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Electroörganic Preparations

XXII. Reduction of Some Carboxylic Acid Derivatives of Thiazole

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The polarographic reduction of 2-thiazolecarboxylic acid and some of its derivatives has been investigated. 2-Thiazolecarboxamide in acid solution is reduced to the aldehyde in good yield whereas the other derivatives give no or lower yield of aldehyde. From the reduction of 2-thiazolecarboxanilide was isolated 2-anilinomethylthiazole which is acid solution can be reduced further to 2-methylthiazole. The first wave of 2-thiazolecarbohydrazide is caused by reduction to the amide.

The electrolytic reduction of an acid derivative to the aldehyde stage in aqueous solution requires *inter alia* that the carbaldehyde group of the product is protected against further reduction by hydration; 2-thiazolecarbaldehyde (Ia) is known to be hydrated in acid solution [1] and the reduction of derivatives of 2-thiazolecarboxylic acid (Ib) has, therefore, been included in the current investigation.

I a) R = CHO
b) R = COOH
c) R = $CONH_2$
d) R = $CONHC_4H_9$
e) R = $CONHCH_2C_6H_5$
f) R = $CONHC_6H_5$
g) R = $CON(CH_3)C_6H_5$
h) R = $CONHNH_2$
i) R = $CH_2NHC_6H_5$
j) R = $COOC_2H_5$
k) R = CH_2OH

POLAROGRAPHIC INVESTIGATION

In Fig. 1 are plotted the half-wave potentials of 2-thiazolecarboxylic acid. The height of the wave is somewhat dependent on the buffer; in citric acid buffers it is lower than in, *e.g.*, acetate buffers of approximately the same pH. About pH 7 the first wave disappears and another wave grows up. The wave in alkaline solution is only approximately half as high as that in acid solution.

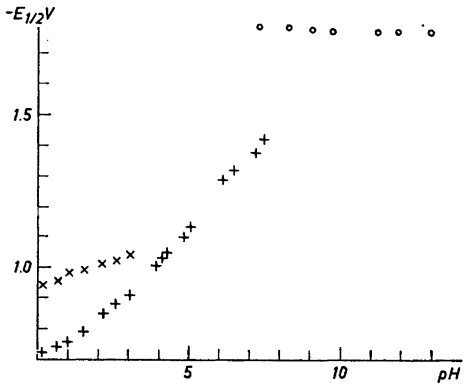

Fig. 1. Dependence on pH of half-wave potentials (S.C.E.) of 2-thiazolecarboxylic acid.

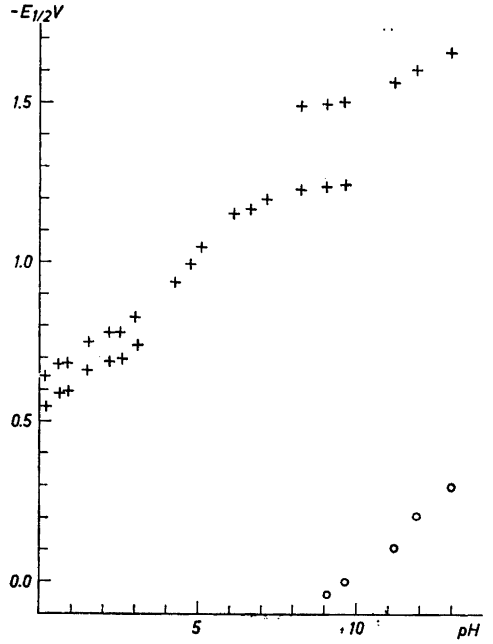

Fig. 2. Dependence on pH of half-wave potentials (S.C.E.) of cathodic (+) and anodic (O) waves of 2-thiazolecarbohydrazide.

The second wave found in acid solution diminishes in height from pH 1 to pH 3, where it disappears.

