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# ANODIC OXIDATION OF PYRONES AND RELATED COMPOUNDS

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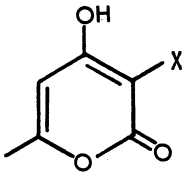
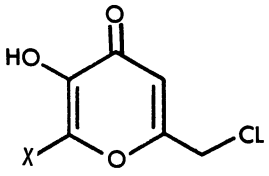
Triacetic lactone, 4-hydroxycoumarins, and kojic acid derivative were subjected to anodic oxidation in MeOH containing $LiClO_4$ or NaCN to afford the corresponding methoxy or cyano compounds. In a basic media, however, dipyrone and dicoumarol were produced from triacetic lactone and 4-hydroxycoumarin, respectively. The formation process of 3-methoxytriacetic lactone as well as of 3-cyanotriacetic lactone is also presented.

Generally, many metabolites produced by mould and fungi are derived biosynthetically *via* the acetate-malonate pathway. Among them, pyrones, which are regarded as masked $\beta$-polyketo carboxylic acids, are quite interesting from view points of their chemical reactivity[1] as well as of their biological activity.[2] We here describe anodic oxidation of triacetic lactone (1), 2-chloromethyl-5-hydroxy-4-pyrone (2), and coumarins (3 and 4) leading to the formation of the corresponding methoxy or cyano compounds. It seems quite difficult to synthesize some of these pyrones without using electrochemical methods.

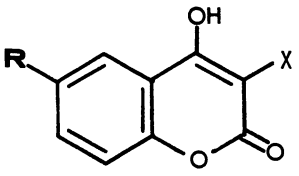
A 200 ml glassy carbon (GC-20) beaker and a GC disk (0.2 $cm^2$) were used as an anode and an auxiliary electrode, respectively, without separation. A solution of triacetic lactone (1) (2.64 mmol) in MeOH (150 ml) containing $LiClO_4$ (52.5 mmol) was electrolyzed at a controlled potential (+1400 mV *vs.* SCE) and quenched at 2 F/mole. The reaction solution was concentrated under reduced pressure below 40 °C, and then was subjected to coloumn chromatography [polymer HP-255; MeOH - $H_2O$ (55 : 45)] to afford the corresponding methoxy compound (5) [mp 65-66 °C; $C_7H_8O_4$ (m/e 156($M^+$)); $\nu_{max}$(KBr)[3] 3120br., 1765, 1685, and 1585 $cm^{-1}$; $\delta(CD_3COCD_3)$ 2.27(3H, s), 3.73(3H, s), and 5.46(1H, s)] in 52% yield,[4] which was readily converted into the corresponding methyl ether (6)[5] on treatment with MeOH containing a small quantity of HCl (room temp., 17 h). We further carried out anodic oxidation of 1 using NaCN instead of $LiClO_4$ as the supporting salt.



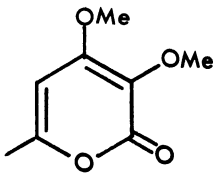
1 X = H
5 X = OMe
7 X = CN



2 X = H
15 X = OMe
16 X = CN



3 R = H, X = H
4 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



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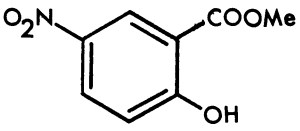

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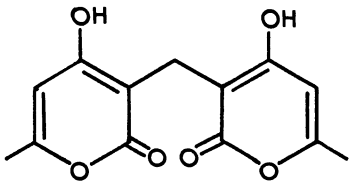

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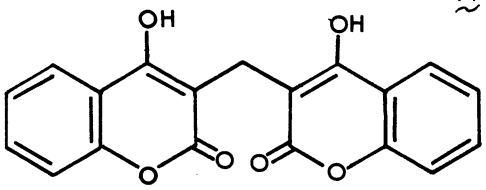

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A solution of 1 (3.0 mmol) in MeOH (150 ml) containing NaCN (12.3 mmol) was electrolyzed at a controlled current density (0.71 mA/cm$^2$) at room temperature to afford 3-cyanotriacetic lactone (7) [mp (dec.) 210 °C; $C_7H_5NO_3$ (m/e 151($M^+$)); $\nu_{max}$(KBr) 3420br., 2205, 1690br., 1640, and 1570 cm$^{-1}$; $\delta(CD_3COCD_3)$ 2.02(3H, s) and 5.58(1H, s)] in almost quantitative yield.[4] Under these conditions, any amount of 5 was not detected. Meanwhile, triacetic lactone (1) was subjected to electrochemical oxidation in MeOH (150 ml) containing NaOH (25.5 mmol) at a controlled potential of +800 mV vs. SCE to give dipyrone (8) in 93% yield. In this case, the MeO anion is readily oxidized to formaldehyde, which is considered to react simultaneously with triacetic lactone to afford 8.

