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Organic Hydroxylamine Derivatives

VII.* Isoxazolin-5-ones. An Investigation of a Reaction Sequence Previously Stated to Give 3-Hydroxyisoxazoles

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The acid catalyzed cyclization of the reaction products of hydroxylamine and β-ketoesters protected at the keto group with benzylamine has been reported [12] in some cases to give 3-hydroxyisoxazoles. A reinvestigation of these reaction sequences resulted in a revision of the structures of the compounds obtained in the different steps of the sequences, *e.g.* the final products claimed to be ethyl 3-hydroxy-5-methylisoxazolyl-4-acetate (IVb) and 3-hydroxy-4-(2-propynyl)-5-methylisoxazole (IVa) were shown to be ethyl 3-methylisoxazolin-5-on-4-yl-acetate (VIIIb) and 3-methyl-4-(2-propynyl)isoxazolin-5-one (VIIIa), respectively.

Analogous reaction sequences were investigated for the preparation of a number of known isoxazolin-5-ones, and one new, namely, 3-ethyl-4-methylisoxazolin-5-one (VIIIc). The extended investigation showed that the method is of general value for the preparation of isoxazolin-5-ones in a pure state.

The 3-hydroxyisoxazole derivatives muscimol (3-hydroxy-5-aminomethylisoxazole) and ibothenic acid [(±)-α-amino-3-hydroxyisoxazolyl-5-acetic acid], which are centrally acting constituents of *Amanita muscaria* [1] have been shown to be γ-aminobutyric acid and glutamic acid agonists, respectively, when applied to single neurones in the mammalian central nervous system.[2] These findings have stimulated the interest in the structural [3] as well as the synthetic aspects of the 3-hydroxyisoxazoles. During the last decade several synthetic routes leading to 3-hydroxyisoxazoles have been described,[4–7] but either the methods have been of limited scope or the yields have been very low.

Reactions between β-ketoesters and hydroxylamine under basic conditions followed by acidification normally afford mixtures of isoxazolin-5-ones and 3-hydroxyisoxazoles.[8] The reactions probably proceed by proton catalyzed

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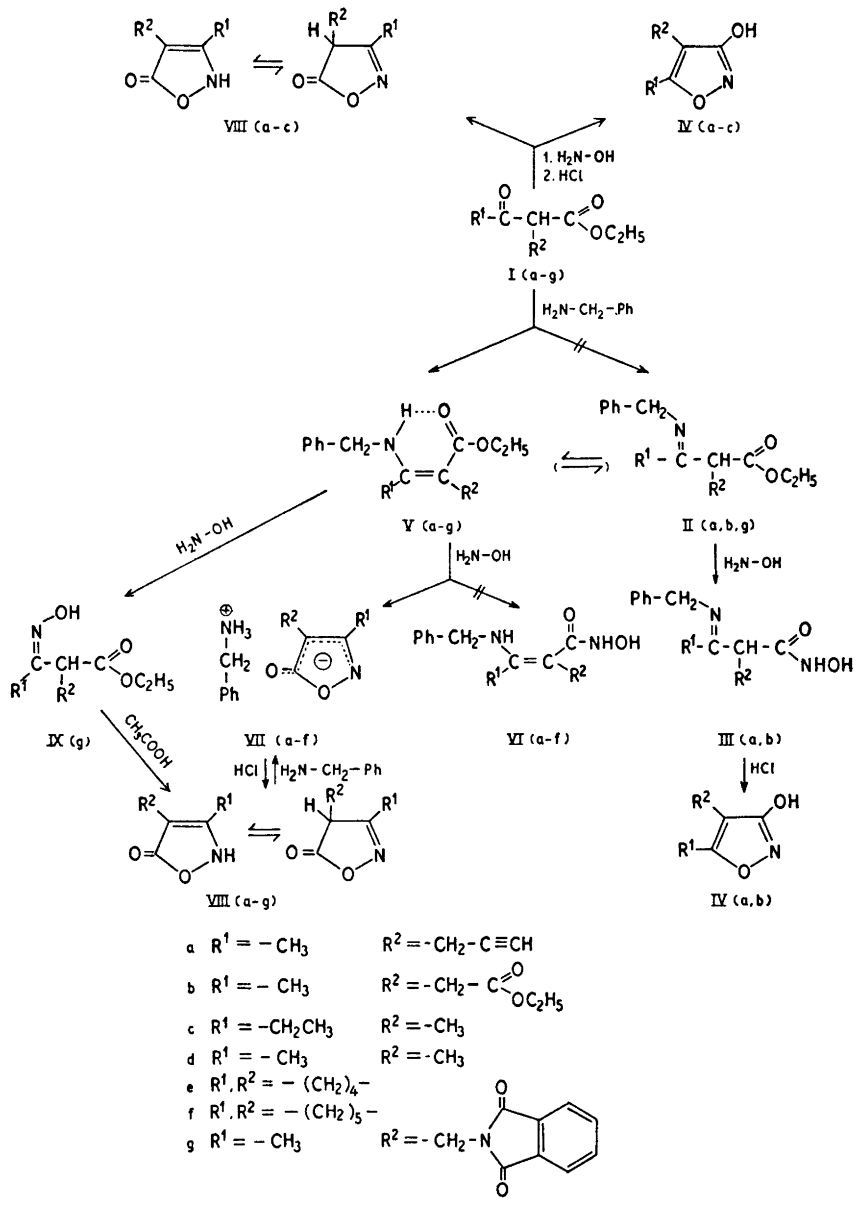

cyclization of the simultaneously formed oxime- and hydroxamic acid-intermediates, respectively.[8,9] The relative amounts of the two isomers strongly depend on the constitutions of the β-ketoesters.[8]

For that reason the preparation of 3-hydroxyisoxazoles, uncontaminated by the isoxazolin-5-one isomers, from β-ketoesters and hydroxylamine usually involves a previous conversion of the keto group into a base resistent derivative, which prior to the cyclization process can be easily cleaved by acid to give the β-ketohydroxamic acid-intermediates. As protection, *e.g.* ketalization of appropriate β-ketoesters with methanol, has been utilized in the syntheses of a few 3-hydroxyisoxazoles.[10,11] The use of this principle was extended by Jacquier *et al.*[4] who shielded the keto groups as ethylene ketals. The overall yields of the 3-hydroxyisoxazoles, especially of the 4,5-disubstituted ones, prepared in this way were rather poor.[4] On the other hand the reaction of ethyl enol ether of diethyl acetylmalonate with hydroxylamine followed by acid catalyzed cleavage and cyclization gave a mixture of 3-hydroxy-4-ethoxycarbonyl-5-methylisoxazole, and the unexpected isomer 3-methyl-4-ethoxycarbonylisoxazolin-5-one.[12]

