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Anodic Decarboxylative Oxidation of Carboxymethyluracil and -thymine Isomers.

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Abstract. The anodic oxidative decarboxylation of isomers of uracil and thymine acetic acids was studied. Electrolysis in methanolic or ethanolic solutions yielded respective alkoxymethyl derivatives *via* carbocationic intermediates. In acetic acid/sodium acetate medium, these were trapped by acetate, resulting in corresponding acetoxymethyl derivatives. Electrolysis in fully deuterated methanol or deuterated acetic acid, allow to obtain respective trideuterated compounds. © 1997, Elsevier Science Ltd. All rights reserved.

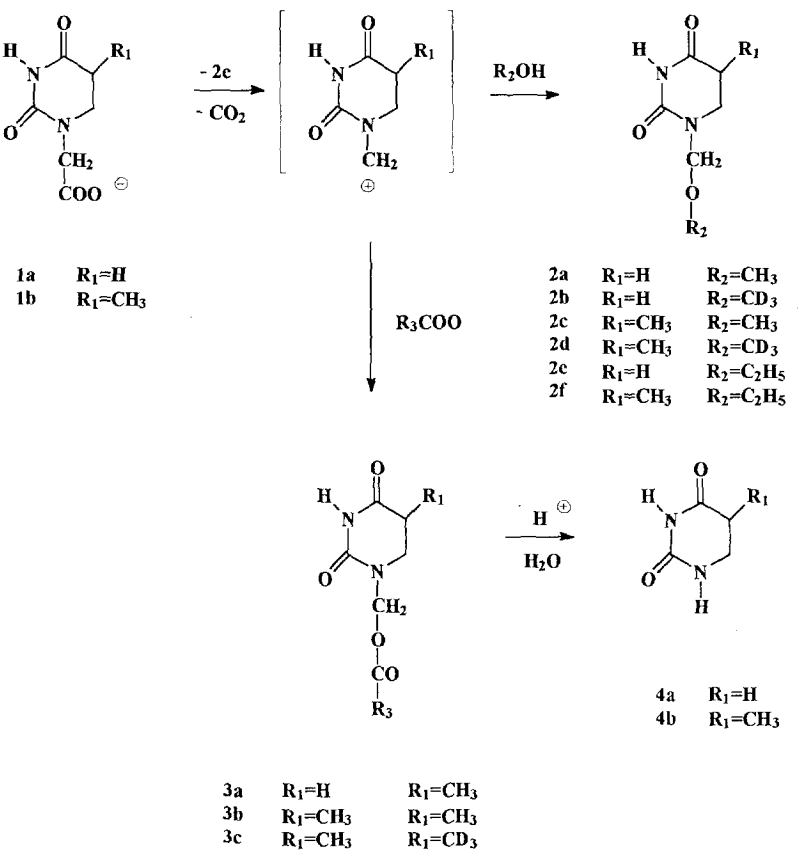
Anodic oxidative decarboxylation of alkanoates (Kolbe reaction), despite its historical character, is still an important synthetic tool in organic synthesis[1a,b]. There are few synthetic applications of Kolbe decarboxylation described in chemistry of nucleic acid derivatives. Biologically important 5-substituted uracils were obtained by electrochemical decarboxylation with simultaneous aromatisation, and by electrochemical conversion of aspartic acid derivatives[2a,b]. Anodic oxidation of uridine 5'-carboxylate yields 4'-methoxy- and 4',2-cycloderivative of 1-erythrofuranosylouracil[3] as two main products. In this study, we examined synthetic potentiality of Kolbe electrolysis using isomeric carboxymethyluracils (uracilacetic acids).

The synthetic utility of Kolbe reaction for isotopic labeling remains practically unexplored. Isotopically labeled groups have only been used once in Kolbe reaction, i.e., in the coupling of trideutero and trifluoromethylradicals in the synthesis of trideuterotrifluoroethane[4]. In our experiments, electrochemically generated intermediate cationic species were trapped by deuterated methanol to introduce trideuteromethoxy group into uracil derivatives.

Results and Discussion

Methanol is commonly used as a solvent for Kolbe electrolysis. However, 1-carboxy-methyluracil[5] (**1a**) and -thymine[6] (**1b**), and their sodium salts we used are poorly soluble in either methanol or ethanol. To overcome this problem, we have applied tributylamine and 1,8-diazabicyclo[5,4,0]-undec-7-en (DBU) salts of **1a** and **1b**. Electrolysis patterns of the alkoholic solutions of these compounds were qualitatively similar, but the amount of minor products was markedly reduced in the case of DBU salts.

