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Anodic Oxidation of Pyrones and Coumarins

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Triacetic lactone, 4-hydroxycoumarins and 2-chloromethyl-5-hydroxy-4-pyrone were subjected to anodic oxidation in methanol containing $LiClO_4$ or NaCN to afford the corresponding methoxy or cyano compounds. In basic media, however, bispyrone and biscoumarol were produced from triacetic lactone (4-hydroxy-6-methyl-2-pyrone) and 4-hydroxycoumarin, respectively. The formation processes of these oxidation products are discussed.

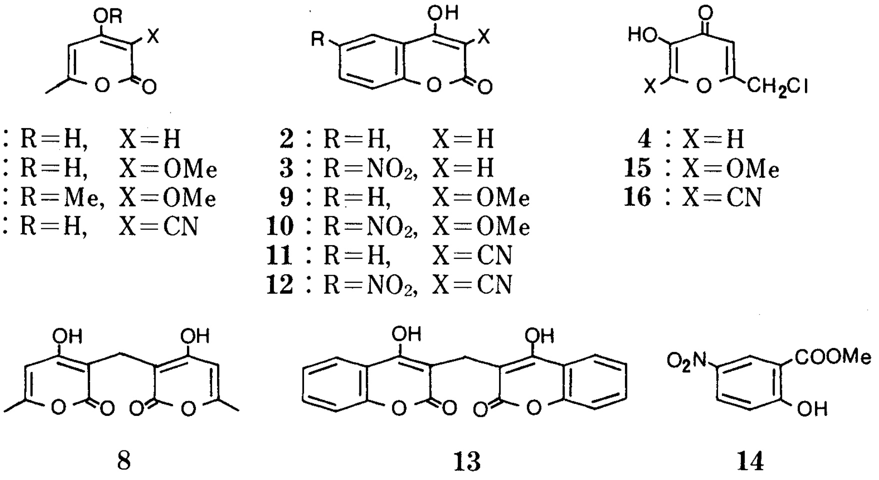
Keywords——pyrone; coumarin; electrochemical oxidation; methoxylation; cyanation

A number of metabolites produced by molds and fungi are derived biosynthetically *via* the acetate–malonate pathway. Among them, pyrones, which can be regarded as masked β-polyketo-carboxylic acids, are quite interesting from the viewpoint of their chemical reactivity[1)] as well as their biological activity.[2)] In the cases of triacetic lactone and 4-hydroxycoumarins, electrophilic substitution reactions usually take place quite easily at the C_3-position, while nucleophilic attack at the same position has not been reported. In these cases, anodic oxidation can be regarded as an "Umpolung" reaction in a sense, as demonstrated below. Thus, we wish to describe the anodic oxidation of triacetic lactone (**1**), 4-hydroxycoumarins (**2** and **3**) and 2-chloromethyl-5-hydroxy-4-pyrone (**4**) leading to the formation of the corresponding methoxy or cyano compounds. It would be quite difficult to synthesize some of these compounds without using electrochemical methods.

Results and Discussion

As can be seen in Fig. 1, the cyclic voltammograms of triacetic lactone (**1**) in neutral as well as basic media show single anodic peaks, having the same current. Therefore, the same electrode processes were expected to occur under both conditions. Electrolysis of **1**, at a controlled potential or current, ceased at 2.0 F/mol in neutral or basic medium, affording only the $-2e$ product.

A solution of triacetic lactone (**1**) in methanol containing $LiClO_4$ as a supporting electrolyte was electrolyzed at a controlled current ($0.31\,mA/cm^2$) and the reaction was quenched at 2.0 F/mol to afford 2-methoxytriacetic lactone (**5**) in 71% yield; this product was further treated with methanol containing conc. HCl to give the corresponding methyl ether (**6**) in 83% yield. When electrolyzed at a controlled current ($0.71\,mA/cm^2$; 2.9 F/mol) in methanol containing NaCN, triacetic lactone (**1**) was readily converted into the corresponding 3-cyano compound (**7**) in almost quantitative yield,[3)] as judged by analytical high performance liquid chromatography (HPLC). Under these conditions, 3-methoxytriacetic lactone (**5**) was not detected. probably, the CN anion is a better nucleophile than MeO^-. Meanwhile, triacetic lactone (**1**) was subjected to anodic oxidation in methanol containing NaOH ($0.17\,N$) at a controlled potential ($+800\,mV$ *vs.* SCE; 2.7 F/mol) to afford bispyrone (**8**) in 93% yield.



