Electrochemical Reduction of Isoxazoles and Related Compounds

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Some isoxazoles, isoxazolines, and their quaternized derivatives have been investigated by polarography and preparative reduction. A reductive cleavage of the oxygen-nitrogen bond without reduction of the carbon-nitrogen double bond was possible in protic medium for the quaternized derivatives, whereas for the parent compounds this was possible only in aprotic medium. By this means, preferentially via quaternization, isoxazoles and isoxazolines may be transformed to β-diketones or β-hydroxyketones. Under suitable conditions, the quaternized isoxazoles and isoxazolines may be reduced to 1,3-aminoalcohols, the *erythro:threo* ratio of the products differing considerably.

Isoxazoles (*1*) and isoxazolines (*2*) are readily available from the reaction between nitrile oxides and alkynes or alkenes.[1,2] Reductive cleavage of the nitrogen-oxygen bond provides a route to β-diketones and β-hydroxyketones. Reducing agents for such a cleavage may be titanium(III),[2,3] or hydrogen with Raney nickel in the presence of boric acid.[4] Reduction of isoxazolines with lithium aluminum hydride, sodium amalgam, and sodium in ethanol yields γ-aminoalcohols, the diastereomer ratio depending on the reducing agent.[5] Electrochemical reduction of *1* and *2* to β-diketones or β-hydroxyketones might be an attractive alternative to the chemical reductions; furthermore, a reduction to aminoalcohol might, through the *erythro:threo* ratio, provide some information on the stereochemistry of some of the steps in the electrochemical reduction of ketones to alcohols.

Isoxazoles and isoxazolines may be regarded as cyclic oximes. The initial step in the electrochemical reduction of oximes in protic solvents is generally a cleavage of the nitrogen-oxygen bond of the protonated compounds,[6,7] but as the resulting azomethine compound usually is more easily reducible than the oxime, the product is the amine.

Two strategies can be visualized for an electrochemical cleavage of the N–O bond without subsequent reduction of the azomethine bond. One method is to quaternize the heterocycle and reduce it in neutral or slightly acid or alkaline solution, where the resulting azomethine compound would not be protonated and reduced at the potential used for cleavage of the N–O bond. An alternative is a reduction in an aprotic medium, where the resulting anion of the ring-opened compound would be reducible at the applied potential.

Some isoxazoles (*1*), isoxazolines (*2*), their *N*-methylated derivatives (*3,4*), and reduction products (*5,6*) were investigated by polarography and controlled potential reduction to establish whether a selective cleavage of the nitrogen-oxygen bond was possible.

2,3-Dimethyl-5-phenylisoxazolium perchlorate and derivatives have been polarographed previously. A simple two-electron wave was observed, and the electrode reaction was suggested to be a saturation of the C–N double bond.[8] 3-Carboxy-5-methylisoxazole is polarographically reducible, and the product has been suggested to be a tetrahydroisoxazole;[9] this suggestion has been considered unlikely.[10]

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Results and Discussion

Polarographic investigation. In aqueous media, *1a* and *1b* were not reducible at the dropping mercury electrode (DME). The protonated form of *1c* may be reduced at pH < 4.5 in a 3:2 (volume) mixture of water and acetonitrile; at pH > 4.5 the wave was covered by the background, the wave height corresponding to a six-electron reduction, Fig. 1. In DMF *1c* gave an irreversible peak in cyclic voltammetry (CV) at −2.1 V (SCE).

The quaternized derivative of *1c*, *3c*, gave a single wave at pH < 2 with $n \sim 4$ F mol^{-1}. At about pH 2, the wave split up into three waves, the first wave remaining constant in potential and height ($n = 2$ F mol^{-1}) until pH > 11, where the compound was attacked by base – possibly in a way similar to that described for isoxazolium salts by alkoxides[11] or sodium hydroxide.[12] The second and third waves were seen between pH 2 and 6, at which pH they merged. Both waves had the height of a two-electron wave, and the combined wave had $n = 4$ (Fig. 2). It is, however, interesting to note that, if the $E_{1/2}$–pH curve of the third wave is extrapolated to pH 0–1, $E_{1/2}$(III) should be −1.0 V and no wave at that potential was seen in the polarographic curve of *3c* at that pH. Apparently, the compound responsible for wave 3 is not formed or formed only slowly during the reduction of *3c* at pH 0.

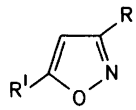
1,3-Diphenyl-3-methylamino-2-propen-1-one (*5c*) was reduced polarographically in a two-electron wave at pH < 2 and two two-electron waves between pH 2 and 7, the two waves merging at pH ~ 7. The waves of *5c* came at the same potentials as wave 2 and 3 of *3c*, and wave 1 below pH 2. In acid solution, *5c* was gradually hydrolyzed to 1,3-diphenylpropane-1,3-dione. At pH < 1, a certain degree of hydrolysis was visible in the polarograms; at pH 0, the compound was hydrolyzed in less than 1 h at 25 °C.