The same authors [12] also described the syntheses of two compounds, which were assigned the structures 3-hydroxy-4-(2-propynyl)-5-methylisoxazole (IVa) and ethyl 3-hydroxy-5-methylisoxazolyl-4-acetate (IVb). The pertinent β-ketoesters (Ia) and (Ib) were treated with benzylamine to give compounds, which were assigned the structures (IIa) and (IIb). These were *via* the postulated hydroxamic acids (IIIa) and (IIIb) expected to be converted to the 3-hydroxyisoxazoles (IVa) and (IVb), respectively, as shown in the scheme. The structural assignments of (IVa) and (IVb) were supported by elemental analyses and were finally based on ^{1}H NMR spectroscopy and on IR and ^{1}H NMR spectroscopy, respectively. The constitution of compound (IVa) was claimed to be unambiguously established by the fact that it could be obtained by the above mentioned sequence *via* (IIa) and (IIIa). Furthermore (IVa) was stated to be obtained from the reaction of hydroxylamine with ethyl 2-(2-propynyl)acetoacetate (Ia). The structure of (IIb) was based on IR spectroscopy and on elemental analyses and those of (IIIa) and (IIIb) only on elemental analyses, exclusively.

In our hands, however, the reaction between ethyl 2-(2-propynyl)acetoacetate (Ia) and hydroxylamine only afforded small amounts of 3-hydroxy-4-(2-propynyl)-5-methylisoxazole (IVa) and almost exclusively 3-methyl-4-(2-propynyl)isoxazolin-5-one (VIIIa). The physical properties of the latter were consistent with those published by Bowden *et al.*[12] for the compound proposed as (IVa). These properties supported by our observations of a strong absorption band in the IR spectrum at 1800 cm^{-1} in chloroform solution and of a strong UV absorption at 259 nm provided conclusive evidence of the constitution of (VIIIa) in accordance with the general spectroscopic findings described by Jacquier *et al.*[13] for isoxazolin-5-ones. 3-Hydroxy-4-(2-propynyl)-5-methylisoxazole (IVa), as shown by elemental analysis, IR, UV, and ^{1}H NMR spectroscopy, was isolated from the reaction mixture by column chromatography.

These facts prompted us to reinvestigate the reaction sequences through the proposed intermediates (IIa)–(IIIa) and (IIb)–(IIIb), respectively, for the syntheses of the compounds, which by Bowden *et al.*[12] were assigned the structures 3-hydroxy-4-(2-propynyl)-5-methylisoxazole (IVa) and ethyl 3-hydroxy-5-methylisoxazolyl-4-acetate (IVb). Thus condensation of ethyl 2-

(2-propynyl)acetoacetate (Ia) and benzylamine turned out to give the enamine (Va) and not the proposed imine (IIa). A strong UV absorption at 295 nm, a carbonyl absorption band at 1640 cm^{-1} in the IR spectrum, and a ^1H NMR spin-spin splitting pattern for the N–H-proton (broadened triplet) and for the benzylic protons (doublet) as expected for compound (Va) provided evidence of the preferential existence of an intramolecular hydrogen bonded enamine form over the imine form. These structural features are in accordance with those generally accepted for related compounds.[14,15]

Reaction of the enamine (Va) with hydroxylamine gave as the only product a crystalline intermediate which upon treatment with hydrochloric acid afforded almost quantitatively a pure compound which was identical with 3-methyl-4-(2-propynylisoxazolin-5-one (VIIIa) as obtained from the above mentioned reaction of ethyl 2-(2-propynyl)acetoacetate (Ia) and hydroxylamine. This finding definitely ruled out a hydroxamic acid intermediate, and prompted us to examine the constitution of the above mentioned intermediate, which after the structure elucidation of compound (Va) was expected to exhibit the enamine hydroxamic acid structure (VIa) rather than the corresponding imine hydroxamic acid structure (IIIa) as proposed by Bowden *et al.*[12] The intermediate showed a transient purple colour with iron(III) chloride. In the IR spectrum, however, carbonyl group signals were absent, while broad absorption over the range 3200 – 2500 cm^{-1} and an absorption band at 2120 cm^{-1} suggested ammonium salt character of the compound. These findings together with the well known acidic properties of 3,4-disubstituted isoxazolin-5-ones [16] strongly pointed towards formula (VIIa) which is isomeric with the postulated products (VIa) and (IIIa). A UV maximum was observed at a wavelength of 255 nm, which is somewhat lower than that expected for the chromophoric system of formula (VIa), but in good agreement with that (255 nm) observed for the isoxazolin-5-one anion by Quin and Pinion.[17] Conclusive evidence could not be obtained from the ^1H NMR spectrum, but a final proof of the structural assignment was accomplished by synthesis of compound (VIIa) by mixing equivalent amounts of 3-methyl-4-(2-propynyl) isoxazolin-5-one (VIIIa) and benzylamine in tetrahydrofuran at room temperature. The precipitated salt was identical with the compound obtained from the enamine (Va) and hydroxylamine as shown by IR spectroscopy.

As mentioned before diethyl acetylsuccinate (Ib) was claimed to afford ethyl 3-hydroxy-5-methylisoxazolyl-4-acetate (IVb) *via* the proposed intermediates (IIb) and (IIIb).[12] A reinvestigation of this sequence disclosed a reaction pattern analogous with that described above for ethyl 2-(2-propynyl)-acetoacetate (Ia) leading to the formation of ethyl 3-methylisoxazolin-5-on-4-yl-acetate (VIIIb) through the intermediates (Vb) and (VIIb).

Ethyl 3-hydroxy-5-methylisoxazolyl-4-acetate (IVb) was detected by TLC as a minor compound together with the isoxazolin-5-one isomer (VIIIb) in the crude product from the reaction between diethyl acetylsuccinate (Ib) and hydroxylamine. It was isolated in a pure state by column chromatography and structure elucidated by spectroscopic methods. Similarly, the reaction between ethyl 2-methyl-3-oxovalerate (Ic) and hydroxylamine gave a mixture of 3-hydroxy-4-methyl-5-ethylisoxazole (IVc) and 3-ethyl-4-methylisoxazolin-5-one (VIIIc), both of which are new compounds.