Scheme 1



Out of five major nucleic acid bases only uracil and thymine do not exhibit polarographic reduction waves. Our unpublished observations on electrolysis in undivided cells of uracil and thymine derivatives in organic solvents revealed decreases in total UV-absorption of the reaction mixtures, in particular at high current densities. TLC-pattern of the electrolytic reaction mixtures appeared similar to that found under chemical oxidation

conditions[7], showing a number of ninhydrine- and Fink reagent-positive[8] spots. For satisfactory results, electrolysis should be performed at a low current density.

Electrolysis of DBU salts of **1a** and **1b** in methanolic or ethanolic solutions provides, respectively, 1-methoxy- and 1-ethoxymethylpyrimidines (**2a,c,e,f**). The use of deuterated methanol leads to corresponding trideuteromethoxymethyl derivatives **2b** and **2d** (Scheme 1).

Depending on experimental conditions and substrate type, the electrodecarboxylation reaction can be described by either a radical or a cationic mechanism[1]. However, HPLC-analysis did not confirm forming of 1-methyluracyl or -thymine and ethylene-1,1'-bispyrimidines which were expected as products of the radical pathway in the experiments we report here. The alternative formation of carbocation *via* „pseudo-Kolbe" electrolysis is not to exclude. The nitrogen atom can be oxidized to radical cation that undergoes decarboxylation to an amino methyl radical that is further oxidized[9a-d]. Formation of compounds **2a-f** confirms the existence of carbonium intermediates trapped by nucleophilic alcohols. The yield of electrochemically formed alkoxymethylpyrimidines depends strongly on current density and alcohol species (Fig 1).

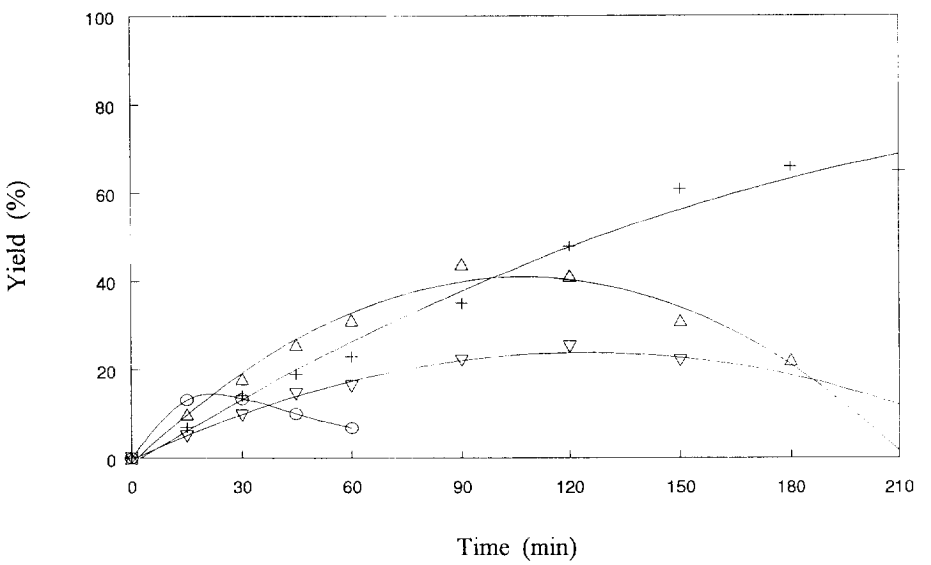


Fig 1. Formation of **2a** during the electrolysis of **1a** at different current densities in methanol. 0,017 A/cm^2 (+), 0,033 A/cm^2 (△), 0,100 A/cm^2 (○), and in ethanol at 0,033 A/cm^2 (▽).

Due to electrochemical oxidation of pyrimidine nucleus, high current density reduces markedly the formation of alkoxymethyl products. The yields of methoxylated products were usually better than those of the corresponding ethoxylated compounds. Because of their structural similarity to biologically important hydroxyethoxymethyl substituted nucleic acid bases (e.g., acyclovir), the alkoxymethyluracils and -thymines described here have previously been synthesised and characterised [10a-c].

Attempts to achieve cross-coupling between acetic acid-derived methyl radical, and radicals presumably formed from either **1a** or **1b**, were unsuccessful. When acetic acid or deuterated acetic acid were used, 1-acetoxymethyl compounds **3a-c** were detected as main products instead of the expected 1-ethylpyrimidines or 1-(2',2',2'-trideuteroethyl)-thymine. This observation supports the existence of carbonium intermediates which undergo nucleophylic substitution by acetate present in the reaction medium. However, the radical substitution mechanism was also observed. Beside of 1-acetoxymethyluracil (**3a**), some amount of 1-acetoxy-methylthymine (**3b**) formed in the case of 1-carboxymethyluracil (**1a**) electrolysis as a result of methyl radical substitution of the pyrimidine nucleus (Fig. 2).