1,3-Diphenyl-3-methylamino-1-propanone (*6c*) was reducible in a single wave at pH < 8. At higher pH, methylamine was eliminated with formation of 1,3-diphenyl-2-propen-1-one (*7*), but in the presence of a large excess of methylamine, the equilibrium between *7* and *6c* was largely shifted toward *6c*. The wave of *6c* came at potentials corresponding to the third wave of *3c* and the second wave of *5c*. At pH < 2, *6c* was reduced at potentials more negative than that of the first wave of *3c*.

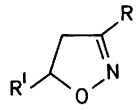
2,3-Dimethyl-5-phenylisoxazolium iodide (*3b*) was reduced in a wave with a height corresponding to $n = 5-6$ F mol^{-1} at pH < 2. Between pH 2 and 5, this wave diminished in height and a wave at a more negative potential grew. At pH > 5, the height of the first wave remained constant at $n = 2$, its half-wave potential being constant from pH 0 to 12. Between pH 4 and 8, the second wave had $n = 4$. At pH > 8, it diminished in height and reached $n \sim 2$ at pH 12 (Fig. 3). It may be noticed that an extrapolation of the $E_{1/2}$-pH curve of the second wave crossed that of the first wave at pH 2.

2,3,5-Trimethylisoxazolium iodide (*3a*) was reduced polarographically at pH > 4. At lower pH, the reduction of protons masked the wave of *3a*. In strongly alkaline solution, *3a* was attacked by base. From pH 4–12 a two-electron wave was seen at −1.38 V (SCE).

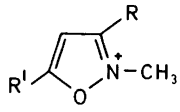
4,5-Dihydro-3,5-diphenylisoxazol (*2c*) is a cyclic oxime and is reduced correspondingly. It showed a four-electron wave in acidic solution; at pH > 6, the height diminished as usual for oximes, indicating that only the protonated form is



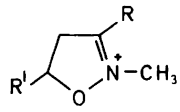
1 *a* R = CH_3 R′ = CH_3
b R = CH_3 R′ = C_6H_5
c R = C_6H_5 R′ = C_6H_5
d R = $CO_2C_2H_5$ R′ = C_6H_5



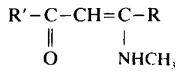
2 *a* R = CH_3 R′ = CH_3
b R = CH_3 R′ = C_6H_5
c R = C_6H_5 R′ = C_6H_5



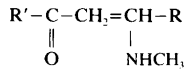
3 *a* R = CH_3 R′ = CH_3
b R = CH_3 R′ = C_6H_5
c R = C_6H_5 R′ = C_6H_5



4 *a* R = CH_3 R′ = CH_3
b R = CH_3 R′ = C_6H_5
c R = C_6H_5 R′ = C_6H_5



5 *a* R = CH_3 R′ = CH_3
b R = CH_3 R′ = C_6H_5
c R = C_6H_5 R′ = C_6H_5



6 *a* R = CH_3 R′ = CH_3
b R = CH_3 R′ = C_6H_5
c R = C_6H_5 R′ = C_6H_5

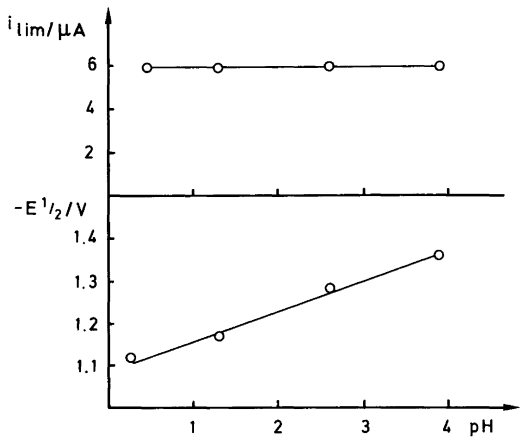


Fig. 1. Polarographic half-wave potentials (vs. SCE) and limiting currents (μA) of 3,5-diphenylisoxazoline (*1c*) in a 3:2 (vol:vol) aqueous acetonitrile. Conc. of *1c* 3.6×10^{-4} M.