1 : R=H, X=H
5 : R=H, X=OMe
6 : R=Me, X=OMe
7 : R=H, X=CN

2 : R=H, X=H
3 : R=NO_2, X=H
9 : R=H, X=OMe
10 : R=NO_2, X=OMe
11 : R=H, X=CN
12 : R=NO_2, X=CN

4 : X=H
15 : X=OMe
16 : X=CN

8 **13** **14**

Chart 1

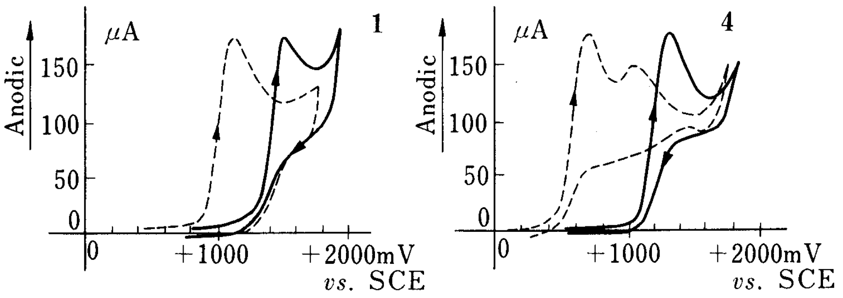


Fig. 1. Cyclic Voltammograms of **1** and **4**

1 (2.8 mmol·l^{-1}), **4** (2.5 mmol·l^{-1}); supporter $LiClO_4$, 0.2 mol·l^{-1}; solvent, MeOH; WE, glassy carbon (0.16 cm^2); sweep rate, 100 mV·s^{-1}; media, —— neutral, ------ basic (NaOMe: 3.0 mmol·l^{-1}).

Clearly, the MeO anion is readily oxidized to formaldehyde, which is considered to react simultaneously with two molecules of triacetic lactone to give **8**. On anodic oxidation (+1000 mV *vs.* SCE) of **1** in methanol including a slight excess of NaOH, as expected, both 3-methoxytriacetic lactone (**5**) and bispyrone (**8**) were detected by analytical HPLC.

The structures of these oxidation products (**5** and **7**) were unambiguously determined on the basis of their proton nuclear magnetic resonance (^1H NMR) and high resolution mass spectra (MS). Interestingly, the ν_{co} value [infrared (IR) (KBr): 1765 cm^{-1}] in **5** in unusually high as compared with those of **1** and **7** [IR (KBr): 1720 cm^{-1} in **1**; 1690 br cm^{-1} in **7**]. Presumably, the newly introduced MeO group interrupts the resonance effect between the OH group and the lactone carbonyl group. Similar phenomena are also seen in the cases of 4-hydroxy-3-methoxycoumarins, as described later.

The formation process of these two oxidation products (**5** and **7**) is shown in Chart 2. On electrolysis using excess NaCN, the highly reactive nucleophile of the CN anion selectively attacks the cationic center at the C_3-position.

On electrolysis at a controlled current[4)] (0.35 mA/cm^2 in **2**; 0.31 mA/cm^2 in **3**) in methanol containing $LiClO_4$ as a supporting electrolyte, the two coumarins (**2** and **3**) were also converted into the corresponding 3-methoxycoumarins (**9** and **10**) in 70 and 67% yields, respectively. On anodic oxidation using excess NaCN, the 3-cyanocoumarins (**11** and **12**) were synthesized in 51 and 50% yields, respectively. The formation process of these C_3-substituted coumarins (**9**—**12**) is considered to be essentially the same as that of the C_3-substituted pyrones (**5** and **7**).