Finally a series of 3,4-disubstituted isoxazolin-5-ones (VIIIc-f), were prepared in good yields through the not previously described intermediates (Vc-f) and (VIIc-f).

On the present basis this reaction sequence is considered to be of general value as a synthetic route to pure 3,4-disubstituted isoxazolin-5-ones.

The reaction between the enamines (Va-f) and hydroxylamine affording the corresponding isoxazolin-5-one benzylammonium salts (VIIa-f) is rather unusual. However, the reaction between the enamine 1,4,5,6-tetrahydronicotinamide and hydroxylamine leading to 4-(3-aminopropyl)-2-isoxazolin-5-one [17] is an analogous process. The mechanism of the process is unknown, but the first step is claimed to be an addition of the nucleophile to the enamine double bond,[17] and thus an oxime is a possible intermediate formed by an addition-elimination mechanism.

A compound assigned the oxime structure (IXg) has been isolated by Bowden *et al.*[12] from the reaction between hydroxylamine and the condensation product of ethyl 2-phthalimidomethylacetoacetate (Ig) and benzylamine. This compound was shown to cyclize to the corresponding isoxazolin-5-one in acidic media.[12]

The condensation product between ethyl 2-phthalimidomethylacetoacetate (Ig) and benzylamine turned out to be an enamine (Vg). A reinvestigation of the reaction between the enamine (Vg) and hydroxylamine confirmed the formation of the oxime intermediate (IXg). From a complex reaction mixture the compound (IXg) was isolated in a pure state by column chromatography and the structure proposed by Bowden *et al.*[12] was confirmed by spectroscopic methods.

EXPERIMENTAL

Melting points, determined in capillary tubes, are corrected. IR spectra were recorded on a Perkin-Elmer grating infrared spectrophotometer, Model 247. UV spectra were recorded in 99.9 % ethanol on a Perkin-Elmer grating ultraviolet-visible spectrophotometer, Model 402. ^{1}H NMR spectra were measured on a JEOL JMN-C-60HL instrument using TMS as an internal standard. The singlet, doublet, triplet, quartet, and multiplet patterns of the ^{1}H NMR spectra are designed s, d, t, q, and m, respectively. Microanalyses were made by Preben Hansen, Microanalytical Department of Chemical Laboratory II, University of Copenhagen.

Ethyl 2-(2-propynyl)acetoacetate (Ia). 20 g (0.10 mol) of ethyl β-morpholinocrotonate [18] were dissolved in excess of 2-propynyl bromide (40 ml). The solution was left at 65°C for 16 h, the excess of 2-propynyl bromide was removed *in vacuo*, and the residue was boiled with 40 ml of water for 15 min. The mixture was extracted with three 20 ml portions of ether. The combined, dried, and filtered ether phases were evaporated. The residue (17.3 g) was distilled to give 12.6 g (39 %) of a colourless oil, b.p. 102–110°C/13 mmHg (Ref. 18, b.p. 71°C/1 mmHg). The IR and ^{1}H NMR data were consistent with the structural assignments.

Ethyl 2-(2-propynyl)-3-benzylaminocrotonate (Va). A mixture of 5.0 g (30 mmol) of (Ia), 3.5 g (33 mmol) of benzylamine, and 15 g of molecular sieve, Union Carbide 3A, was refluxed in 60 ml of benzene for 4.5 h. The mixture was filtered and concentrated *in vacuo* to give 6.7 g (87 %) of a pale yellow oil. Distillation of an analytical sample at 0.05 mmHg afforded (Va) as a pale yellow oil. (Found: C 74.80; H 7.43; N 5.55. Calc. for $C_{16}H_{19}NO_2$: C 74.68; H 7.44; N 5.44). λ_{max} 298 nm ($\varepsilon = 1.72 \times 10^4$). IR data (neat) cm^{-1}: 3300, m (NH and HC≡C); 1640, s (C=O); 1600, s (C=C). ^{1}H NMR data (CCl_4) δ: 9.8 (broadened t ($J = 6$ cps), 1 H, CH_2-NH-C); 7.15 (slightly broadened s, 5 H, C_6H_5); 4.32 (d ($J = 6$ cps), 2 H, $C-CH_2-NH$); 4.02 (q ($J = 7$ cps), 2 H, $O-CH_2-CH_3$);

3.03 (d ($J=3$ cps), 2 H, C$-$CH_2-C); 1.90 (s, 3 H, CH_3-C=); 1.70 (t ($J=3$ cps), 1 H, $HC\equiv$C); 1.22 (t ($J=7$ cps), 3 H, CH_3-CH_2).

Benzylammonium salt of 4-(2-propynyl)-3-methylisoxazolin-5-one (VIIa). Method a. 115 mg (5 mmol) of sodium were reacted with methanol (12 ml) and to the solution were added 350 mg (5 mmol) of hydroxylammonium chloride. After stirring for 5 min 1.28 g (5 mmol) of (Va) were added and the mixture was refluxed for 4 h. After filtration and evaporation to dryness *in vacuo* a crystalline residue was obtained. Recrystallization from tetrahydrofuran (THF) afforded 500 mg (41 %) of (VIIa), m.p. 148$-$151°C (decomp.) (Ref. 12, m.p. 153$-$155°C for the proposed hydroxamic acid (IIIa)). λ_{max} 255 nm ($\varepsilon=0.89\times10^4$). IR data (KBr) cm^{-1}: 3200$-$2300 and 2160, m (NH_3^+); 1620, s and 1510$-$1470, several bands (isoxazole-ring). ^{1}H NMR data (DMSO-d_6) δ: 7.82 (perturbed s, 3 H, $CH_2-NH_3^+$); 7.32 (slightly broadened s, 5 H, C_6H_5); 3.92 (s, 2 H, C$-$C$H_2-NH_3^+$); 2.82 (d ($J=3$ cps), 2 H, C$-$CH_2-C); 2.40 (t ($J=3$ cps), 1 H, $HC\equiv$C); 1.89 (s, 3 H, C$-$CH_3).