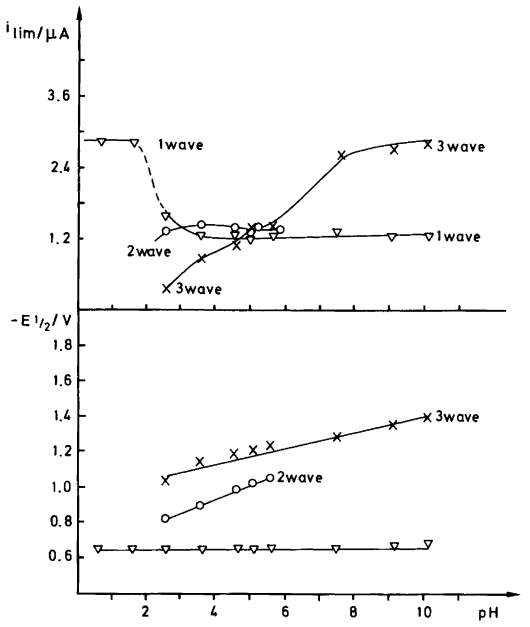


Fig. 2. Polarographic half-wave potentials (SCE) and limiting currents (μA) of 2-methyl-1,3-diphenylisoxazolium iodide (*3c*) in aqueous buffers. Conc. of *3c* 2.2×10^{-4} M; ▽ 1. wave, ○ 2. wave, × 3. wave.

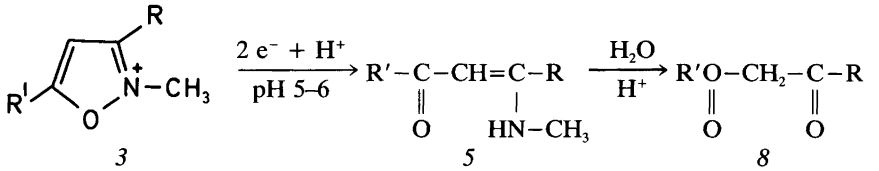
reducible. In alkaline solution, it was attacked by base with formation of 1,3-diphenyl-2-propen-1-one.

4,5-Dihydro-3,5-diphenyl-2-methylisoxazolium perchlorate (*4c*) was hydrolyzed at pH > 5. At pH < 2, three waves were found: the first a two-electron wave with nearly constant $E_{1/2}$ and wave-height; the second small at pH 0 and growing to the height of a two-electron wave at pH 2.5, at which pH the third wave disappeared (Table 1).

4,5-Dihydro-2,3-dimethyl-5-phenylisoxazolium perchlorate (*4b*) was hydrolyzed at pH > 5. The $E_{1/2}$ of the first wave was only slightly dependent on pH and the height nearly constant until pH 5, where hydrolysis became noticeable. The second wave, visible at pH < 2.5, had a height corresponding to $n \sim 1$, whereas the third wave which was seen at pH > 2.5 had $n = 2$, Table 2.

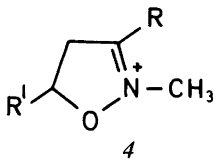
Preparative reductions of isoxazolium compounds. Reduction in neutral or slightly acidic solution (pH 5–6) at the potential of the first wave of *3b* and *3c* gave, respectively, 3-methylamino-1-phenyl-2-buten-1-one (*5b*) and 3-methylamino-1,3-diphenyl-2-propen-1-one (*5c*) in good yield. These enamines were easily hydrolyzed to the corresponding 1,3-diketones on boiling with dilute hydrochloric acid. The results were thus at variance with those previously published.[8]

The reduction is best performed in nearly neutral solution. In strongly acidic solution, the reduction goes further; in strongly alkaline solution, the quaternized compound is attacked by hydroxide ions.[11,12] The results show that an isoxazole after quaternization can be ring-opened in good yield to a derivative of a β-diketone (*8*), eqn. (1).

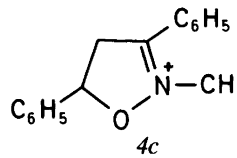


3 *5* *8* (1)

$$\underset{6c}{C_6H_5COCH_2CH(NHCH_3)C_6H_5} \xrightarrow[\text{pH 5}]{2\,e^- + 2\,H^+} \underset{9c}{C_6H_5CHOHCH_2CH(NHCH_3)C_6H_5} \quad (2)$$



$$\xrightarrow{2\,e^- + H^+} R'CHOHCH_2C(=NCH_3)R \xrightarrow[-H_2NCH_3]{H_2O} R'CHOHCH_2COR \quad (3)$$



$$\xrightarrow[E = -1.05\ V]{4\,e^- + 4\,H^+} \underset{9c}{C_6H_5CHOHCH_2CH(NHCH_3)C_6H_5} \quad (4)$$

At a more negative potential, *3b* can be reduced to 3-methylamino-1-phenyl-1-butanol (*9b*): a 48:52 mixture of *erythro* and *threo*. Compound was reduced similarly to 1,3-diphenyl-3-methylamino-1-propanol (*9c*), but the *erythro* : *threo* ratio was much lower (16:84). In the polarographic curves, *3c* was reduced in three two-electron waves, but preparatively it was difficult to separate wave II and III. Comparison of the $E_{1/2}$ of 1,3-diphenyl-3-methylamino-1-propanone (*6c*) with the $E_{1/2}$ of the 3rd wave of *3c* suggested that the electrode reaction corresponding to the second wave of *3c* is a saturation of the carbon-carbon double bond. This is in accordance with the fact that the reduction of *6c* at the same pH gave a *erythro* : *threo* ratio similar to that for *3c*, eqn. (2).