As seen in the anodic oxidation of triacetic lactone (**1**) in basic media, 4-hydroxy-

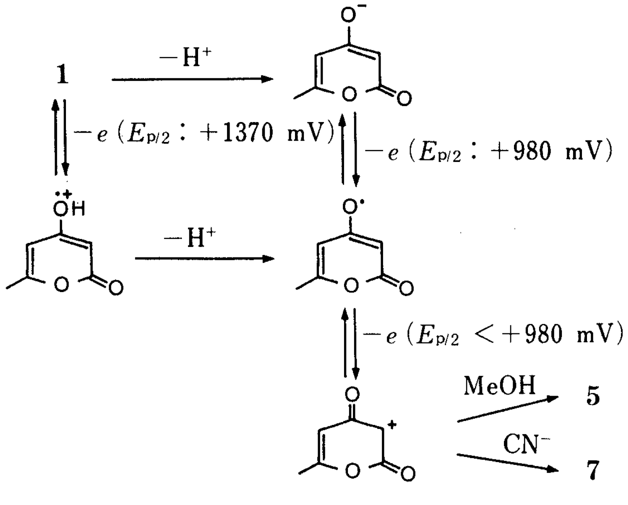


Chart 2. Anodic Oxidation of Triacetic Lactone (**1**)

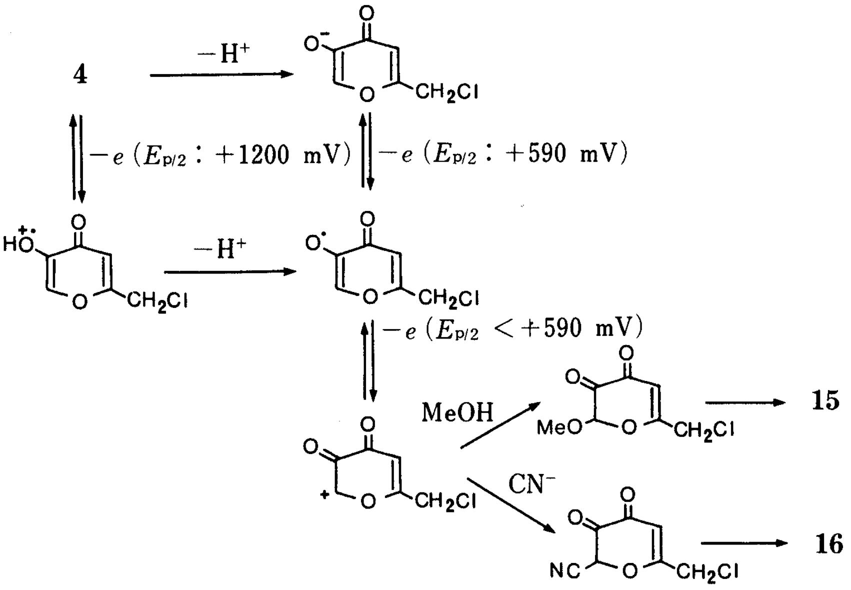


Chart 3. Anodic Oxidation of 2-Chloromethyl-5-hydroxy-4-pyrone (**4**)

coumarin (**2**) was electrolyzed at a controlled potential (+1300 mV *vs.* SCE; 2.0 F/mol) in methanol containing NaOMe (0.025 N) to afford both 4-hydroxy-3-methoxycoumarin (**9**) and biscoumarol (**13**) in 31 and 54% yields, respectively. In the case of a large excess of NaOMe, only the latter was detected by analytical HPLC. The nitro compound (**3**), in methanol containing $NaHCO_3$, was readily converted into methyl 2-hydroxy-5-nitrobenzoate (**14**) in 67% yield.