In Fig. 2 are plotted the half-wave potentials of the hydrazide (Ih). In acid solution the half-wave potentials of the amide (Ic) are the same as those of the second wave of Ih or — at higher pH — the combined wave. In alkaline solution the wave of the hydrazide appears at more negative potentials than that of Ic, as Ih loses a proton in strongly alkaline solution.

The wave-height of the amide corresponds at pH 0 to that of a two-electron wave; it grows with pH and reaches at pH 6 the height of a four-electron wave. About pH 8 it disappears and another wave grows at more negative potentials to the height of a two-electron wave. Ih behaves in a similar way. The height of the anodic wave corresponds to a four-electron oxidation.

The half-wave potentials of the anilide (If) are plotted in Fig. 3. The height of the wave in acid solution is constant and corresponds to a four-electron reduction; about pH 8 this wave disappears and another wave — approximately half as high as the first wave — appears. The half-wave potentials of the second wave found in acid solution are close to those of 2-anilinomethylthiazole (Ii).

The *N*-butylamide (Id) and the *N*-benzylamide (Ie) behave polarographically more like the anilide than like the amide (Ic); a four-electron wave

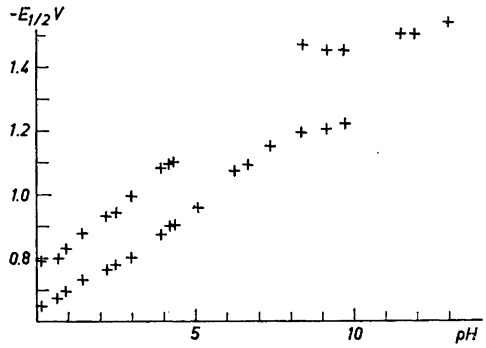

Fig. 3. Dependence on pH of half-wave potentials of 2-thiazoleanilide.

is found in acid solution and a two-electron wave in alkaline solution. The *N*-methylanilide (Ig) behaves similarly. In none of these cases, however, were observed two waves in acid solution as found in the reduction of the anilide.

MACROSCALE REDUCTIONS

The derivatives of 2-thiazolecarboxylic acid Ib—Ij were reduced in acid solution and the yields of the aldehyde Ia are given in Table 1; the reductions were performed at about 0° and at 25°.

Table 1. Polarographically determined yields (%) of aldehyde in electrolytic reduction of various derivatives of 2-thiazolecarboxylic acid on a ½ g scale in mineral acid solution.

Functional group	0°C	25°C
Carboxylic acid	25	17
Carboxamide	93	86
N-Butylcarboxamide		58
N-Benzylcarboxamide	60	47
Carboxanilide	6	3
N-Methylcarboxanilide		0
Carbohydrazide		50
Carboxylic ester	72	59

The electrolytic reduction of 2-thiazolecarboxylic acid gave some aldehyde together with unidentified products. The solution turned yellow during the reduction and smelled of sulphur-containing compounds.

The electrode reaction corresponding to the second wave of 2-thiazolecarboxylic acid in acid solution is not known. The formation of the aldehyde is not the main reaction of the first step and the second wave is not due to the reduction of the aldehyde; the major product may contain a partly reduced thiazole nucleus or products of hydrolysis from this as judged from the smell

of the reduced solution, but no products were identified. The second wave may be caused by a further reduction of the partly reduced nucleus or its product of hydrolysis; 2-thiazolemethanol (Ik) does not give a wave at this potential.

2-Thiazolecarboxamide (Ic) was reduced in 0.5 N hydrochloric acid to Ia in good yield in a two-electron reduction. In an acetate buffer (pH 4.5) the reduction consumed four electrons per molecule and 2-thiazolemethanol was the isolated product.

2-Thiazolecarboxanilide (If) was reduced in acid solution to a mixture of 2-anilinomethylthiazole (Ii) and 2-thiazolemethanol (Ik) in a four-electron reduction; traces of the aldehyde Ia were also found. 2-Thiazole-*N*-methylcarboxanilide was under the same conditions reduced to the carbinol (Ik) in a four-electron reduction. No traces of the aldehyde Ia or 2-methylanilinomethylthiazole were detected polarographically.