Reduction of *3c* at −0.9 V (SCE) in an emulsion of dichloromethane in 0.8 N hydrochloric acid gave a mixture of *5c* and benzalacetophenone. The latter is probably formed by elimination of methylamine from *6c*. This also suggests that *5c* is reduced to *6c* or its enol. A wave corresponding to the reduction of *6c* was not seen in the polarographic curve of *3c* at pH 0–1; a relatively slow step must thus occur after the uptake of the first four electrons and protons. The primarily formed product may tentatively be suggested to be the enol of *6c* or the protonated 1,3-diphenyl-3-methylamino-1-propen-1-ol, formed by a 1,4-reduction of the conjugated double bonds.

sensitive to attack by base than isoxazolium salts, and preparative reductions are possible only under acidic conditions. However, in slightly acidic solution, pH 3–5, *4* can be reduced stepwise according to eqn. (3).

Quaternization of isoxazolines activates the cleavage of the nitrogen-oxygen bond sufficiently to make it reducible at a less negative potential than the azomethine group and thus makes it possible to prepare β-hydroxyketones from isoxazolines. Reduction in aqueous acidic solution of isoxazolines gives, when possible, the β-aminoalcohol in a 4-electron reduction. On reduction on the second wave, *4* similarly gives γ-aminoalcohols, eqn. (4).

It is noteworthy that the six-electron reduction of *3c* to *9c* gave mainly the *threo* *9c* (*threo* : *erythro* ~ 6:1), whereas the four-electron reduction of *4c* to *9c* gave *erythro* : *threo* ~ 2:1. A similar 2:1 *erythro* : *threo* *9c* mixture was obtained on Raney nickel reduction of 3,5-diphenyl-2-methylisoxazolidine obtained from the cycloaddition of styrene to *N*-methyl-*C*-phenylnitrone. Reduction of *2c* with lithium tetrahydridoaluminate in diethyl ether gave 95:5 *erythro* : *threo* 3-amino-1,3-diphenyl-1-propanol (*10*), whereas reduction with sodium amalgam in aqueous ethanol gave a 3:2 ratio.[5] Preliminary results using derivatives of β-aminopropiophenones suggest that the protonated amino group is active in the protonation step, and the C-protonation takes place from the side of the amino group, whereas the β-hydroxy group formed during the reduction of *4c* through hydrogen bonding to the carbonyl group makes

the C-protonation from the back side more likely.

Reduction of *1c* and *2c* in aqueous alcoholic hydrochloric acid gave mixtures of *erythro* and *threo 10* in a six- and four-electron reduction, respectively, as expected, without the possibility of limiting the reduction to a two-electron cleavage of the O-N bond. In aprotic medium, *1b* and *1c* are reducible. Preparative reductions in acetonitrile which were stopped after 2 F mol^{-1} gave a product which, after protonation and hydrolysis, gave the expected β-diketone. It is probably important in order to avoid further reduction that the anion is not protonated during the electrolysis, as the reduction potential of such an anion is considerably more negative than that of the parent β-diketone or β-iminoketone, eqn. (5).

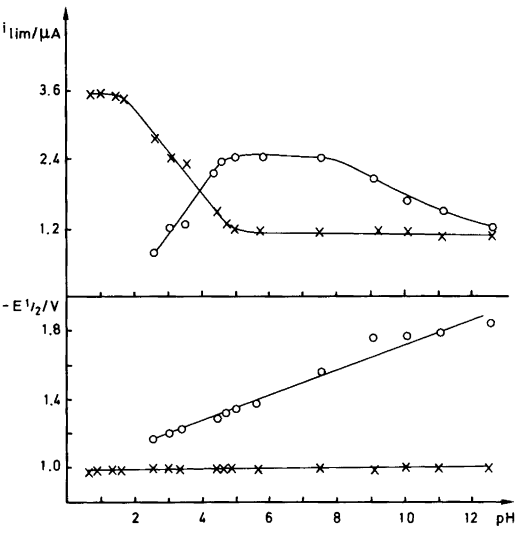
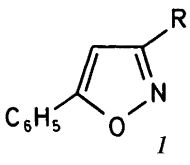


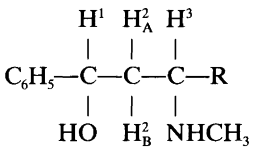
Fig. 3. Polarographic half-wave potentials (SCE) and limiting currents of 2,3-dimethyl-5-phenylisoxazolium iodide (*3b*) in aqueous buffers. Conc. of *3b* 3.7×10^{-4} M; × 1. wave, ○ 2. wave.