Finally, 2-chloromethyl-5-hydroxy-4-pyrone (**4**) was subjected to anodic oxidation at a controlled current (0.21 mA/cm^2) in methanol containing $LiClO_4$ as a supporting electrolyte, and the reaction was quenched at 2.0 F/mol to afford the corresponding methoxy-4-pyrone (**15**) in 54% yield. This product may be converted into the corresponding 2-pyrone by removing the hydroxyl group at the C_5- position[5] followed by demethylation. Furthermore, cyanation of **4** was also carried out at a controlled current (0.31 mA/cm^2; 2.0 F/mol) using excess NaCN to afford a cyano compound (**16**) in low yield.[6] These two pyrones (**15** and **16**) seem to be synthetically useful because of the possibility of further modification of the chloromethyl group at the C_2-position. The formation process of these two oxidation products (**15** and **16**) is presented in Chart 3.

Experimental

All the melting points were measured on Shimadzu or a Mitamura Riken melting point apparatus and are uncorrected. IR spectra were recorded on a Hitachi 215 or Shimadzu IR-400 spectrophotometer. Ultraviolet (UV) spectra were taken on a Hitachi 214 spectrophotometer. ^{1}H NMR spectra were taken on a JEOL JNM-PS 100 (100 MHz) spectrometer. Chemical shifts are given in ppm from tetramethylsilane (TMS) as an internal standard. Coupling constants are given in Hz (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet). MS were obtained on a Hitachi M-52 mass spectrometer operating with an ionization energy of 70 eV. High resolution MS were also taken on a Hitachi M-80 mass spectrometer operating with an ionization energy of 70 eV.

Preparative HPLC was carried out on a glass column [HP-255 (22 mm$\phi \times$ 300 mm)] using an APUS-24 pump (Gasukuro Kogyo Inc.) and both RI model R-403 (Waters Associates Inc.) and UV model 502 (Gasukuro Kogyo Inc.) detectors, unless otherwise stated. Analytical HPLC was also carried out on a column [HP-125 (4 mm$\phi \times$ 300 mm)] using MeOH (flow rate: 0.5 ml/min), unless otherwise stated.

Instruments Used for Electrode Reactions——A PARCO model 173 instrument (Princeton Applied Research Co., Ltd.) was used as a potentio/galvanostat. A PARCO model 175 universal programmer was also used as a function generator. Cyclic voltammograms with rapid sweep rate were observed on a digital storage oscilloscope, model DS-334 (NF Circuit Design Block Co., Ltd.) and recorded on a Technicorder type 3077 (Yokogawa Electric Works Ltd.). On anodic oxidation, a 200 ml glassy carbon beaker (Tokai Carbon GC-20) and a platinum electrode (1.0 mm$\phi \times$ 10 mm) were used as an anode and an auxiliary electrode, respectively, without separation. The quantity of electricity was measured using a PARCO model 179 digital coulometer and/or a detonating gas coulometer.

Anodic Oxidation of Triacetic Lactone (1) in Methanol——A solution of **1** (253 mg) in MeOH (200 ml) containing $LiClO_4$ (4.3 g) was electrolyzed at a controlled current (50 mA; 0.31 mA/cm^2) and the reaction was quenched at 2.0 F/mol. The reaction solution was concentrated under reduced pressure below 40 °C, and then extracted with AcOEt. The AcOEt extract was dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and subjected to preparative HPLC (column: 15 mm$\phi \times$ 300 mm, HP-255) using MeOH–H_2O (55 : 45). Fractions 9—18 (10.0 ml/F) were successively combined, concentrated under reduced pressure, extracted with AcOEt, dried over anhydrous Na_2SO_4, and then filtered. The filtrate was concentrated under reduced pressure to leave **5** as a crystalline solid (200 mg). Fractions 19—28 were combined and concentrated under reduced pressure to give the starting material (25 mg).

5: mp 65—66 °C (from hexane–benzene). IR (KBr): 3120 br, 1765, 1685, 1585 cm^{-1}. ^{1}H NMR (acetone-d_6) δ: 2.27 (3H, s), 3.73 (3H, s), 5.46 (1H, s). *Anal.* Calcd for $C_7H_8O_4$: *m/e* 156.0422. Found: *m/e* 156.0402.