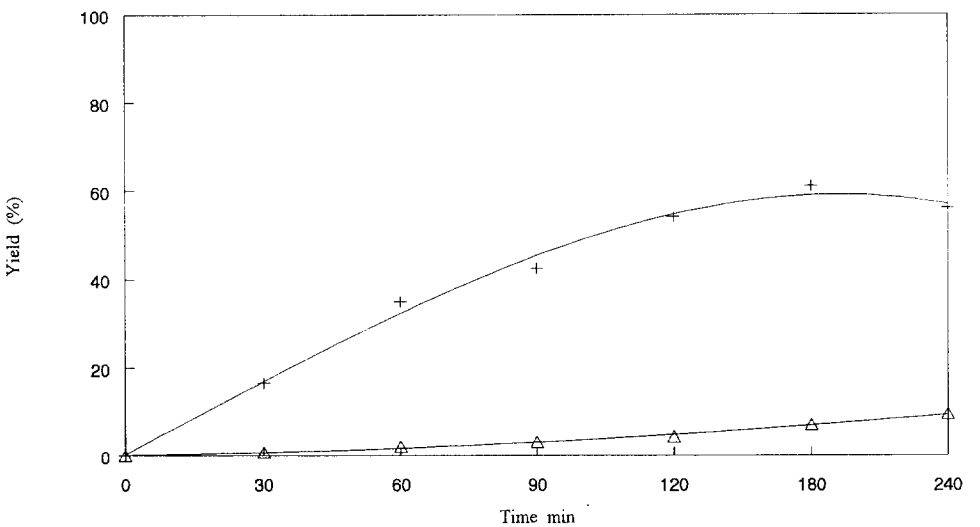


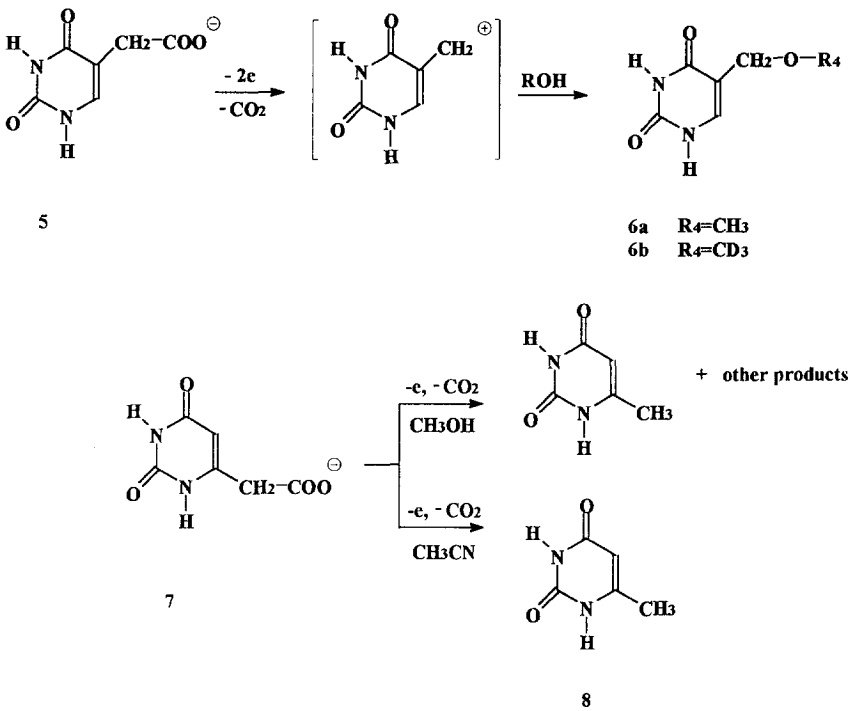
Fig 2. Kinetic of electrolysis of 1a in acetic acid / sodium acetate at current density 0,033A/cm^2. **3a** (+), **3b** (△).

Acidic hydrolysis of the electrochemically obtained esters **3a** and **3b** gave exclusively uracil (**4a**) and thymine (**4b**), respectively. This was explained by the reported instability of N-hydroxymethyluracil and thymine derivatives[11].

1-Carboxymethyluracil (**1a**) and -thymine (**1b**) are N-substituted oxopyrimidines. Electrolysis of their C-substituted analogues 5-carboxymethyluracil[12] (**5**) and 6-carboxy-methyluracil[13] (**7**) was also studied (Scheme 2).

