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Organic Electrosyntheses

II.* Preparation of Some Heterocyclic Aldehydes

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The possibility of extending earlier small-scale electrolytic reductions of some carboxylic acid derivatives of the pyridine, thiazole, and imidazole series into useful syntheses of the corresponding carbaldehydes has been investigated. 2- and 4-Pyridinecarboxamides, 2-thiazolecarboxamides, and 2-imidazolecarboxylic acids have been used as substrates in acid medium on a 0.2 mole scale. The yields are mostly reasonably good compared with chemical methods, but the electrolytic preparation does not offer special advantages.

In earlier work from this laboratory the possibility of preparing heteroaromatic carbaldehydes by electrolytic reduction of the corresponding carboxylic acids or their derivatives has been demonstrated in the pyridine,[1] imidazole,[2] and thiazole [3] series. In these papers electrolyses were carried out only on a small scale, and the aldehydes were mostly isolated as derivatives. The present investigation was undertaken as an attempt to develop useful electrosyntheses of such aldehydes by working on a larger scale with a powerful potentiostat and an earlier constructed macroscale electrolytic cell.[4] At the same time some new substrates have been included.

RESULTS AND DISCUSSION

Polarography. The basis of the method is the fact that certain heterocyclic carbaldehydes are strongly hydrated in acid aqueous solution.[2,5,6] The polarographically easily reducible carbonyl function is partially converted into a

$$\text{N-HetAr-CHO} \xrightarrow{H^+} \overset{+}{\text{HN}}\text{-HetAr-CHO} \underset{-H_2O}{\overset{+H_2O}{\rightleftharpoons}} \overset{+}{\text{HN}}\text{-HetAr-CH(OH)}_2$$

I

* Ref. 4 is considered as part I of this series; in part presented at the 13th Scandinavian Chemistry Meeting, Copenhagen, August 19th–23rd, 1968.

non-reducible *gem*-diol (I) thus explaining the anomalous pH-dependence of the height of the polarographic waves for these compounds. This behaviour is illustrated on Fig. 1 with an example from each of the 3 heterocyclic systems

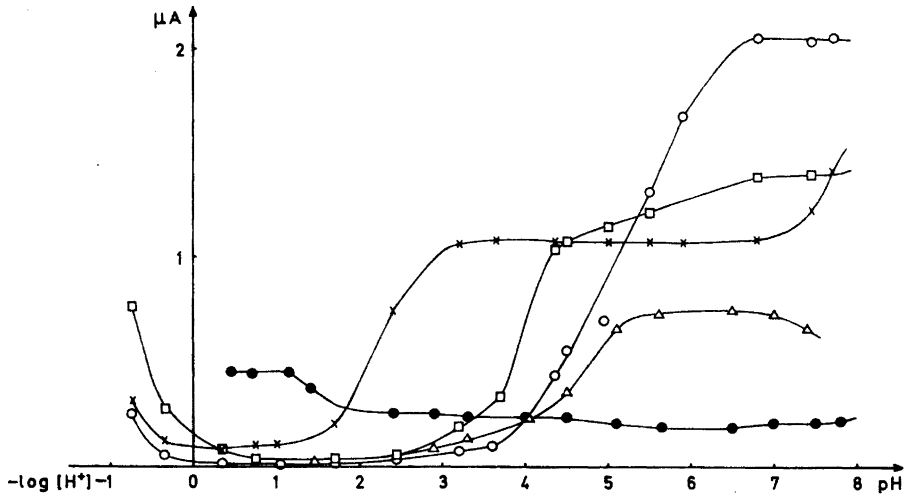


Fig. 1. Dependence on pH of the limiting currents of picolinaldehyde □, 4-methyl-2-thiazolecarboxaldehyde ×, *N*-benzyl-2-imidazolecarboxaldehyde ○, 1-isoquinolinecarboxaldehyde △, and 2-benzothiazolecarboxaldehyde ●. Concentration 5×10^{-4} M, 20 % ethanol, 25°.