1

$$\xrightarrow[CH_3CN]{2\,e^- + H^+} C_6H_5{-}C(O^-){=}CH{-}C(NH){-}R \xrightarrow[-NH_3]{H_2O} C_6H_5COCH_2COR \qquad (5)$$

Determination of the erythro-threo *relationship in* 9. *Erythro* and *threo 9c* are known (*threo 9c* m.p. 147–148 °C; *erythro 9c* 121 °C).[12,13] The crude product from the reduction of *3c* had m.p. 144–146 °C, suggesting a predominance of *threo 9c*. The ^{1}H NMR spectrum of the mixture substantiated the assignment.



9

The coupling constants (Hz) for the minor component, presumed to be *erythro 9c*, were: $J(H^1,H^2_A)$ 11.04; $J(H^1,H^2_B)$ 2.62; $J(H^2_A,H^3)$ 10.62; $J(H^2_B,H^3)$ 2.49. The predominant conformation of *erythro 9c* is assumed to have hydrogen bonding between the hydroxy and the amino groups; models of this conformation indicate that the bonds C^1-H^1, C^2-H^2_A, and C^3-H^3 are nearly parallel. Large couplings from H^2_A both to H^1 and H^3 are then to be expected, and this was found. In the major isomer, presumed to be *threo 9c*, a similar conformation with hydrogen bonding between hydroxy and amino groups does not indicate a C-H^2 bond parallel to both C-H^1 and C-H^3; the coupling constants were (Hz): $J(H^1,H^2_A)$ 6.37; $J(H^1,H^2_B)$ 3.85; $J(H^2_A,H^3)$ 3.52; $J(H^2_B,H^3)$ 8.41. A large coupling of H^2_A to both H^1 and H^3 was thus taken as an indication of an *erythro 9*. One of the isomers of *9b* had the following coupling constants (Hz): $J(H^1,H^2_A)$ 10.7; $J(H^1,H^2_B)$ 2.25; $J(H^2_A,H^3)$ 10.85; $J(H^2_B,H^3)$ 2.45. The other isomer had $J(H^1,H^2_A)$ 7.50; $J(H^1,H^2_B)$ 3.50; $J(H^2_A,H^3)$ 3.16; $J(H^2_B,H^3)$ 3.44. On the basis of these coupling constants, the former isomer was assigned the *erythro* configuration.

Experimental

The ^{1}H NMR spectra were recorded at 360 MHz on a Varian XL-360 spectrometer, ^{13}C NMR spectra at 25.2 MHz on a Varian XL-100 spec-

Table 1. Polarographic half-wave potentials (SCE) and limiting currents (μA) for 4,5-dihydro-3,5-diphenyl-2-methylisoxazolium perchlorate (*4c*) in aqueous buffers, concentration 2.3×10^{-4} M.

Buffer	pH	$E_{1/2}$/V			i_{lim}/μA		
		1. wave	2. wave	3. wave	1. wave	2. wave	3. wave
HCl	0.49	0.48	0.77	0.91	1.24	0.24	1.24
HCl	0.79	0.48	0.77	0.91	1.24	0.36	1.12
HCl	1.3	0.48	0.77	0.92	1.24	0.44	1.04
HCl	1.5	0.48	0.785	0.95	1.24	0.80	0.64
Glycine	2.5	0.51	0.835	–	1.08	0.92	–
Citrate	3.08	0.51	0.835	–	1.08	0.92	–
Citrate	3.4	0.51	0.835	–	1.00	0.88	–
Citrate	4.4[a]	–	–	–	–	–	–

[a]The compound was hydrolyzed.

trometer with TMS as internal standard, MS spectra on a Micromass 7070E spectrometer operating at 70 eV using direct inlet.

The quaternized compounds were prepared on reaction between the parent compound in acetonitrile with methyl iodide (*3a, 3b*) at 60–70 °C for 24 h or by treatment with dimethyl sulfate, either neat or in carbon tetrachloride, at 60–70 °C for 24 h (*3c, 4b, 4c*), as exemplified below.