Anodic decarboxylation of DBU salt of **5** in methanol and deuterated methanol yielded 5-methoxy-methyluracil[14] (**6a**) and its deuterated derivative (**6b**), respectively. This indicates that the cationic reaction pathway is valid both for 5- and N_1-substituted uracil acetates.

Scheme 2



A different reaction pattern was observed during the electrolysis of the DBU salt of 7. Electrodecarboxylation of the latter in methanol resulted in a complex mixture of products, including a considerable amount (13%) of 6-methyluracil (**8**). Using dry acetonitrile instead of methanol, **8** has been found as a sole product of the electrolysis. These experimental results suggest the presence of radical intermediates. In particular, the results of electrolysis in acetonitrile can be explained by hydrogen transfer from N-1 to anodically generated radical species.

The electrolytically obtained compounds were compared with those synthesized by known procedures. Additional characterisation by UV, ^{1}H NMR and mass spectroscopy, and elemental analyses if necessary, confirmed the structure and introduction of deuterium label into electrochemically synthesized products. The introduction of trideuteromethoxy group shifted molecular peak by 3 m/z units, while the positions of other peaks were generally identical with those for unlabeled compounds. ^{1}H NMR results (Table 1) also indicated a successful introduction of trideuteromethoxy group.

The electrochemical approach used in this study will also allow for the introduction of ^{13}C and tritium labelled methoxy group from the respective commercially available methanols.

Table 1. Chemical shifts (in ppm vs internal TMS) of substituted uracil and thyminederivatives in D_3COD at 20°C.

Compd.	N_1-CH_2	OCH_3 or OC_2H_5	5-H or 5-CH_3	6-H	O_2CCH_3	5-CH_2
2a	5.093	3.367	5.694	7.615	-	-
2b	5.092	-	5.695	7.616	-	-
2c	5.069	3.355	1.881	7.455	-	-
2d	5.670	-	1.880	7.455	-	-
2e	5.680	3.587, 1.188	5.691	7.621	-	-
2f	5.114	3.575, 1.182	1.880	7.459	-	-
3a	5.664	-	5.667	7.698	2.080	-
3b	5.676	-	1.863	7.526	2.075	-
3c	5.645	-	1.863	7.526	-	-
6a[a]	-	3.211	-	7.394	-	4.007
6b[a]	-	-	-	7.393	-	4.005

a) in DMSO-D_6

Experimental

Solvents for electrolysis were anhydrous. DBU was purchased from a commercial source (Aldrich). Preparative TLC was carried out on Kieselgel PF_{254} (Merck) (2 mm thickness). Analytical TLC was performed on precoated silica gel 60 F_{254} (Merck). Melting points (uncorr.) were measured on a Boetius microscope hot stage. HPLC was performed on a Shimadzu LC 6A instrument (UV detector , λ=254 nm) with a column C_{18} (4,6 X 25 mm) (Beckman) (water-MeOH). In the kinetic measurements, standardisation curves were considered. Mass spectra (70 eV) were obtained with a model AMD-604 (Intectra) spectrometer. UV spectra were recorded on Kontron Uvikon 940 spectrophotometer. NMR spectra were measured with a Varian UNITYplus 500 MHz spectrometer. Electrolyses were performed in an undivided water-coated cell equipped with two 3 cm^2 platinum electrodes 5 mm apart[15].

1-Methoxymethyluracyl (2a). To the stirred suspension of **1a**[5] (255 mg, 1.5 mmol) in MeOH (30 ml) DBU (245 mg, 1.6 mmol) was added. The clear solution formed after few minutes was electrolysed for 5 hours at a constant current density (0.017 A/cm^2). The resulting pale yellow solution was concentrated and applied onto five prep. TLC plates (20 X 20 cm). Chromatography ($CHCl_3$-MeOH, 9:1, Rf = 0.45) and crystallisation from ethyl acetate /petrolether gave needles (130 mg, 55%). M.p. 157-159 °C (lit.[9a] 159 °C). MS: m/z (%) = 156 (M^+, 48), 141 (85), 127 (17), 112 (11).

1-Trideuteromethoxymethyluracil (2b). Analogously to **2a,** in deuterated methanol. M.p. 158-160 °C. MS: m/z (%) = 159 (M^+, 46), 141 (81), 127 (15), 112 (10). Anal. calcd. for $C_6H_5D_3N_2O_3$ (159.17): C 45.28 H,D 6.96; N 17.60. Found: C 45.20; H,D 7.00; N 15.51.