of the present study; the curves of two benzohomologues hitherto not reported have also been included. Only the more relevant acid region is shown, and in cases where the wave is split into two the total wave height has been plotted. 1-Isoquinolinecarboxaldehyde is seen to be strongly hydrated quite similarly to the 2- and 4-quinolinecarboxaldehydes investigated by Laviron,[5] and below pH 1 the wave height was too small to be accurately measured. The curve of 2-benzothiazolecarboxaldehyde, however, is quite different from those of the other aldehydes; the wave height is considerably lower than expected and practically independent of pH in a rather broad region. The wave height was found to be nearly independent of the height of the mercury reservoir at pH 5.6, and consequently the current must be controlled by some kinetic process, but certainly different from the "normal" acid-catalyzed hydration shown by the other related aldehydes. The electrode reactions of the condensed heterocyclic aldehydes have not been explored in detail, and their possible electrosynthesis from carboxamide precursors has not been included in the present investigation.

Macro-scale electrolysis. As the carbaldehyde function is reducible at a less negative potential than the corresponding carboxylic acid or derivatives thereof it is only possible to stop the reduction at the aldehyde stage (at least partially) under conditions where the carbaldehyde is protected as the *gem*-

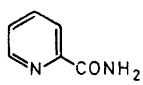
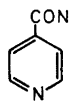
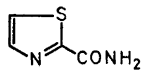
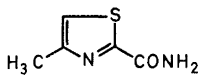
diol derivative, *i.e.* the electrolytic reduction must be carried out in aqueous acid solution. Starting with a carboxamide the non-reducible species (intermediate at the electrode surface) may more correctly be formulated as a *gem*-aminoalcohol (II) which might then be transformed into the *gem*-diol (I) in the bulk of the solution:

$$\overset{+}{\mathrm{HN}}\text{-HetAr-CONH}_2 \xrightarrow{2e^- + 2H^+} [\overset{+}{\mathrm{HN}}\text{-HetAr-CH(NH}_2\text{)OH}] \rightarrow \text{N-HetAr-CHO}$$

II

On the other hand, the hydration is a reversible process and a small, but detectable part of the carbaldehyde is always present in the reducible form during the electrolysis, thus making a 100 % conversion of the starting material into the desired product impossible. The identity of the product of further reduction in acid medium has not been proved, but a 2-electron wave has been postulated on the basis of polarographic data.[5] This is in good accordance with the high carbinol/pinacol ratio found in the reduction of 2-acetylpyridine [7] in acid solution and the isolation of carbinols from reduction of isonicotinic amide [1c] in citrate buffer and 2-thiazolecarboxamide [3] in acetate buffer.

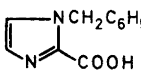
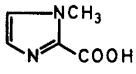
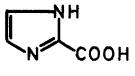
Table 1. Results from electrolytic reduction of heteroaromatic amides at −0.8 V *vs.* Ag/AgCl on a mercury cathode in 2 N hydrochloric acid solution on a 0.2 mole scale.

Starting material	Temperature	Polarographic analysis % Amide	% Aldehyde	% Isolated aldehyde	*n* *F*/mole
	10–15°	2	72.5	53.5	2.29
	20–25°	5	72	39	2.24
	10–15°	6	67	49	2.33
	20–25°	4	65.5	39	2.24
	10–15°	3	81.5	44	2.34
	20–25°	2	63	28	3.09
	10–15°	12	82.5	52.5	2.12
	20–25°	9.5	62	31	2.96

The results from electrolyses of pyridine and thiazolecarboxamides are given in Table 1. As the rate of dehydration has been found to be dependent on temperature, giving higher yields of carbaldehyde at lower temperature,[2,3] experiments were carried out at two temperatures. Because of a rather high ohmic resistance the water-cooled electrolytic cell [4] could not be operated below 10° with currents of 3 – 5 A, and better cooling facilities have not been avail-

able. The yields of fractionated product are especially for the 2-thiazolecarbaldehydes rather low compared with the analytical findings reflecting some difficulties in separation from by-products by simple laboratory distillation techniques. It is seen that temperature control is more important with the thiazole compounds than with the pyridine compounds which are more like the imidazoles.[2] As the yields would not be expected to be substantially better than those obtained by known chemical methods even with more careful work-up procedure, oxidation of the carbinols with selenium dioxide for the pyridinecarbaldehydes [8,9] and reaction of the lithium derivatives with dimethylformamide for the thiazolecarbaldehydes [10] seem to be the methods of choice for the preparation of these compounds.