4,5-Dihydro-2,3-dimethyl-5-phenylisoxazolium perchlorate, 4b. 4,5-Dihydro-3-methyl-5-phenylisoxazole (3 g) was dissolved in CCl_4 (25 ml) and dimethyl sulfate (6 ml) added. The solution was kept in a closed vessel for 24 h at 65 °C. Two phases formed. Diethyl ether (50 ml) was added and the product layer separated and washed with ether. The crude product was dissolved in a mixture of water (25 ml) and diethyl ether (25 ml) and the aqueous layer slowly run into an aqueous solution of sodium perchlorate (6 g in 25 ml H_2O). The precipitate was filtered, dried, and dissolved in dichloromethane. On addition of diethyl ether, the product perchlorate *4b* crystallized; m.p. 113–114.3 °C.

Table 2. Polarographic half-wave potentials (SCE) and limiting currents (μA) for 4,5-dihydro-2,3-dimethyl-5-phenylisoxazolium perchlorate (*4b*) in aqueous buffers, concentration 2.8×10^{-4} M.

Buffer	pH	$E_{1/2}$/V			i_{lim}/μA		
		1. wave	2. wave	3. wave	1. wave	2. wave	3. wave
HCl	0.39	0.74	0.93	–	1.76	0.88	–
HCl	0.79	0.745	0.945	–	1.72	0.92	–
HCl	1.3	0.745	0.955	–	1.72	0.84	–
HCl	1.5	0.745	0.985	–	1.72	0.88	–
Glycine	2.5	0.745	1.07	1.18	1.72	0.42	1.24
Citrate	3.08	0.79	–	1.185	1.68	–	1.72
Citrate	3.4	0.795	–	1.195	1.68	–	1.76
Citrate	4.4	0.82	–	1.25	1.68	–	1.68
Citrate	4.7	0.82	–	1.26	1.68	–	1.80
Acetate	4.9	0.82	–	1.26	1.68	–	1.80
Acetate	5.6	0.82	–	1.28	1.36	–	1.60
Succinate	5.9	0.825	–	1.29	1.12	–	1.34
Phosphate	6.9[a]	–	–	–	–	–	–

[a]The compound was hydrolyzed.

Reduction of 2,3-dimethyl-5-phenylisoxazolium iodide (3b). Compound *3b* (1 g) was reduced in a phosphate buffer, pH 6, containing 40 % ethanol at −1.2 V (SCE) using 2 F mol^{-1}. The reduction completed, the ethanol was removed *in vacuo*, a solution of excess of potassium carbonate added, the resulting slurry filtered (Product A), and the filtrate extracted with diethyl ether. The ethereal layer was washed with water, dried ($MgSO_4$), and the ether removed *in vacuo*. The residue and product A (together 476 mg, 85 %) were identified as 3-methylamino-1-phenyl-2-buten-1-one, *5b*, (m.p. 72.6–74.2 °C) from the NMR, IR, and MS spectra and its hydrolysis in dilute hydrochloric acid to 1-phenyl-1,3-butanedione. ^{1}H NMR ($CDCl_3$): δ 2.06 (3H, s), 2.90 (3H, d, 5Hz), 5.57 (1H, s), 7.15-7.40 (3H, m), 7.6–7.85 (2H, m). MS (*m/e*, % rel. int.): 175 (18), 174 (100), 158 (43), 105 (13.5), 98 (74), 77 (16.5), 56 (13). IR spectrum (KBr, cm^{-1}): 2800–3100 (w), 1600 (s), 1577 (s), 1538 (s), 1521 (s), 1441 (m), 1319 (s), 1289 (s), 1060 (m), 735 (m).

Using a similar procedure, *3c* was reduced in an acetate buffer, pH 4, at −0.9 V (SCE). The product (yield 75 %) 1,3-diphenyl-3-methylamino-2-propen-1-one, m.p. 56–58 °C, was identified from spectroscopic data. ^{1}H NMR ($CDCl_3$): δ 2.81 (3H, d, 5 Hz), 5.62 (1H, s), 7.21–7.45 (8H, m), 7.6–7.8 (2H, m). MS (*m/e*, % rel. int.): 237 (79), 236 (98), 221 (9), 220 (100), 160 (85), 105 (44), 103 (45). IR spectrum (KBr, cm^{-1}): 2900-3100 (w), 1595, 1585 (s), 1568 (br.s), 1481 (m), 1329 (s), 1299 (m), 1269 (w), 1226 (m), 1146 (m), 1058 (m), 745 (s), 700 (s).