1-Methoxymethylthymine (2c). Analogously to **2a,** from **1b**[6]. (58 %). M.p. 140-142°C (lit[10c]. 143-143°C). MS: m/z (%) = 170 (M^+, 32), 155 (61), 139 (20), 127 (11).

1-Trideuteromethoxymethylthymine (2d) Analogously to **2a,** in deuterated methanol. M.p. 141-143°C. MS: m/z (%) = 173 (M^+, 34), 155 (64), 139 (23), 127 (15). Anal. calcd. for $C_7H_7D_3N_2O_3$ (173.20): C 48.54; H,D 7.57; N 16.17. Found: C 48.59; H,D 7.63; N 16.09.

1-Ethoxymethyluracil (2e). Analogously to **2a,** from **1a**[5], in ethanol. (35%). M.p. 125°C. (lit[10b] 125-126°C)

1-Ethoxymethylthymine (2f). Analogously to **2a,** from **1b**[6], in ethanol. (28%). M.p. 108-109°C (lit.[10b] 108-109°C).

1-Acetoxymethyluracyl (3a). A solution of **1a**[5] (255 mg, 1,5 mmol) and sodium acetate (1,5 g) in acetic acid (30 ml) was electrolysed for 3 hours at a constant current density (0.033 A/cm^2). The resulting pale yellow mixture was evaporated to dryness, and the residue dissolved in water (30 ml). This was extracted with ethyl acetate (4 X 30 ml), the extracts were concentrated and applied onto 5 prep. TLC plates (20 X 20 cm). Chromatography ($CHCl_3$-MeOH, 9:1, Rf = 0.55) and crystallisation from ethyl acetate/petrolether gave needles (125 mg, 45%): M.p. 177-179 °C. UV (MeOH): 256 (9300). MS: m/z (%) =184 (M^+, 24), 154 (32), 141 (36), 126 (36), 112 (35). Anal. calcd. for $C_7H_8N_2O_4$ (184.15): C 45.66; H 4.38; N 15.21. Found: C 45.57; H 4.33; N 15.30.

1-Acetoxymethylthymine(3b). Analogously to **3a,** from **1b**[6]. Rf = 0.60, M.p. 133-135° C, (52%). UV (MeOH): 262 (9500), MS: m/z (%) = 198 ($M.^+$, 29), 168 (32), 155 (9), 139 (19), 126 (100).

Anal calcd. for $C_8H_{10}N_2O_4$ (198.18): C 48.49; H 5.09; N 14.14. Found: C 48.42; H 5.01; N 14.11.

1-Trideuteroacetoxymethylthymine (3c). Analogously to **3a,** from **1b**[6], in deuterated acetic acid and deuterated sodium acetate. Rf = 0.60. M.p. 135-137 °C. UV (MeOH): 262 (9500), MS: m/z (%) = 201 (M^+, 51), 171 (45), 155 (10), 139 (30), 127 (95). Anal. calcd. for $C_8H_7D_3N_2O_4$ (201.21): C 47.76; H,D 6.51; N 13.92. Found: C 47.83; H,D 6.66; N 13.82.

Uracil (4a). The suspension of **3a** (92 mg, 0.5 mmol) in 0.5 M HCl (10 ml) was refluxed for 1 hr. The mixture became clear after 15 min. From the cooled solution crystallised uracil (45 mg, 80%) chromatographically and spectrally identical with authentic sample.

Thymine (4b) . Analogously to **4a,** from **3b**. (75 %)

5-Methoxymethyluracil (6a). To the stirred suspension of **5**[12] (255 mg, 1.5 mmol) in MeOH (30 ml) DBU (245 mg, 1.6 mmol) was added. The clear solution formed after few minutes was electrolysed for 4 hours at a constant current density (0.017 A/cm^2). The resulting pale yellow solution was concentrated and applied onto five prep. TLC plates (20 X 20 cm). Chromatography ($CHCl_3$-MeOH, 9:1, Rf = 0.40) and crystallisation from ethanol-water gave needles (110 mg, 46 %). M.p. 201-203 °C. (lit.[14] 202-204 °C). MS: m/z (%) = 156 ($M.^+$, 16), 141 (100), 126 (66), 125 (18).

5-Trideuteromethoxymethyluracil (6b). Analogously to **6a**, from **5** in deuterated methanol.

M.p. 202-204 °C. MS: m/z (%) = 159 ($M.^+$, 15), 141 (100), 127 (47), 125 (15).

Anal, calcd. for $C_6H_5D_3N_2O_3$ (159.16): C 45.28; H,D 6.96; N 17.60. Found: C 45.22; H,D 7.06; N 17.51.

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