Table 2. Results from electrolytic reduction of 2-carboxyimidazoles at −1.2 V *vs.* Ag/AgCl at a mercury cathode in 2 N hydrochloric acid solution at room temperature on a 0.2 mole scale.

Starting material	Pure acid		Impure acid	
	Analysis	Isolated	Analysis	Isolated
	88	78.5	89	77
	—	—	71	59
	83.5	60 [a]	71	46.5 [a]

[a] Diethylacetal derivative.

The results from electrolyses of 2-imidazolecarboxylic acids are given in Table 2. In the imidazole series the more readily available free carboxylic acids are as good substrates as the carboxamides;[2] this is one of the rare cases where a carboxylic acid group can be directly reduced into the carbaldehyde function. In earlier work [2] only a slight temperature dependence of the yield of carbaldehyde was found, and all electrolyses in Table 2 were made at room temperature with the passage of 2.3 *F*/mole; the starting materials could then no longer be detected polarographically. As the *N*-methyl-2-imidazolecarboxylic acid has been isolated only in low yield [11] and our attempts to raise the yield were without much success, it was decided instead to use a solution of the crude product from carbonation of the lithium compound as starting material. For comparison the same was done with the *N*-benzyl-2-carboxyimidazole and with a solution of the crude product from its debenzylation in liquid ammonia.

With the *N*-benzyl-2-carboxyimidazole practically no difference was found between experiments with the pure and the impure acid as substrate; this

means that the metallation of *N*-benzylimidazole [11] in the 2-position by butyllithium (5 % excess) is quantitative. However, though the yield of electrolytically prepared *N*-benzyl-2-imidazolecarboxaldehyde is quite good, the route *via* selenium dioxide oxidation of the carbinol [10] should be preferred. With the *N*-methylimidazole some metallation has been detected also in the 5-position,[11] but yield of carbaldehyde from reduction of the crude acid gives evidence that the metallation-carbonation procedure is much more effective than expected from the low yield of isolated *N*-methyl-2-carboxyimidazole.[11] The yield of electrolytically prepared *N*-methyl-2-imidazolecarboxaldehyde is only slightly lower than that from the reaction of the lithium derivative with dimethylformamide,[10] but the latter method is preferable because the imidazolyllithium is already involved in the preparation of the carboxylic acid.

For the unsubstituted parent compound the electrosynthesis was expected to be a valuable alternative, but the results show that this hope has not been fulfilled. A recent modification [12] of our original procedure [10] now presents the most attractive way of preparing 2-imidazolecarboxaldehyde, as the yield in the manganese dioxide oxidation of 2-imidazolemethanol has been found to depend on the amount of reagents used due to a strong adsorption of the product to the oxidant.[14]

EXPERIMENTAL

Apparatus. Polarograms were recorded on a Radiometer PO4 polarograph with a capillary of $m=1.82$ mg/sec and $t=4.65$ sec. (water, open circuit). Electrolyses were run in a cell of the type earlier described [4] only that the beaker had been provided with a water-jacket connected in series with the inner cooling coil. The reference electrode was a piece of silver wire in a saturated aqueous potassium chloride solution; the potential of this half-cell is about 50 mV negative *vs.* the S.C.E. The potential of the mercury cathode was controlled by a fully transistorized potentiostat (40V/25A) developed in collaboration with Tage Juul Electronics, Herlev, Denmark, and the amount of electricity was measured by a conventional 10 A DC-Kwh meter from Laur. Knudsen A/S, Copenhagen.

