions of ether. The combined ether phases were dried, and the ether was evaporated *in vacuo* to give 1.25 g of a mixture of the two oximes as colourless crystals. Column chromatography of the mixture of isomers (120 g of silica gel; eluent: methylene chloride to which increasing amounts of ethyl acetate were added), and rechromatography of appropriate fractions afforded 0.2 g of the apolar isomer (IIa) and 0.5 g of the polar isomer (IIIa). Recrystallization (water) gave (IIa) as colourless crystals, m.p. 132–133 °C. (Found: C 46.35; H 5.26; N 18.20. Calc. for $C_6H_8N_2O_3$: C 46.15; H 5.16; N 17.94). Recrystallization (water) afforded (IIIa) as colourless crystals, m.p. 134–135 °C. (Found: C 45.95; H 5.33; N 17.90. Calc. for $C_6H_8N_2O_3$: C 46.15; H 5.16; N 17.94).

Beckman rearrangement of Z-3-methoxy-5-(1-hydroxyiminoethyl)isoxazole (IIa). A suspension of 52 mg (0.24 mmol) of phosphorus pentachloride in ether (1 ml) was added at 0 °C to a solution of 25 mg (0.16 mmol) of (IIa) in ether (2 ml). The stirred mixture was allowed to warm to room temperature, stirred for further 1.5 h, and then poured over crushed ice. The organic phase was isolated, washed with 2 ml of an aqueous solution of sodium carbonate (1 M), dried and concentrated *in vacuo* to give 20 mg of a crystalline product, which was submitted to column chromatography (3.9 g of silica gel; eluent: methylene chloride to which increasing amounts of ethyl acetate were added) to give 4.5 mg (18 %) of colourless crystals. The IR spectrum was identical with that of (IVa), prepared from (VI) and (VIIa).

Beckmann rearrangement of E-3-methoxy-5-(1-hydroxyiminoethyl)isoxazole (IIIa). (IIIa) (139 mg; 0.89 mmol) was rearranged and the reaction product isolated as described above for (IIa). *N*-(3-Methoxyisoxazol-5-yl)acetamide (Va) (13 mg; 10 %) was obtained as colourless crystals, m.p. 156–157.5 °C (benzene). (Found: C 46.05; H 5.21; N 17.83. Calc. for $C_6H_8N_2O_3$: C 46.15; H 5.16; N 17.94).

N-Methyl-3-methoxyisoxazole-5-carboxamide (IVa). To 1 ml of a 40 % aqueous solution of methylamine was added at 0 °C a solution of

322 mg (2.0 mmol) of (VI) in ether (1 ml). After stirring for 15 min the precipitate was isolated and recrystallized (water) to give (IVa) (161 mg; 50 %) as colourless crystals, m.p. 154.5—155.5 °C. (Found: C 46.05; H 5.27; N 18.10. Calc. for $C_6H_8N_2O_3$: C 46.15; H 5.16; N 17.94).

Z-3-Methoxy-5-(1-hydroxyiminopropyl)isoxazole (IIb) and E-3-methoxy-5-(1-hydroxyiminopropyl)isoxazole (IIIb). (Ib) (1.55 g; 10 mmol) was converted into a mixture of the isomeric oximes (IIb) and (IIIb) as previously described.[1] The reaction mixture was worked up as described above for (IIa) and (IIIa) to give (IIb) (0.46 g; 27 %) as colourless needles, m.p. 96—98 °C (water-ethanol), (Found: C 49.85; H 6.18; N 16.17. Calc. for $C_7H_{10}N_2O_3$: C 49.40; H 5.92; N 16.46) and (IIIb) (0.50 g; 28 %) as colourless crystals, m.p. 114.5—118.5 °C (water-ethanol). (Found: C 49.45; H 5.99; N 16.48. Calc. for $C_7H_{10}N_2O_3$: C 49.40; H 5.92; N 16.46).