Reduction of 2,3-dimethyl-5-phenylisoxazolium iodide, 3b. Compound *3b* (1 g) was reduced in an acetate buffer, pH 5, containing 40 % ethanol, first at −1.2 V (to *5b*) and afterwards at the second wave at −1.5 V, $n = 6$ F mol^{-1}. After the reduction, the ethanol was removed *in vacuo,* the aqueous solution made alkaline with potassium carbonate and the product extracted with diethyl ether. The ether solution was washed with water, dried, and the ether removed leaving 495 mg (83 %) of a 52:48 mixture of *threo* and *erythro* 3-methylamino-1-phenyl-1-butanol, *9b*. ^{1}H NMR ($CDCl_3$), *threo:* δ 1.202 (3H, d, 6.56 Hz), 1.75 (1H, m, $J_{2A,2B}$ −14.55 Hz, $J_{1,2B}$ 3.50 Hz, $J_{2B,3}$ 3.44 Hz), 1.88 (1H, m, $J_{2A,2B}$ − 14.55 Hz, $J_{1,2A}$ 7.50 Hz, $J_{2A,3}$ 3.16 Hz), 2.441 (3H, s), 2.826 (1H, m, $J_{3,4}$ 6.56 Hz, $J_{2B,3}$ 3.44 Hz, $J_{2A,3}$ 3.16), 5.086 (1H, dd, $J_{1,2A}$ 7.50 Hz, $J_{1,2B}$ 3.50 Hz), 7.2–7.4 (5H, m); *erythro:* δ 1.145 (3H, d, 6.38 Hz), 1.52 (1H, m, $J_{2A,2B}$ − 14.50 Hz, $J_{1,2B}$ 2.25 Hz, $J_{2B,3}$ 2.45 Hz), 1.71 (1H, m, $J_{2A,2B}$ − 14.50 Hz, $J_{1,2A}$ 10.7 Hz, $J_{2A,3}$ 10.85 Hz), 2.94 (1H m, $J_{2B,3}$ 2.45 $J_{2A,3}$ 10.85, $J_{3,4}$ 6.38), 4.932 (1H, dd, $J_{1,2B}$ 2.25 Hz, $J_{1,2A}$ 10.7 Hz), 7.2–7.4 (5H, m). IR spectrum (*erythro + threo,* film, cm^{-1}): 3400 (br, m), 2800–3100 (s), 1445 (m), 760 (m), 702 (s).

In a similar way, *3c* (300 mg) was reduced at −0.9 V, −1.2 V, and finally −1.5 V, $n = 6$ F mol^{-1}. Isolated were 186 mg (75 %); m.p. 144–146 °C. ^{1}H NMR spectra showed the product to be a mixture of 86 % *threo* and 14 % *erythro* 1,3-diphenyl-3-methylamino-1-propanol. ^{1}H NMR ($CDCl_3$), *erythro:* δ 1.923 (1H, m, $J_{2A,2B}$ −14.46 Hz, $J_{2B,3}$ 2.62 Hz, $J_{2B,1}$ 2.49 Hz), 1.962 (1H, m, $J_{2A,2B}$ −14.46 Hz, $J_{2A,3}$ 11.04 Hz, $J_{2A,1}$ 10.62 Hz), 2.304 (3H, s), 3.439 (1H, m, $J_{2B,3}$ 2.62 Hz, $J_{2A,3}$ 11.04 Hz, $J_{1,3}$ 0.34 Hz), 5.029 (1H, dd, $J_{1,2A}$ 10.62 Hz, $J_{1,2B}$ 2.49 Hz, $J_{1,3}$ 0.34 Hz), 7.15–7.40 (10H, m); *threo:* δ 2.06 (1H, m, $J_{2A,2B}$ − 14.45 Hz, $J_{2A,1}$ 6.37 Hz, $J_{2A,3}$ 3.52 Hz), 2.18 (1H, m, $J_{2A,2B}$ − 14.45 Hz, $J_{2B,1}$ 3.85, $J_{2B,3}$ 8.41), 2.308 (3H, s), 3.64 (1H, dd, $J_{2B,3}$ 8.41 Hz, $J_{2A,3}$ 3.52 Hz), 4.946 (1H, dd, $J_{1,2A}$ 6.37 Hz, $J_{1,2B}$ 3.85 Hz), 7.15–7.40 (10H, m). IR (KBr, cm^{-1}): 3450 (br.m), 3300 (m, sharp), 2700–3200 (br.m), 1491, 1481 (m), 1115 (m), 1079 (m), 1049 (w), 1019 (m), 755 (m), 700 (s). MS (*m/e,* %): 241 (23), 211 (6.5), 121 (28), 120 (100).