Formation of the Methyl Ether (6) from 3-Methoxytriacetic Lactone (5)——A solution of **5** (50 mg) in MeOH (20 ml) containing one drop of conc. HCl was stirred at room temperature for 17 h, and then quenched with H_2O (200 ml). The aqueous solution was neutrallized with $NaHCO_3$ and then extracted with ether. The ethereal solution was dired over anhydrous Na_2SO_4 and then filtered. The filtrate was concentrated under reduced pressure to give **6** as a colorless oil (45 mg): IR (film): 1765, 1705, 1600 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.35 (3H, s), 3.47 (3H, s), 3.81 (3H, s), 5.49 (1H, s). MS *m/e*: 170 (M^+ for $C_8H_{10}O_4$).

Anodic Oxidation of Triacetic Lactone (1) in the Presence of NaCN——A solution of **1** (378 mg) in MeOH (150 ml) containing NaCN (600 mg) was electrolyzed at a controlled current (100 mA; 0.71 mA/cm^2; +720—960 mV *vs.* SCE) and the reaction was quenched at 2.9 F/mol. The reaction solution was neutralized with 10% HCl, concentrated under reduced pressure below 40 °C, and then subjected to preparative HPLC using MeOH–H_2O (55 : 45). The desired fractions were combined and concentrated under reduced pressure, then purified by preparative thin-layer chromatography (TLC) (Kieselgel PF_{254}) using acetone to afford **7** as an amorphous powder (136 mg): IR (KBr): 3420 br, 2205, 1690 br, 1640, 1570 cm^{-1}. ^{1}H NMR (acetone-d_6) δ: 2.02 (3H, s), 5.58 (1H, s). *Anal.* Calcd for $C_7H_5NO_3$: *m/e* 151.0269. Found: *m/e* 151.0303.

Anodic Oxidation of Triacetic Lactone (1) in Basic Media——A solution of **1** (378 mg) in MeOH (145 ml) containing 5 N NaOH (5 ml) and $LiClO_4$ (2.1 g) was electrolyzed at a controlled potential (+800 mV *vs.* SCE; 150—70 mA) and the electrolysis was quenched at 2.7 F/mol. The reaction solution was successively neutralized with 10% HCl, concentrated under reduced pressure, and then extracted with AcOEt. The AcOEt extract was dried over anhydrous Na_2SO_4 and then filtered. The filtrate was concentrated under reduced pressure to afford a known bispyrone (**8**) (370 mg).

Anodic Oxidation of 4-Hydroxycoumarin (2) in Methanol——A solution of **2** (486 mg) in MeOH (150 ml) containing $LiClO_4$ (3.2 g) was electrolyzed at a controlled current (50 mA; 0.35 mA/cm^2; +1680—1880 mV *vs.* SCE), and the reaction was quenched at 2.0 F/mol. The reaction solution was concentrated under reduced pressure, and directly subjected to preparative HPLC using MeOH–H_2O (50 : 50). After elution of the salt, fractions 78—84 were combined and concentrated under reduced pressure, then extracted with AcOEt to afford **9** (282 mg). According to the same procedure as described above, the following fractions were also purified to afford the starting material (144 mg).

9: mp 106—107 °C (from MeOH). IR (KBr): 3330 br, 1755, 1720, 1610 cm^{-1}. ^{1}H NMR (CD_3OD) δ: 3.72

(3H, s), 7.06—7.28 (2H, complex), 7.60—7.82 (2H, complex). *Anal.* Calcd for $C_{10}H_8O_4$: *m/e* 192.0442. Found: *m/e* 192.0447.