Method b. To a solution of 137 mg (1 mmol) of the isoxazolin-5-one (VIIIa) in 1 ml of THF was added a solution of 107 mg (1 mmol) of benzylamine in 2.5 ml of THF. Upon standing at room temperature for 20 h 200 mg (82 %) of colourless crystals were isolated, m.p. 148$-$151°C (decomp.) (Found: C 68.95; H 6.69; N 11.52. Calc. for $C_{14}H_{16}N_2O_2$: C 68.83; H 6.60; N 11.47). The IR and UV spectra were identical with those of the product of method a.

3-Methyl-4-(2-propynyl) isoxazolin-5-one (VIIIa) and 3-hydroxy-4-(2-propynyl)-5-methylisoxazole (IVa). To 1.68 g (10 mmol) of ethyl 2-(2-propynyl)acetoacetate (Ia) was added a solution of 800 mg (20 mmol) of sodium hydroxide and 695 mg (10 mmol) of hydroxylammonium chloride in 5 ml of water at 0°C. The mixture was stirred until homogeneous and left at 4°C for 16 h. The mixture was acidified to pH ~2 with concentrated hydrochloric acid (*ca.* 1 ml) and left at 4°C for further 24 h. The crystalline precipitate (500 mg) was collected, dried, and recrystallized (ether) to give 400 mg (29 %) of compound (VIIIa) as colourless crystals, m.p. 90$-$93°C (Ref. 12, m.p. 91$-$93°C for the proposed 3-hydroxyisoxazole (IVa)). λ_{max} 259 nm ($\varepsilon=0.90\times10^4$). IR data ($CHCl_3$) cm^{-1}: 1800, s and 1740, s (ring C=O). The ^{1}H NMR data ($CDCl_3$-DMSO-d_6 (4:1)) supported the structural assignments of compound (VIIIa) and agreed with those published for the compound which was assigned the structure (IVa) [12] except for a broad peak which we observed at δ 11.5$-$10.5, 0.7 H (N*H*).

The aqueous mother liquor was evaporated and the residue was extracted with ether. Evaporation of the ether extract gave 700 mg of a residue, which by TLC (silica gel GF_{254} (Merck), benzene-ethyl acetate-formic acid (30:30:1)) was shown to be a mixture of two compounds, which were separated by column chromatography on silica gel (0.05$-$0.20 mm, Merck) (26 g). The eluent was benzene-ethyl acetate-formic acid (60:40:1) to which increasing amounts of ethyl acetate were added. 120 mg (9 %) of compound (IVa) and 300 mg (22 %) of compound (VIIIa) were isolated. (IVa) was recrystallized (cyclohexane) to give 100 mg of colourless needles, m.p. 102$-$104°C. (Found: C 61.15; H 5.20; N 10.42. Calc. for $C_7H_7NO_2$: C 61.31; H 5.15; N 10.21). λ_{max} 229 nm ($\varepsilon=3.5\times10^3$). IR data (KBr) cm^{-1}: 3200$-$2200, s (OH); 1660, s and 1550, s (isoxazole-ring). ^{1}H NMR data ($CDCl_3$) δ: 11.52 (s, 1 H, O*H*); 3.22 (d ($J=2$ cps), 2 H, C$-$CH_2-C); 2.32 (s, 3 H, C$-$CH_3; 2.02 (t ($J=2$ cps), 1 H, $HC\equiv$C).

3-Methyl-4-(2-propynyl)isoxazolin-5-one (VIIIa). 244 mg (1 mmol) of the benzylammonium salt (VIIa) were dissolved in 7.5 ml of water. Upon addition of 2.5 ml of concentrated hydrochloric acid the solution was continuously extracted with ether for 30 min. The extract was dried, filtered, and evaporated. Recrystallization of the residue afforded 100 mg (73 %) of (VIIIa) as pale yellow crystals, m.p. 90$-$93°C (ether), identical with (VIIIa) obtained from the above described reaction of ethyl 2-(2-propynyl)acetoacetate (Ia) and hydroxylamine as shown by IR spectroscopy.

Ethyl 3-ethoxycarbonyl-4-benzylamino-3-pentenoate (Vb). (Vb) was synthesized as described above for (Va) using 5.4 g (25 mmol) of diethyl acetylsuccinate (Ib) and 2.7 g (25 mmol) of benzylamine to give 7.8 g of crude product as a colourless oil. The oil was dissolved in 100 ml of petroleum ether and cooling overnight at $-$18°C gave colourless crystals, 3.9 g, m.p. 38$-$39°C (Ref. 12, described as an oil with the proposed structure (IIb)). λ_{max} 297 nm ($\varepsilon=1.93\times10^4$). IR data (KBr) cm^{-1}: 3280, m (NH); 1640, s (C=O); 1600 s (C=C). ^{1}H NMR data ($CDCl_3$) δ: 9.90 (broadened t, 1 H, C$-$N*H*$-$CH$_2$; 7.34 (s, 5 H, C_6H_5); 4.47 (d ($J=7$ cps), 2 H, NH$-$CH_2-C); 4.14 (q ($J=7$ cps), 4 H

($2\times O-CH_2-CH_3$); 3.30 (s, 2 H, $C-CH_2-C$); 1.95 (s, 3 H, $CH_3-C=$); 1.25 (t ($J=7$ cps), 6 H ($2\times CH_2-CH_3$)).

Benzylammonium salt of ethyl 3-methylisoxazolin-5-on-4-yl-acetate (VIIb). Method a. (VIIb) was synthesized as described above for (VIIa) using 3.0 g (10 mmol) of (Vb) and 0.76 g (11 mmol) of hydroxylammonium chloride to give 3.5 g of an oil which solidified upon standing. The crude product was recrystallized from ethyl acetate to give 1.7 g (58 %) of (VIIb), m.p. 122–124°C (decomp.). (Ref. 12, m.p. 120–122°C for the proposed hydroxamic acid (IIIb)). λ_{max} 255 nm ($\varepsilon=0.88\times10^4$). IR data (KBr) cm^{-1}: 3300–2300 and 2100, m (NH_3^+), 1720, s (C=O), 1625, s, and 1520–1480, several bands (isoxazole-ring). ^1H NMR data ($CDCl_3$-DMSO-d_6 (5:1)) δ: 7.93 (slightly broadened s, 3 H, $CH_2-NH_3^+$); 7.40–7.25 (m, 5 H, C_6H_5); 4.02 (q ($J=7$ cps), 2 H, $O-CH_2-CH_3$); 3.96 (s, 2 H, $NH_3^+-CH_2-C$); 3.00 (s, 2 H, $=C-CH_2-C$); 1.97 (s, 3 H, $CH_3-C=$); 1.20 (t ($J=7$ cps), 3 H, CH_2-CH_3).