Reagents. 2-Imidazole- and *2-thiazolecarboxaldehydes* were prepared according to published procedures.[10] *Isonicotinaldehyde* was obtained from Fluka, Buchs, Switzerland, and *picolinaldehyde* was prepared according to Schaefer and Bertram.[8] *2-Benzothiazolecarboxaldehyde* [15] was obtained from the methyl derivative in 30 % yield by selenium dioxide oxidation in refluxing dioxane [10] instead of the original xylene solvent. The same procedure was adopted for the synthesis of *1-isoquinolinecarboxaldehyde* [16] obtained in 65 % yield from *1-methylisoquinoline.*[17] *Picolinamide* and *isonicotinamide* were either commercial products (Reilly) or prepared in 85 % and 79 % yield, respectively, by the mixed anhydride method [18] analogously to the *2-thiazolecarboxamide* [3,19] and *4-methyl-2-thiazolecarboxamide* from the corresponding carboxylic acids,[21] (90—95 % yield, m.p. 151—152° after recrystallization from 50 % aqueous ethanol; lit.[20] m.p. 152°).

Application of the same procedure [21] in the imidazole series gave 91—94 % of N-*benzyl-2-carboxyimidazole* [11] (reverse addition), while the N-*methyl-2-carboxyimidazole* [11] was only isolated as an impure Li-salt from the ethereal solution after carbonation; the height of the cathodic wave of the crude salt suggested a high degree of conversion in the metallation-carbonation reaction, but a suitable solvent for its purification could not be found and the salt was not further characterized. Instead 0.2 mole of N-*methylimidazole* (BASF) was rapidly metallated between −10° and −20° with 5 % excess ethereal butyllithium; the resulting practically clear reddish solution was stirred for further 30—45 min and poured into a slurry of carbon dioxide in ether. After 2—3 h the white precipitate was dissolved in 100 ml of hydrochloric acid and electrolyzed as such. *2-Carboxyimidazole* was prepared in 60—65 % yield according to Jones,[22] but the claimed yield of 80 % has never been obtained in this laboratory. For the solution of the impure acid the residue after evaporation of the ammonia was taken up in 200 ml of 2 N hydrochloric acid,

washed with ether to remove the toluene formed in the debenzylation step, and used directly in the electrolytic cell.

Reduction of 4-methyl-2-thiazolecarboxamide. The following procedure is typical for all the compounds in the present study. 0.2 mole of the substrate was reduced at −0.8 V *vs.* Ag/AgCl in a medium consisting of 100 ml of conc. hydrochloric acid +300 ml of 96 % ethanol +300 ml of water. The time of electrolysis was 3−4 h at room temperature and 5−6 h at 10−15°. After the reduction the catholyte was diluted to 1000 ml with water, a 1.0 ml sample was withdrawn and further diluted to 25.0 ml; aliquots of the latter solution was polarographed in an acetate buffer of pH 5 and the concentrations of *4-methyl-2-thiazolecarboxaldehyde* and the amide determined simultaneously by means of standard curves. The catholyte was evaporated under reduced pressure on a water bath below 50°, the residue cautiously neutralized with addition of excess potassium carbonate or sodium hydrogen carbonate and 200−300 ml of water; the mixture was extracted with 200 ml + 3×100 ml of ether which was dried over sodium sulphate. The solvent was stripped off and the dark oily residue fractionated *in vacuo* collecting 13.3 g (52.5 %) of *4-methyl-2-thiazolecarboxaldehyde*, b.p.$_{10}$ 73−78°, n_D^{23} 1.5590; (lit.[10] b.p.$_{11}$ 75.5−76°, n_D^{25} 1.5580).

In reductions of the pyridinecarboxamides and the 2-carboxyimidazoles it was not necessary to add ethanol to dissolve the substrates and the aldehyde products were extracted with chloroform instead of ether. With the 2-carboxyimidazoles the reduction potential was −1.2 V *vs.* the Ag/AgCl reference electrode. The polarographic analyses were done in phosphate buffers at pH 7 for the pyridine and pH 7.5 for the imidazole derivatives.

The free *2-imidazolecarboxaldehyde* was not isolated because of difficulties with separation from by-products. The catholyte was instead evaporated to dryness, the residue extracted with hot absolute ethanol, dry hydrogen chloride gas added, and the solution refluxed for 8 h. After cooling excess sodium hydrogen carbonate was added, the solution filtered and evaporated. The brownish crude product, m.p. 96−100°, was purified by sublimation in 5 g portions at 90°, 0.2 mm giving 60 % of pure, white *2-imidazole carboxaldehyde diethylacetal*, m.p. 115−6°; (lit.[10] m.p. 116°).

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