2-Anilinomethylthiazole (Ii) was reduced in acid solution to aniline and 2-methylthiazole in a two-electron reduction.

The first wave of 2-thiazolecarbohydrazide (Ih) was found to be caused by a two-electron reduction to the amide (Ic); the second wave is due to the reduction of the amide thus formed.

DISCUSSION

The chemical reduction of a derivative of a carboxylic acid to an aldehyde can be performed with different reagents, *e.g.* with some complex metal hydrides, but only few reports of the reduction of a free carboxylic acid to an aldehyde have been published. Lithium aluminium hydride reduces oxalic acid and certain aromatic *o*-hydroxyacids to the aldehyde in a rather low yield,[2] and lithium in ethylamine reduces several carboxylic acids to the aldehyde in fair to good yields.[3]

The electrolytic reduction of a carboxylic acid to the aldehyde is possible in some cases. The previous [4,5] and the present investigation show that certain requirements must be fulfilled for this reduction to take place.

a) The carboxyl group must be activated by a strongly electron-withdrawing group.

b) The carbaldehyde group formed must be protected against further reduction by forming a non-reducible derivative, *e.g.* by hydration to the *gem-diol.*

c) The reduction of the molecule must take place in the carboxyl group and not at other positions within the molecule.

The electron-withdrawing groups capable of rendering a carboxyl group reducible include carboxyl groups and their derivatives (*e.g.* in oxalic acid),[6] deactivated phenyl groups (*e.g.* ethylphthalate,[7] *p*-cyanobenzamide [8]), and certain heterocyclic rings.[4,5]

The substituents which make a carboxyl group reducible often activate the corresponding carbaldehyde group so that hydration occurs, but exceptions exist.[8]

The carboxyl group to be reduced activates, however, also the electron-withdrawing group, and the overall reduction may take place either at the

carboxyl group or at the activating group. A nitro group would be expected to be a sufficiently strong electron-withdrawing group to activate a carboxyl group for the reduction, but the very easy electrolytic reduction of the nitro group makes it useless as an activating group. The six-membered π-electron deficient heterocyclic rings containing two or more nitrogen atoms are reduced rather easily, and the carboxyl derivatives of pyridazine, phthalazine, cinnoline, quinazoline, pyrazine, and quinoxaline are reduced in the nucleus in preference to the carboxyl group.

In the less easily reduced six-membered π-electron deficient heterocyclic compounds as pyridine, quinoline, isoquinoline, and in the five-membered heterocyclic rings as imidazole, thiazole, and their benzoderivatives the reduction may take place in the carboxyl group or in the nucleus depending on the experimental conditions. In alkaline solution the reduction mostly takes place in the nucleus.

In the different positions in these heterocyclic systems the carboxyl group is activated to different degrees. The 2 and 4 positions of pyridine and quinoline, and the 1-position of isoquinoline are more activated than the 3-positions of these heterocyclic rings, and the 2-positions of thiazole and imidazole differ markedly from the 4- and 5-positions. These differences in reducibility run parallel to the chemical reactivity; the activated positions mentioned are thus the most vulnerable sites for nucleophilic attack, and methyl groups in these positions are activated enough to enter into aldol-like condensations.

A great difference in the yield of aldehyde is found between the electrolytic reduction in hydrochloric acid of 2-imidazolecarboxylic acid and 2-thiazolecarboxylic acid; the yields are 67 % and 25 %, respectively. The yield of 4-pyridinecarbaldehyde from the reduction of isonicotinic acid was at pH 0.1 30 %, close to the yield of Ia from Ib; at pH 3 the yield of 4-pyridinecarbaldehyde was 65 %, approximately the same as the yield of 2-imidazolecarbaldehyde from the acid.