Reduction of 3c *in a two-phase system.* Compound *3c* (1 g) was reduced at −0.9 V (SCE) in a well stirred suspension of 120 ml 0.8 N HCl and 30 ml dichloromethane, $n = 2.7$. The reduction was followed by polarography directly on the reduction mixture; in the final polarogram, a wave with $E_{1/2} = 1.1$ V remained. After reduction, the two phases were separated, the dichloromethane phase washed with water and dried ($MgSO_4$). Evaporation of the solvent left 0.47 g of pure *5c*. The aqueous phase was made alkaline with potassium carbonate, extracted with dichloromethane, which was washed with water, dried ($MgSO_4$) and evaporated leaving 0.26 g of slightly impure benzalacetophenone.

Reduction of 2,3-dimethyl-5-phenylisoxazolinium perchlorate 4b. Compound *4b* (300 mg) was reduced in an aqueous-ethanolic (40 %) acetate buffer, pH 5, at −1.1 V, $n = 2$ F mol^{-1} (work-up

as described for *3b*) when 133 mg (75 %) of 4-hydroxy-4-phenyl-2-butanone, a yellowish liquid, were isolated. ^{1}H NMR ($CDCl_3$): δ 1.99 (3H, s), 2.55–2.75 (2H, m), 3.00 (1H, br.s), 4.88 (1H, dd, $J_{3A,4}$ 7.0 Hz, $J_{3B,4}$ 5.7 Hz), 6.95–7.00 (5H, m). IR spectrum (film, cm^{-1}): 3400 (br.m), 1713 (s), 750 (m), 700 (m). MS (*m/e*, %): 164 (36), 146 (65), 145 (41), 107 (82), 106 (89), 105 (96), 103 (69), 79 (67), 77 (100).

Reduction of 4,5-dihydro-2,3-dimethyl-5-phenylisoxazolium perchlorate (4b). Compound *4b* (300 mg) was dissolved in an aqueous acetate buffer containing 40 % ethanol and reduced at −1.5 V (SCE; potential of the second wave), $n = 4.5$ F mol^{-1}. The ethanol was removed *in vacuo*, the aqueous phase made alkaline with potassium carbonate and extracted with diethyl ether, which was dried (molecular sieves 4A) and evaporated, leaving 140 mg (72 %) of a 3:1 mixture of *threo* and *erythro* 3-methylamino-1-phenyl-1-butanol.

Reduction of 4,5-dihydro-3,5-diphenyl-2-methylisoxazolium perchlorate (4c). Compound *4c* (300 mg) was reduced in 0.4 N hydrochloric acid, containing 10 % ethanol, at −0.6 V. After work-up as described above, 136 mg (71.5 %) of 1,3-diphenyl-3-hydroxy-1-propanone, m.p. 51–53 °C (hexane), were isolated (50–50.5 °C)[14] ^{1}H NMR ($CDCl_3$): δ 3.35 (2H, d, *J* 6 Hz), 5.31 (1H, t, 6 Hz), 7.2–7.5 (8H, m), 7.8–8.0 (2H, m). IR (film, cm^{-1}): 3400 (s, br.), 2800–3100 (m), 1682 (s), 1598 (m), 1581 (w), 1450 (m), 1214 (m), 750 (s), 702 (s), 690 (s). MS (*m/e*, %): 226 (2.6), 208 (15), 120 (27), 106 (40), 105 (100), 77 (79).

Reduction of 4c *(2).* Compound *4c* (300 mg) was reduced as above, but at −1.05 V, $n = 4$ F mol^{-1}. Work-up as above gave 180 mg (84 %) of a mixture (m.p. 126–131 °C) of *erythro* and *threo* 1,3-diphenyl-3-methylamino-1-propanol (*erythro* : *threo* 2:1, measured by ^{1}H NMR).

Reduction of 3-methyl-5-phenylisoxazole 1b. Compound *1b* (500 mg) was reduced in acetonitrile/$TBABF_4$ at −1.8 V (Ag/AgI, 0.1 M I^-). After the passage of 2 F mol^{-1}, the electrolysis was discontinued and the solution made acidic with sulfuric acid. After standing for 3 h, the acetonitrile was removed *in vacuo* and the residue extracted with diethyl ether. After washing with water, the ether was dried and evaporated leaving 430 mg (83 %) of benzoylacetone, identified from the ^{1}H NMR spectrum.

3,5-Diphenylisoxazole was reduced similarly to dibenzoylmethane; yield 85 %.

Reduction of 3,5-diphenylisoxazoline in acid solution. Compound *2c* (300 mg) was reduced in 0.16 N hydrochloric acid, containing 40 % methanol, at −1.1 V, $n = 4$ F mol^{-1}. After electrolysis, the methanol was removed *in vacuo*, and the aqueous phase extracted with chloroform, then made alkaline with 25 % ammonia and extracted with diethyl ether. The ethereal layer was washed with water, dried, and evaporated leaving 225 mg (74 %) of white crystals of 3-amino-1,3-diphenyl-1-propanol.

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