Method b. To a solution of 74 mg (4 mmol) of the isoxazolin-5-one (VIIIb) in 0.2 ml of THF was added a solution of 43 mg (4 mmol) of benzylamine in 1 ml of THF. After standing overnight at room temperature 100 mg (85 %) of (VIIb) were isolated, m.p. 126.5–128.5°C (decomp.). The IR spectrum was identical with that of (VIIb) prepared according to method a.

Ethyl 3-methylisoxazolin-5-on-4-yl-acetate (VIIIb). 2.92 g (10 mmol) of (VIIb) were dissolved in a mixture of 6 ml of water and 1.5 ml of concentrated hydrochloric acid. The solution was continuously extracted with ether for 1 h and the extract was dried ($MgSO_4$), filtered, and evaporated to give 1.70 g of a pale yellow oil which crystallized upon standing. Recrystallization from ethyl acetate yielded 0.8 g (43 %) of colourless crystals, m.p. 75.5–76.5°C (Ref. 12, m.p. 78–79°C for a compound with the proposed structure (IVb)). λ_{max} 259 nm ($\varepsilon=1.02\times10^4$). IR data ($CHCl_3$) cm^{-1}: 1795, s (ring-C=O); 1740–1720, several strong bands (ring-C=O and ester-C=O). ^1H NMR data (DMSO-d_6) δ: 4.05 (q ($J=7$ cps), 2 H, $O-CH_2-CH_3$); 3.20 (s, 2 H, $=C-CH_2-C$); 2.09 (s, 3 H, $=C-CH_3$); 1.18 (t ($J=7$ cps), 3 H, CH_2-CH_3).

Ethyl 3-hydroxy-5-methylisoxazolyl-4-acetate (IVb). A mixture of 10 ml of 2 N NaOH, 0.70 g (10 mmol) of hydroxylammonium chloride, and 2.16 g (10 mmol) of diethyl acetylsuccinate (Ib) was stirred at 0°C for 1 h. The mixture was extracted with two 10 ml portions of ether and the pooled extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give 0.3 g of an oil consisting mainly of diethyl acetylsuccinate (Ib). The aqueous phase was acidified to pH *ca.* 0 with concentrated hydrochloric acid and continuously extracted for 1 h with ether-methylene chloride (4:1). The extract was dried ($MgSO_4$) and evaporated to dryness *in vacuo* to give 1.5 g of an oil. TLC (silica gel GF_{254} (Merck), benzene-ethyl acetate-formic acid (50:50:1)) showed the oil to be a complex mixture containing a compound with the same R_F-value as (VIIIb) which like (VIIIb) gave a violet colour using $FeCl_3$ as a spraying reagent. The oil was submitted to column chromatography on 50 g of silica gel (0.05–0.20 mm, Merck) using benzene-ethyl acetate-formic acid (50:50:1) as an eluent. It was not possible to isolate any (VIIIb) as it is probably destroyed on the column during the elution. 379 mg of crude (IVb) were isolated. Recrystallization twice from cyclohexane-benzene (4:1) yielded colourless crystals, m.p. 100.5–102.5°C. (Found: C 51.50; H 5.80; N 7.57. Calc. for $C_8H_{11}NO_4$: C 51.88; H 5.99; N 7.56). λ_{max} 212 nm ($\varepsilon=5.04\times10^3$). IR data (KBr) cm^{-1}: 3300–2100, s (OH); 1715, s (C=O); 1663 and 1550, s (isoxazole-ring). ^1H NMR data ($CDCl_3$) δ: 10.20 (s, 1 H, $=C-OH$); 4.06 (q ($J=7$ cps), 2 H, $O-CH_2-CH_3$); 3.21 (s, 2 H, $=C-CH_2-C$); 2.20 (s, 3 H, $=C-CH_3$); 1.20 (t ($J=7$ cps), 3 H, CH_2-CH_3).

Ethyl 2-methyl-3-benzylamino-2-pentenoate (Vc). (Vc) was synthesized as described above for (Va) using 7.9 g (50 mmol) of ethyl 2-methyl-3-oxovalerate (Ic) [19] and 5.85 g (55 mmol) of benzylamine. Yield 4.2 g (30 %) of a colourless oil, b.p. 140–144°C/0.4 mmHg, m.p. *ca.* 8°C (Found: C 72.95; H 8.55; N 5.75. Calc. for $C_{15}H_{21}NO_2$: C 72.84; H 8.56; N 5.66). λ_{max} 303 nm ($\varepsilon=1.73\times10^4$). IR data (neat) cm^{-1}: 3250, m (NH); 1640, s (C=O); 1600, s (C=C). ^1H NMR data (CCl_4) δ: 9.6 (broadened t ($J=6$ cps), 1 H, $C-NH-CH_2$); 7.20 (slightly broadened s, 5 H, C_6H_5); 4.31 (d ($J=6$ cps), 2 H, $NH-CH_2-C$); 4.02 (q ($J=6$ cps), 2 H, CH_3-CH_2-O); 2.23 (q ($J=7$ cps), 2 H, $CH_3-CH_2-C=$); 1.75 (s, 3 H, CH_3-C); 1.22 (t ($J=6$ cps), 3 H, CH_3-CH_2-O); 1.00 (t ($J=7$ cps), 3 H, $CH_3-CH_2-C=$).

Benzylammonium salt of 3-ethyl-4-methylisoxazolin-5-one (VIIc). Method a. (VIIc) was synthesized as described above for (VIIa). As starting materials were used 12.4 g

(50 mmol) of (Vc) and 3.5 g (50 mmol) of hydroxylammonium chloride. After recrystallization (THF) 2.8 g (25 %) of colourless crystals of (VIIc) were obtained, m.p. 110–111°C (decomp.). (Found: C 66.40; H 7.81; N 11.90. Calc. for $C_{13}H_{18}N_2O_2$: C 66.64; H 7.74; N 11.96). λ_{max} 258 nm ($\varepsilon = 0.91 \times 10^4$). IR data (KBr) cm^{-1}: 3200–2300 and 2160, m (NH_3^+); 1630, s and 1500–1440, several bands (isoxazole-ring). ^1H NMR data (DMSO-d_6) δ: 7.88 (slightly broadened s, 3 H, $CH_2-NH_3^+$); 7.43 slightly broadened s, 5 H, C_6H_5); 3.98 (s, 2 H, $C-CH_2-NH_3^+$); 2.24 (q ($J = 6$ cps), 2 H, CH_3-CH_2-C); 1.54 (s, 3 H, CH_3-C); 1.04 (t ($J = 6$ cps), 3 H, CH_3-CH_2-C).