The basicities of imidazoles and thiazoles are quite different. The pK of the parent compounds are 7.2 and 2.5, respectively. 2-Imidazolecarboxylic acid exists mainly as the zwitterion in slightly acid solution ($pK_1 = 1.0$, $pK_2 = 6.4$)[5] whereas 2-thiazolecarboxylic acid only to a minor degree is found as the zwitterion. In the reduction of isonicotinic acid the highest yield of aldehyde was found in the pH-region where the acid existed as the zwitterion.[4]

The yield of aldehyde is generally higher at 0° than at 25°. One of the reasons is that the rate of dehydration of the hydrated aldehyde is lower at the low temperature, the aldehyde thus being better protected against further reduction. Possibly also the rates of the competing reductions are affected by the change in temperature.

For the preparation of the aldehydes by electrolytic reduction of an acid derivative in aqueous solution the derivative of choice usually is the amide, except in the preparation of the 2-imidazolecarbaldehydes where just as good results are obtained by using the acids as starting materials.[5]

The reduction of the anilide (If) to a mixture of 2-anilinomethylthiazole (Ii) and 2-thiazolemethanol (Ik) is similar to the reduction of the corresponding pyridine derivative,[4] and a reduction route involving a partial hydrolysis of the intermediate reduction product seems probable. Also the reduction of the

N-methylanilide (Ig) to the carbinol (Ik) and methylaniline without the formation of detectable amounts of the aldehyde (Ia) or the possible tertiary amine is parallel to the reduction of the corresponding pyridine derivative.

2-Anilinomethylthiazole (Ii) is reduced to 2-methylthiazole and aniline; 4-anilinomethylpyridine behaves similarly, whereas *N*-benzyl-2-anilinomethylimidazole is not reducible polarographically.[5] Activated methylene groups carrying electronegative groups are often reduced to methyl groups.[9,10]

The reduction of the hydrazide (Ih) to the amide (Ic) in acid solution is similar to the reduction of isoniazide to isonicotinic amide.[4]

EXPERIMENTAL

The polarographic, electrolytic, and spectroscopic equipment was that used previously.[5]

2-Thiazolecarboxylic acid (Ib), m.p. 102° (decomp.) was prepared in 75—90 % yield (0.2 mole) according to Beyerman *et al.*[11]

2-Thiazolecarboxamide (Ic), m.p. 118°, was prepared in 80 % yield from Ib and ammonia through the mixed anhydride with ethyl chloroformate analogously to the preparation of *N*-benzylimidazole-2-carboxanilide.[5]

Analogously were prepared:

2-Thiazole-N-butylcarboxamide (Id) (0.02 mole) isolated as the slightly hygroscopic *hydrochloride* in 65 % yield, m.p. 112—113° (abs. ethanol-ether containing hydrogen chloride). (Equiv. wt. of chloride: Found: 222. Calc.: 220.7).

2-Thiazolecarboxanilide (If) (0.02 mole). 75 % yield, m.p. 89° (ethanol). (Found: C 59.10; H 3.99. Calc. for $C_{10}H_8ON_2S$: C 58.82; H 3.95).

2-Thiazole-N-methylcarboxanilide (Ig) (0.02 mole). 52 % yield, m.p. 73—74° (ethanol). (Found: C 60.60; H 4.58. Calc. for $C_{11}H_{10}ON_2S$: C 60.54; H 4.62).

Ethyl 2-thiazolecarboxylate (Ij) was prepared according to Erlenmeyer *et al.*[12]

2-Thiazolecarbohydrazide (Ih), m.p. 175—176° (173)[13] (ethanol), was prepared in 80—90 % yield according to Beyerman and Bontekoe[13] (70 %).

2-Thiazole-N-benzylcarboxamide (Ie), m.p. 125° (ethanol), was prepared by refluxing an alcoholic solution of the ethyl ester with excess of benzylamine for 2 h (90 %). (Found: C 60.57; H 4.55. Calc. for $C_{11}H_{10}ON_2S$: C 60.54; H 462).