Anodic Oxidation of 4-Hydroxy-6-nitrocoumarin (3) in Methanol——A solution of **3** (414 mg) in MeOH (200 ml) containing $LiClO_4$ (4.3 g) was electrolyzed at a controlled current (50 mA; 0.31 mA/cm^2; +1400—1900 mV *vs.* SCE) and the reaction was quenched at 4.0 F/mol. The reaction solution was concentrated under reduced pressure and directly separated by preparative HPLC using MeOH–H_2O (70—30). After elution of the salt, the following fractions were combined, concentrated under reduced pressure, and then purified by preparative TLC (Kieselgel PF_{254}; AcOEt) to afford **10** (316 mg): mp 167—170 °C (from MeOH). IR (KBr): 3300 br, 1770, 1725, 1615, 1600, 1535 cm^{-1}. ^{1}H NMR (CD_3OD) δ: 3.76 (3H, s), 7.35 (1H, d, $J=8$ Hz), 8.44—8.72 (2H, complex). *Anal.* Calcd for $C_{10}H_7NO_6$: *m/e* 237.0272. Found: *m/e* 237.0250.

Anodic Oxidation of 4-Hydroxycoumarin (2) in the Presence of NaCN——A solution of **2** (324 mg) in MeOH (200 ml) containing NaCN (392 mg) was electrolyzed at a controlled current (30 mA; 0.19 mA/cm^2; +1000—1450 mV *vs.* SCE) and the reaction was quenched at 3.0 F/mol. The reaction solution was neutralized with 10% HCl, and then concentrated under reduced pressure and directly subjected to preparative HPLC using MeOH–H_2O (40 : 60). After removal of the salt, further elution afforded **11** as a crystalline powder (190 mg): mp 300 °C (dec.) (from MeOH). IR (KBr): 3430 br, 2240, 1660, 1605, 1560 cm^{-1}. ^{1}H NMR (CD_3OD) δ: 7.16 (1H, br d, $J=8$ Hz), 7.20 (1H, td, $J=8$, 1.5 Hz), 7.50 (1H, td, $J=8$, 2 Hz), 7.88 (1H, dd, $J=8$, 1.5 Hz). *Anal.* Calcd for $C_{10}H_5NO_3$: *m/e* 187.0269. Found: *m/e* 187.0290.

Anodic Oxidation of 4-Hydroxy-6-nitrocoumarin (3) in the Presence of NaCN——A solution of **3** (414 mg) in MeOH (200 ml) containing NaCN (392 mg) was electrolyzed at a controlled potential (+1000 mV *vs.* SCE; 50—21 mA) and the reaction was quenched at 4.0 F/mol. The reaction solution was neutralized with 10% HCl and concentrated under reduced pressure, then separated by preparative HPLC using MeOH–H_2O (40 : 60). After elution of the salt, further elution afforded **12** as a white powder (232 mg): mp 300 °C (dec.) (from MeOH). IR (KBr): 3430 br, 2240, 1660, 1605, 1530 cm^{-1}. ^{1}H NMR (CD_3OD) δ: 7.37 (1H, d, $J=8$ Hz), 8.33 (1H, dd, $J=8$, 2.5 Hz), 8.73 (1H, d, $J=2.5$ Hz). *Anal.* Calcd for $C_{10}H_4N_2O_5$: *m/e* 232.0120. Found: *m/e* 232.0145.

Anodic Oxidation of 4-Hydroxycoumarin (2) in Basic Media——A solution of **2** (364 mg) in MeOH (200 ml) containing 1 N NaOMe (5.0 ml) and $LiClO_4$ (4.3 g) was electrolyzed at a controlled potential (+1300 mV *vs.* SCE; 150—90 mA) and the reaction was quenched at 2.0 F/mol. After acidification (*ca.* pH 4) with 10% HCl, the reaction solution was concentrated under reduced pressure, and then poured into MeOH–H_2O (60 : 40). The precipitate, which consisted of a known biscoumarol (**13**) (107 mg), was collected on a glass filter G-4. The filtrate was separated by preparative HPLC [column: 20 mmϕ × 500 mm, Develosil ODS-10; MeOH–H_2O (60 : 40)]. After removal of the salt, fractions 10—17 were combined and concentrated under reduced pressure to give **9** (80 mg). From fractions 27—36, the starting material (119 mg) was obtained. Fractions 63—71 were also combined and concentrated under reduced pressure to leave a known biscoumarol (**13**) (15 mg).