Method b. 25.4 mg (0.2 mmol) of the isoxazolin-5-one (VIIIc) were dissolved in a solution of 21.4 mg (0.2 mmol) of benzylamine in 100 µl of THF. After standing for 20 h at room temperature 28 mg (60 %) of (VIIc) were isolated, m.p. 110–111°C (decomp.). The IR spectrum was identical with that of (VIIc) as prepared by method a.

3-Ethyl-4-methylisoxazolin-5-one (VIIIc) and 3-hydroxy-4-methyl-5-ethylisoxazole (IVc). To a solution of 4.0 g (100 mmol) of sodium hydroxide and 3.45 g (50 mmol) of hydroxylammonium chloride in 25 ml of water were added 7.90 g (50 mmol) of ethyl 2-methyl-3-oxavalerate (Ic) at 0°C and the solution was stirred until homogeneous. After standing at 4°C for 16 h the mixture was acidified to pH ~2 with concentrated hydrochloric acid (7 ml) and the mixture was left at 4°C for further 24 h. The mixture was extracted with two 20 ml portions of ether. The combined, dried, and filtered extracts were evaporated to give 6.4 g of a mixture of two compounds as shown by TLC (silica gel GF_{254} (Merck), benzene-ethyl acetate-formic acid (30:30:1)). The mixture was submitted to column chromatography as described for the separation of (VIIIa) and (IVa) to give 2.6 g (41 %) of (VIIIc) and 3.3 g (52 %) of (IVc). Recrystallization of (IVc) (cyclohexane) afforded colourless crystals, m.p. 50–51°C. (Found: C 56.90; H 7.17; N 11.16. Calc. for $C_6H_9NO_2$: C 56.68; H 7.14; N 11.02). λ_{max} < 220 nm. IR data (KBr) cm^{-1}: 3200–2200, s (OH); 1660, s and 1530, s (isoxazole-ring). ^1H NMR data (CCl_4) δ: 11.22 (s, 1 H, O*H*); 2.52 (q ($J = 7$ cps), 2 H, CH_3-CH_2-C); 1.82 (s, 3 H, CH_3-C); 1.22 (t ($J = 7$ cps), 3 H, CH_3-CH_2-C). Compound (VIIIc) was distilled twice *in vacuo* to give a colourless oil, b.p. 98°C/0.5 mmHg. (Found: C 56.75; H 7.32; N 10.98. Calc. for $C_6H_9NO_2$: C 56.68; H 7.14; N 11.02). λ_{max} 264 nm ($\varepsilon = 8.2 \times 10^3$). IR data ($CHCl_3$) cm^{-1}: 1800, s and 1740, s (ring-C=O). ^1H NMR data (CCl_4) δ: 11.4–11.0 (broad signal, 0.7 H, N*H*); 2.51 (q ($J = 7$ cps), 2 H, CH_3-CH_2-C); 1.70 (s, 3 H, CH_3-C); 1.20 (t ($J = 7$ cps), CH_3-CH_2-C).

3-Ethyl-4-methylisoxazolin-5-one (VIIIc). (VIIIc) was obtained as described above for (VIIIa). 2.27 g (9.7 mmol) of the benzylammonium salt (VIIc) gave 700 mg of an oil, which was distilled to give 600 mg (49 %) of a colourless oil, b.p. 98°C/0.5 mmHg. The IR spectrum showed the product to be identical with (VIIIc) prepared as described above from ethyl 2-methyl-3-oxovalerate and hydroxylamine.

Ethyl 2-methyl-3-benzylaminocrotonate (Vd). (Vd) was synthesized as described above for (Va) using 7.2 g (50 mmol) of ethyl 2-methylacetoacetate (Id) and 5.9 g (55 mmol) of benzylamine as starting materials. Yield 10.2 g (88 %) of a pale yellow oil, b.p. 121–122°C/0.1 mmHg, m.p. *ca.* 8°C. (Found: C 72.65; H 8.13; N 6.50. Calc. for $C_{14}H_{19}NO_2$: C 72.07; H 8.21; N 6.00). λ_{max} 301 nm ($\varepsilon = 1.5 \times 10^4$). IR data (neat) cm^{-1}: 3250, m (NH); 1640, s (C=O); 1595, s (C=C). ^1H NMR data (CCl_4) δ: 9.6 (broadened t ($J = 6$ cps), 1 H, $C-NH-CH_2$); 7.15 (s, 5 H, C_6H_5); 4.26 (d ($J = 6$ cps), 2 H, $NH-CH_2-C$); 4.02 (q ($J = 6$ cps), 2 H, CH_3-CH_2-O); 1.78 (s, 3 H, $CH_3-C=$); 1.74 (s, 3 H, $CH_3-C=$); 1.00 (t ($J = 6$ cps), 3 H, CH_3-CH_2-O).

Benzylammonium salt of 3,4-dimethylisoxazolin-5-one (VIId). Method a. (VIId) was synthesized as described above for (VIIa) using 7.78 g (33 mmol) of (Vd) and 2.57 g (37 mmol) of hydroxylammonium chloride. Upon recrystallization (THF) 4.2 g (58 %) of (VIId) were obtained as colourless crystals, m.p. 101–103°C (decomp.). (Found: C 65.65; H 7.39; N 12.93. Calc. for $C_{12}H_{16}N_2O_2$: C 65.43; H 7.32; N 12.72). λ_{max} 258 nm ($\varepsilon = 0.86 \times 10^4$). IR data (KBr) cm^{-1}: 3300–2300 and 2200, m (NH_3^+); 1622, s and 1520–1420, several bands (isoxazole-ring). ^1H NMR data (DMSO-d_6) δ: 7.38 (slightly broadened s, 3 H, $CH_2-NH_3^+$); 7.31 (s, 5 H, C_6H_5); 3.92 (s, 2 H, $C-CH_2-NH_3^+$); 1.87 (s, 3 H, CH_3-C); 1.55 (s, 3 H, CH_3-C).