2-Anilinomethylthiazole (Ii) was prepared analogously to *N*-benzyl-2-anilinomethylimidazole.[5] Yield 10 % of a light-brown hygroscopic dihydrochloride which was recrystallized twice from ethanol containing hydrogen chloride, m.p. 187—188° (decomp., closed tube). (Found: C 45.66; H 4.74; N 10.42. Calc. for $C_{10}H_{12}Cl_2N_2S$: C 45.50; H 4.91; N 10.61). Thin-layer chromatography with a 1:1 mixture of butanol and methanol on silica gel showed the presence of only one component. The pure compound is not very hygroscopic.

Reduction of 2-thiazolecarboxamide at pH∼0 (Ic). 5.0 g of the amide was reduced at −0.75 V *vs.* S.C.E. in 150 ml of prereduced 2 N hydrochloric acid with consumption of 2.1 electrons/molecule. The temperature was kept at about 10°; the reduction was stopped, when a polarogram of the catholyte showed two waves (aldehyde and amide) of the same size. A sample polarographed in an acetate buffer showed the presence of 92 % aldehyde and 3.8 % of amide. The rest of the catholyte was made alkaline by addition of potassium carbonate and continuously extracted overnight (16 h) with ether which was then dried over magnesium sulphate. The ether was removed and the oily residue fractionated *in vacuo* giving 2.5 g (57 %) of *2-thiazolecarbaldehyde* $b.p._{11}$ 63—70°, n_D^{25} 1.5700 ($b.p._{10.5}$ 63°, n_D^{25} 1.5720).[14]

Reduction of 2-thiazolecarboxamide at pH 4.3 (Ic). 0.50 g of the amide was reduced at −1.05 V *vs.* S.C.E. in a prereduced acetate buffer (pH 4.30) containing 20 % of ethanol with consumption of 4.0 electrons/molecule. To the colourless catholyte were added 20 ml of conc. hydrochloric acid and the solution was evaporated to dryness *in vacuo*. The residue was extracted with hot ethanol, which after filtration and evaporation left 0.7 g of solid material; this was dissolved in a small amount of abs. ethanol, filtered and

precipitated with ether giving 350 mg (59 %) of a yellowish product, identified as *2-thiazolemethanol hydrochloride* from its m.p. 115—120° (126—127°)[14] and IR-spectrum.

Reduction of 2-thiazolecarbohydrazide (1. wave) (Ih). 0.50 g of the hydrazide was reduced at −0.55 V *vs.* S.C.E. in 150 ml of prereduced 0.8 N hydrochloric acid with consumption of 3.0 electrons/molecule. Polarographic analysis of the catholyte showed the presence of 7 % aldehyde and 74 % amide. The catholyte was made alkaline by potassium carbonate and continuously extracted overnight (16 h) with ether, which was then dried over magnesium sulphate. Removal of the solvent *in vacuo* after filtration left 200 mg (45 %) of light-brown material, identified as *2-thiazolecarboxamide* from its m.p. 113—115° (118°)[12] and IR-spectrum.

Reduction of 2-thiazolecarbohydrazide (2. wave). 0.50 g of the hydrazide was reduced at −0.65 V *vs.* S.C.E. in 150 ml of prereduced 0.8 N hydrochloric acid with consumption of 4.9 electrons/molecule. Polarographic analysis of the catholyte showed the presence of 50 % aldehyde and 4 % hydrazide. The remaining catholyte was divided into two equal parts A and B. To A was added 400 mg of 2,4-dinitrophenylhydrazine in 100 ml of warm 4 N hydrochloric acid; the yellow precipitate was filtered off and dried at 80°, 220 mg (21.5 %), identified as the *2-thiazolecarbaldehyde 2,4-dinitrophenylhydrazone* from its m.p. 242—244° (243°)[14] and IR-spectrum. B was neutralized to pH 4—5 by sodium acetate, 1 ml of phenylhydrazine was added and the mixture warmed for 15 min and then left cold overnight. The precipitated yellowish crystals were filtered off and dried *in vacuo* over calcium chloride, 150 mg (21 %), identified as the *2-thiazolecarbaldehyde phenylhydrazone* from its m.p. 116—8° (117—118°)[14] and IR-spectrum.