Beckmann rearrangement of Z-3-methoxy-5-(1-hydroxyiminopropyl)isoxazole (IIb). (IIb) (300 mg; 1.77 mmol) was rearranged and the reaction product isolated as described above for (IIa) to give colourless crystals (20 mg; 7 %), m.p. 75—77 °C (benzene-cyclohexane), the IR spectrum of which was identical with that of (IVb), prepared from (VI) and (VIIb).

Beckmann rearrangement of E-3-methoxy-5-(1-hydroxyiminopropyl)isoxazole (IIIb). (IIIb) (113 mg; 0.59 mmol) was rearranged and the reaction product isolated as described above for (IIa) to give (Vb) (20 mg; 18 %) as colourless crystals, m.p. 95.5—97.5 °C (benzene-cyclohexane). (Found: C 49.45; H 5.97; N 16.55. Calc. for $C_7H_{10}N_2O_3$: C 49.40; H 5.92; N 16.46).

N-Ethyl-3-methoxyisoxazole-5-carboxamide (IVb). A solution of 322 mg (2 mmol) of 3-methoxy-5-chloroformylisoxazole in ether (2 ml) was slowly added to a solution of 225 mg (5 mmol) of ethylamine in ether (3 ml) at 0 °C. The mixture was allowed to warm to room temperature, washed with two 5 ml portions of water, dried, and concentrated *in vacuo* to give 151 mg of crystals. (IVb) (99 mg; 29 %) was obtained as colourless crystals, m.p. 74.5—76.5 °C (benzene-cyclohexane). (Found: C 49.15; H 5.91; N 16.55. Calc. for $C_7H_{10}N_2O_3$: C 49.40; H 5.92; N 16.46).

Z-3-Methoxy-5-(1-hydroxyiminobutyl)isoxazole (IIc) and E-3-methoxy-5-(1-hydroxyiminobutyl)isoxazole (IIIc). (Ic) (1.69 g; 10 mmol) was converted into a mixture of the isomeric oximes (IIc) and (IIIc) as previously described.[1] The reaction mixture was worked up as described above for (IIa) and (IIIa) to give (IIc) as colourless needles, m.p. 119—121 °C (benzene), (Found: C 52.25; H 6.67; N 15.17. Calc. for $C_8H_{12}N_2O_3$: C 52.16; H 6.57; N 15.21) and (IIIc) (1.0 g; 54 %) as colourless needles, m.p. 97—98 °C (cyclohexane). (Found: C 52.10; H 6.32; N 15.23. Calc. for $C_8H_{12}N_2O_3$: C 52.16; H 6.57; N 15.21).

Beckman rearrangements of Z-3-methoxy-5-(1-hydroxyiminobutyl)isoxazole (IIc). (IIc) (300 mg; 1.63 mmol) was rearranged and the reaction product solated as described above for (IIa) to give *N*-propyl-3-methoxyisoxazole-5-carboxamide (IVc) (25 mg; 8 %) as colourless crystals, m.p. 74.5—75 °C (cyclohexane). The IR spectrum was identical with that of (IVc) prepared from (VI) and (VIIc).

Beckmann rearrangement of E-3-methoxy-5-(1-hydroxyiminobutyl)isoxazole (IIIc). (IIIc) (200 mg; 1.09 mmol) was rearranged as described above for (IIa) to give (Vc) (32 mg; 16 %) as colourless crystals, m.p. 113—114 °C (benzene-cyclohexane). (Found: C 52.20; H 6.55; N 15.32. Calc. for $C_8H_{12}N_2O_3$: C 52.16; H 6.57; N 15.21).

N-Propyl-3-methoxyisoxazole-5-carboxamide (IVc). (IVc) was synthesized as described above for (IVb). As starting materials were used 242 mg (1.50 mmol) of (VI) and 300 mg (5.0 mmol) of propylamine (VIIb). Obtained was 197 mg (71 %) of (IVc) as colourless crystals. An analytical sample was recrystallized (cyclohexane) to give (IVc) as colourless crystals, m.p. 75—77 °C. (Found: C 52.35; H 6.62; N 15.30. Calc. for $C_8H_{12}N_2O_3$: C 52.16; H 6.57; N 15.21).

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