Method b. To 275 mg (2.4 mmol) of 3,4-dimethylisoxazolin-5-one (VIIId) dissolved in 0.5 ml of THF was added a solution of 260 mg (2.4 mmol) of benzylamine in 6 ml of THF. 11 ml of ether were added and upon standing at room temperature for 2 h 420 mg

(79 %) of colourless crystals, m.p. 105.5 – 106.5°C (decomp.), were isolated. The IR spectrum was identical with that of compound (VIId) as obtained by method a.

3,4-Dimethylisoxazolin-5-one (VIIId). To a solution of 3.6 g (16 mmol) of (VIId) in 20 ml of water were added 5 ml of concentrated hydrochloric acid and the solution was extracted continuously with ether-methylene chloride (4:1) for 1 h. The dried and filtered organic phase was evaporated. The crystalline residue (1.8 g) was sublimed twice *in vacuo* (70°C/0.2 mmHg) to give 1.2 g (65 %) of (VIIId) as colourless crystals, m.p. 47 – 50°C. λ_{max} 261 nm (log $\varepsilon = 4.0$). (Ref. 20, m.p. 49 – 51°C. λ_{max} 259 nm (log $\varepsilon = 3.9$) (CH_3OH)). The IR and ^1H NMR spectra were consistent with the structural assignments.

1-Benzylamino-2-ethoxycarbonylcyclohexene (Ve). (Ve) was synthesized as described above for (Va). As starting materials were used 45 g (0.27 mol) of 2-ethoxycarbonylcyclohexanone (Ie) [21] and 31 g (0.29 mol) of benzylamine. The yield of (Ve) was 57 g (83 %) obtained as a pale yellow oil, which crystallized by standing at – 18°C. An analytical sample was recrystallized (petroleum ether) to give (Ve) as colourless crystals, m.p. 20 – 22°C. (Found: C 74.15; H 8.33; N 5.51. Calc. for $C_{16}H_{21}NO_2$: C 74.10; H 8.16; N 5.40). λ_{max} 303 nm ($\varepsilon = 1.47 \times 10^4$). IR data (neat) cm^{-1}: 3260, m (NH); 1650, s (C=O); 1600, s (C=C). ^1H NMR data (CCl_4) δ: 9.3 (broadened t ($J = 6$ cps), 1 H, C – N*H* – CH_2); 7.14 (s, 5 H, C_6H_5); 4.28 (d ($J = 6$ cps), 2 H, NH – CH_2 – C); 3.98 (q ($J = 6$ cps), 2 H, CH_3 – CH_2 – O); 2.4 – 1.9 (m, 4 H, CH_2 – CH_2 – C=C – CH_2 – CH_2); 1.7 – 1.4 (m, 4 H, CH_2 – $(CH_2)_2$ – CH_2); 1.21 (t ($J = 6$ cps), 3 H, CH_3 – CH_2).

Benzylammonium salt of 3,4-tetramethyleneisoxazolin-5-one (VIIe). Method a. (VIIe) was synthesized as described above for (VIIa), using 10 g (39 mmol) of (Ve) and 2.8 g (39 mmol) of hydroxylammonium chloride to give 11.1 g of crystalline crude product. Recrystallization (THF) afforded 4.1 g (42 %) of (VIIe), m.p. 112 – 114°C (decomp.). (Found: C 68.10; H 7.54; N 11.25. Calc. for $C_{14}H_{18}N_2O_2$: C 68.27; H 7.37; N 11.37). λ_{max} 261 nm ($\varepsilon = 0.91 \times 10^4$). IR data (KBr) cm^{-1}: 3100 – 2250 and 2160, m (NH_3^+); 1610, s and 1500 – 1420, several bands (isoxazole-ring). ^1H NMR data (DMSO-d_6) δ: 7.76 (s, 3 H, CH_2 – NH_3^+); 7.4 (slightly broadened s, 5 H, C_6H_5); 3.94 (s, 2 H, C – CH_2 – NH_3^+); 2.6 – 1.8 (m, 4 H, CH_2 – CH_2 – C=C – CH_2 – CH_2); 1.8 – 1.3 (m, 4 H, CH_2 – $(CH_2)_2$ – CH_2).

Method b. (VIIe) was synthesized as described for (VIIa) from 13.9 mg (0.1 mmol) of the isoxazolin-5-one (VIIIe) and 10.7 mg (0.1 mmol) of benzylamine. Yield 8 mg (32 %) of (VIIe), m.p. 111 – 113°C (decomp.). The IR spectrum was identical with that of (VIIe) as prepared by method a.

3,4-Tetramethyleneisoxazolin-5-one (VIIIe). A solution of 1.0 g (40 mmol) of (VIIe) in 20 ml of an aqueous solution of sodium bicarbonate (5 %) was continuously extracted with ether for 3 h. Upon addition of 3 ml of 4 N hydrochloric acid the mixture was again continuously extracted with ether for 30 min. The extract of the acidified mixture was dried, filtered, and evaporated. After recrystallization of the residue (ether) were obtained 300 mg (54 %) of (VIIIe) as colourless crystals, m.p. 65 – 69°C. λ_{max} 262 nm ($\varepsilon = 0.97 \times 10^4$). (Ref. 22, m.p. 66 – 67°C. λ_{max} 258 nm ($\varepsilon = 0.906 \times 10^4$) (0.01 M sulphuric acid)). IR and ^1H NMR data were consistent with those reported in the literature.[22]

1-Benzylamino-2-ethoxycarbonylcycloheptene (Vf). (Vf) was synthesized as described above for (Va), using 7.6 g (41 mmol) of 2-ethoxycarbonylcycloheptanone (If) [23] and 4.8 g (45 mmol) of benzylamine as starting materials to give 11.9 g of crude product, which crystallized upon standing at – 18°C. Recrystallization (petroleum ether) afforded 6.8 g (61 %) of (Vf) as colourless crystals, m.p. 42 – 45°C. (Found: C 74.85; H 8.53; N 5.16. Calc. for $C_{17}H_{23}NO_2$: C 74.69; H 8.48; N 5.12). λ_{max} 309 nm ($\varepsilon = 1.52 \times 10^4$). IR data (neat) cm^{-1}: 3250, m (NH); 1640, s (C=O); 1600, s (C=C). ^1H NMR data (CCl_4) δ: 9.6 (broadened t ($J = 6$ cps), 1 H, C – N*H* – CH_2); 7.18 (s, 5 H, C_6H_5); 4.34 (d ($J = 6$ cps), 2 H, NH – CH_2 – C); 4.00 (q ($J = 7$ cps), 2 H, CH_3 – CH_2 – O); 2.6 – 2.1 (m, 4 H, CH_2 – CH_2 – C=C – CH_2 – CH_2); 1.8 – 1.1 (m, 6 H, CH_2 – $(CH_2)_3$ – CH_2); 1.22 (t ($J = 7$ cps), 3 H, CH_3 – CH_2).