Similarly were reduced *2-thiazolecarboxylic acid* (0.85 V *vs.* S.C.E., 3.9 electrons/molecule, 17 % of aldehyde), *2-thiazolecarboxamide* (−0.75 V, n = 2.2, 86 %), *2-thiazole-N-butylcarboxamide* (−0.85 V, n = 2.7, 58 %), *2-thiazole-N-benzylcarboxamide* (40 % ethanol, −0.75 V, n = 3.7, 47 %), and *ethyl 2-thiazolecarboxylate* (40 % ethanol, −0.85 V, n = 3.3, 59 %); the produced aldehyde was usually isolated as the 2,4-dinitrophenylhydrazone. During the reduction of the acid and its ester the catholyte became yellow and had an unpleasant "sulphur smell". In the reductions carried out about 0° crushed ice was added to the catholyte instead of water, and the cathode compartment was externally cooled in an ice-salt mixture.

Reduction of 2-thiazolecarboxanilide. 0.50 g of the anilide was reduced at −0.7 V in 150 ml of prereduced 0.8 N hydrochloric acid containing 60 % of ethanol, n = 4.5. The catholyte was polarographically analyzed for aldehyde (2.5 %) and 2-anilinomethylthiazole (51 %) and spectrophotometrically for aniline after diazotation and coupling (51 %). The remaining catholyte was made slightly alkaline by addition of potassium carbonate and evaporated to nearly dryness *in vacuo* on a water bath below 50° to remove the aniline. The residue was taken up in 50 ml of water and extracted twice with ether which was then dried over potassium hydroxide. Addition of dry hydrogen chloride to the ethereal solution precipitated 323 mg (50 %) of nearly white crystals which were dried *in vacuo* over phosphorus pentoxide and identified as *2-anilinomethylthiazole dihydrochloride* from the m.p. 184—186° and IR-spectrum.

Reduction of 2-thiazole-N-methylcarboxanilide. 0.50 g of the *N*-methylanilide was reduced at −0.65 V *vs.* S.C.E. in 150 ml of prereduced 1 N hydrochloric acid containing 20 % of ethanol with consumption of 4.0 electrons/molecule. The catholyte was polarographically analyzed for aldehyde (0 %) and *N*-methylaniline (99.5 %), then made alkaline by addition of potassium carbonate and extracted with ether which was then dried over potassium hydroxide. Addition of dry hydrogen chloride to the ethereal solution gave a precipitate, 450 mg, identified as a mixture of *N-methylaniline hydrochloride* and *2-thiazolemethanol hydrochloride* from the IR-spectrum.

Reduction of 2-anilinomethylthiazole. 0.25 g of the dihydrochloride was reduced at −1.0 V *vs.* S.C.E. in 150 ml of prereduced 0.8 N hydrochloric acid; the catholyte was spectrophotometrically analyzed for aniline (90 %) (after diazotation and coupling) and then diazotized at room temperature by addition of 1 g of sodium nitrite in 5 ml of water; after standing for ½ h 10 g of sodium hypophosphite in 20 ml of water and 10 ml of conc. hydrochloric acid were added and the mixture left overnight. The solution was made strongly alkaline with sodium hydroxide and continuously extracted for 20 h with ether to which was then added excess of picric acid in ethereal solution. The yellow precipitate (150 mg, 50 %) had m.p. 152—155° (ethanol) and was identified as *2-methylthiazole picrate* from its m.p. (153°)[15] and IR-spectrum.

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