Anodic Oxidation of 4-Hydroxy-6-nitrocoumarin (3) in the Presence of $NaHCO_3$——A solution of **3** (414 mg) in MeOH (200 ml) containing $NaHCO_3$ (2.0 g) and $LiClO_4$ (4.3 g) was electrolyzed at a controlled potential (+1200 mV *vs.* SCE) and the reaction was quenched at 2.0 F/mol.[7] The reaction solution was concentrated under reduced pressure and directly subjected to preparative HPLC [column: 22 mmϕ × 300 mm, LiChroprep RP-18; MeOH–H_2O (50 : 50)]. After removal of the salt, further elution afforded methyl 2-hydroxy-5-nitrobenzoate (**14**) (265 mg).

Anodic Oxidation of 2-Chloromethyl-5-hydroxy-4-pyrone (4)[4] in Methanol——A solution of **4** (161 mg) in MeOH (150 ml) containing $LiClO_4$ (3.2 g) was electrolyzed at a controlled current (30 mA; 0.21 mA/cm^2; +1350—1700 mV *vs.* SCE) and the reaction was quenched at 2.0 F/mol. The reaction solution was concentrated under reduced pressure, and then separated by preparative HPLC using MeOH–H_2O (50 : 50). After elution of the salt, further elution afforded only **15** (103 mg); mp 106—110 °C (from MeOH). IR (KBr): 3205 br, 1660, 1625, 1550 cm^{-1}. ^{1}H NMR (CD_3OD) δ: 4.14 (3H, s), 4.57 (2H, s), 6.50 (1H, s). MS *m/e* 192 and 190 (M^+ for $C_7H_7ClO_4$).

Anodic Oxidation of 2-Chloromethyl-5-hydroxy-4-pyrone (4) in the Presence of NaCN——A solution of **4** (321 mg) in MeOH (200 ml) containing NaCN (600 mg) and $NaClO_4$ (1.2 g) was electrolyzed at a controlled current (20 mA; 0.13 mA/cm^2; +500—750 mV *vs.* SCE) and the reaction was quenched at 2.0 F/mol. After neutralization with 10% HCl, the reaction solution was concentrated under reduced pressure and directly separated by preparative HPLC using MeOH–H_2O (50 : 50). After elution of the salts, further elution with the same solvent system afforded **16** (30 mg); mp 107—108 °C (from MeOH). IR (KBr): 3200 br, 3080, 2250, 1640 cm^{-1}. ^{1}H NMR (CD_3OD) δ: 4.52 (2H, s), 6.63 (1H, s). MS *m/e*: 187 and 185 (M^+); *Anal.* Calcd for $C_7H_4{}^{35}ClNO_3$: *m/e* 184.9878. Found: *m/e* 184.9860.

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References and Notes

1) T. Money, *Chem. Rev.*, **70**, 553 (1970); T. M. Harris and C. M. Harris, *Tetrahedron*, **33**, 2159 (1977) and many

references cited therein.

2) T. Goto and S. Yamamura, "Pyran Compounds," in Methodicum Chimicum, Vol. 11, Part 3, ed. by F. Korte and M. Goto, Academic Press, New York, 1978, p. 134.

3) Analytical HPLC showed only one peak corresponding to **7**, although this cyano compound could not be isolated in high yield. In fact, **7** is readily soluble in H_2O.

4) During the electrolysis, the potential of the working electrode was monitored by means of a Corning model 125 potentiometer.

5) K. Hashizume, S. Yamamura, and S. Inoue, *Chem. Pharm. Bull.*, **16**, 2292 (1968).

6) Analytical HPLC using 0.5% AcOH in MeOH–H_2O (70 : 30) showed only one peak corresponding to **16**, although this cyano compound could not be isolated in high yield, because of its instability.

7) Analytical HPLC indicated the presence of a trace amount of 4-hydroxy-3-methoxy-6-nitrocoumarin (**10**), although it could not be isolated.