Benzylammonium salt of 3,4-pentamethyleneisoxazolin-5-one (VIIf). Method a. (VIIf) was synthesized as described above for (VIIa), using 10.6 g (39 mmol) of (Vf) and 2.76 g (40 mmol) of hydroxylammonium chloride as starting materials to give 11.2 g of crystalline crude product. Recrystallization (THF) afforded 5.9 g (58 %) of (VIIf), m.p. 148 – 150°C (decomp.). (Found: C 68.95; H 7.79; N 10.83. Calc. for $C_{15}H_{20}N_2O_2$: C 69.20; H 7.74; N 10.76). λ_{max} 260 nm ($\varepsilon = 0.88 \times 10^4$). IR data (KBr) cm^{-1}: 3200 – 2200 and 2160, m (NH_3^+); 1630, s and 1500 – 1450, several bands (isoxazole-ring). ^1H NMR data (DMSO-d_6)

δ: 7.34 (perturbed s, 5 H, C_6H_5); 7.1 (s, 3 H, $CH_2-NH_3^+$); 3.88 (s, 2 H, $C-CH_2-NH_3^+$); 2.5 – 1.8 (m, 4 H, $CH_2-CH_2-C=C-CH_2$); 1.8 – 1.0 (m, 6 H, $CH_2-CH_2)_3-CH_2$).

Method b. (VIIf) was synthesized as described for (VIIa) from 15.3 mg (0.1 mmol) of the isoxazolin-5-one (VIIIf) and 10.7 mg (0.1 mmol) of benzylamine. Yield 15 mg (58 %) of (VIIf), m.p. 152 – 154°C (decomp.). The IR spectrum was identical with that of (VIIf) as prepared by method a.

3,4-Pentamethyleneisoxazolin-5-one (VIIIf). (VIIIf) was obtained as described above for (VIIIa). 700 mg (27 mmol) of the benzylammonium salt (VIIf) gave 300 mg of crude product. Recrystallization (ether) afforded 200 mg (49 %) of (VIIIf), m.p. 83 – 86°C (Ref. 8, m.p. 80°C). λ_{max} 264 nm (log $\varepsilon = 3.97$). (Ref. 13, λ_{max} 262 nm (log $\varepsilon = 3.90$)). IR and ^{1}H NMR data were consistent with those reported in the literature.[13]

Ethyl 2-phthalimidomethyl-3-benzylaminocrotonate (Vg). (Vg) was synthesized as described above for (Va) using 9.0 g (30 mmol) of ethyl 2-phthalimidomethylacetoacetate (Ig) [12] and 3.4 g (33 mmol) of benzylamine as starting materials to give a crystalline crude product. Recrystallization from ethanol gave 4.2 g (37 %) of pale yellow crystals, m.p. 157.5 – 158°C (Ref. 12, m.p. 160 – 162°C for the proposed compound (IIg)). λ_{max} 294 nm ($\varepsilon = 2.00 \times 10^4$). IR data (KBr) cm^{-1}: 3450, m (NH); 1770, m and 1710, s (phthalimido-C=O); 1645, s (ester-C=O); 1605, s (C=C). ^{1}H NMR data (CCl_4 – DMSO-d_6 (3:2)) δ: 9.95 (broadened t, 1 H, $=C-NH-CH_2$); 7.61 (s, 4 H, C_6H_4); 7.27 (s, 5 H, C_6H_5); 4.30 (perturbed d, 2 H, $NH-CH_2-C$); 3.94 (q ($J = 7$ cps), 2 H, $O-CH_2-CH_3$); 3.02 (s, 2 H, $N-CH_2-C$); 2.22 (s, 3 H, $CH_3-C=$); 1.12 (t ($J = 7$ cps), 3 H, CH_2-CH_3).

Ethyl 2-phthalimidomethyl-3-hydroxyiminobutyrate (IXg). A mixture of 2.26 g (6 mmol) of the enamine (Vg), 0.46 g (6.6 mmol) of hydroxylammonium chloride, 0.15 g (6.6 mmol) of sodium and 10 ml of methanol was refluxed for 2 h. After cooling the mixture was filtered and concentrated under reduced pressure to an oil which was column chromatographed (silica gel 0.05 – 0.20 mm, Merck, ethyl acetate-methanol (99:1)), to give 650 mg of crude product. Recrystallization from ether-petroleum ether yielded 240 mg of the oxime (IX), m.p. 149.5 – 151°C. (Ref. 12, m.p. 139 – 141.5°C). (Found: C 59.25; H 5.35; N 9.21. Calc. for $C_{15}H_{16}N_2O_5$: C 59.20; H 5.30; N 9.21). IR data (KBr) cm^{-1}: 3500, s (OH); 1790, m (phthalimido-C=O); 1720 – 1700, s, two bands (phthalimido-C=O and ester-C=O). ^{1}H NMR data ($CDCl_3$) δ: 8.28 (s, 1 H, $=N-OH$); 7.90 – 7.50 (m, 4 H, C_6H_4); 4.25 – 3.05 (complex pattern, 3 H, $N-CH_2-CH-C$); 4.13 (q ($J = 7$ cps), 2 H, $O-CH_2-CH_3$); 1.87 (s, 3 H, $CH_3-C=$); 1.20 (t ($J = 7$ cps), 3 H, CH_2-CH_3).

Treatment of (IXg) with acetic acid under reflux for 1 h yielded a compound of which the IR-spectrum (KBr) was identical with that of 3-methyl-4-phthalimidomethylisoxazolin-5-one (VIIIg) prepared as described by Bowden *et al.*[12]

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