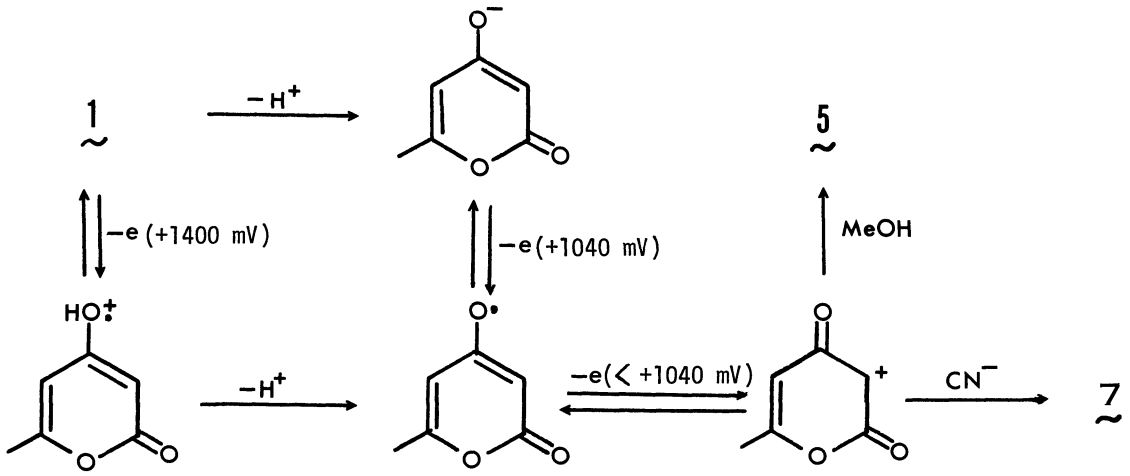
On electrolysis at a controlled current density (0.35 mA/cm$^2$ in 3; 0.31 mA/cm$^2$ in 4) in MeOH containing $LiClO_4$, the two coumarins (3 and 4) were also converted into the corresponding 3-methoxy compounds (9 and 10)[3,6] in 70 and 62% yields, respectively. On anodic oxidation using NaCN instead of $LiClO_4$ as the supporting salt, the 3-cyanocoumarins (11 and 12)[7] were also obtained in 51 and 50% yields, respectively. Under the similar conditions as that of 1, 3 was electrolyzed in the basic media to afford dicoumarol (13) in high yield. However, the nitro compound (4) was readily converted into methyl 2-hydroxy-5-nitrobenzoate (14) in 61% yield.[8]

Finally, 2-chloromethyl-5-hydroxy-4-pyrone (2) (1.0 mmol) was subjected to anodic oxidation, which was carried out in MeOH (150 ml) containing $LiClO_4$ (30 mmol) at a controlled current density (0.21 mA/cm$^2$) to afford the corresponding methoxy compound (15) [mp ca. 110 °C; $C_7H_7O_4Cl$ (m/e 192 and 190($M^+$)); $\nu_{max}$(KBr) 3205br., 1660, 1625, and 1550 cm$^{-1}$; $\delta(CD_3OD)$ 4.14(3H, s), 4.57(2H, s), and

6.50(1H, s)] in 54% yield, which may be converted into the corresponding $\alpha$-pyrone by removing the OH group at $C_5$-position[9] followed by demethylation. Furthermore, cyanation of 2 was also carried out at a controlled current density (0.31 mA/cm$^2$) to afford the corresponding cyano compound (16) [mp 107-108 °C; $C_7H_4NO_3Cl$ (m/e 187 and 185($M^+$)); $\nu_{max}$(KBr) 3080, 3000br., 2250, and 1640 cm$^{-1}$; $\delta(CD_3OD)$·4.52(2H, s) and 6.63(1H, s)] in low yield. These two pyrones (15 and 16) seem to be synthetically useful because of further modification of the chloromethyl group as the side chain.

As a typical example, the formation process of 5 and 7 is shown in Scheme 1 on the basis of the voltammetric and coulometric studies on triacetic lactone (1).[10] In this case, the highly reactive nucleophile of the CN anion attacks selectively the cationic center at $C_3$-position.

Scheme 1. Anodic oxidation of triacetic lactone (1)




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. 11-3 (F. Korte and M. Goto Ed.), p. 134, Academic Press, New York (1978).

3. The $\nu_{CO}$ value (1765 cm$^{-1}$) in 5 is unusually high as compared with that in 1 [$\nu_{max}$(KBr) 1720 cm$^{-1}$]. Presumably, the newly introduced MeO group interrupts the resonance effect of the OH group on the CO group. The similar phenomena are also seen in the cases of 9 and 10.

4. Only one peak corresponding to this compound was detected by HPLC of the electrolysis mixture [HP 125 ($\phi$4 mm x 300 mm) / MeOH; flow rate: 0.5 ml/min].

5. 6: $C_8H_{10}O_4$ (m/e 170($M^+$)); $\nu_{max}$(film) 1765, 1705, and 1600 cm$^{-1}$; $\delta(CDCl_3)$ 2.35(3H, s), 3.47(3H, s), 3.81(3H, s), and 5.49(1H, s).

6. 9: mp 106-107 °C; $C_{10}H_8O_4$ (m/e 192($M^+$)); $\nu_{max}$(KBr) 3330br., 1755, 1720, and 1610 cm$^{-1}$; $\delta(CD_3OD)$

3.72(3H, s), 7.06-7.28(2H, complex), and 7.60-7.82(2H, complex). 10: mp 167-170 °C; $C_{10}H_7NO_6$ (m/e 237($M^+$)); $\nu_{max}$(KBr) 3300br., 1770, 1725, 1615, 1600, and 1535 $cm^{-1}$; $\delta(CD_3OD)$ 3.76(3H, s), 7.35(1H, d, J= 8Hz), and 8.44-8.72(2H, complex).

7. 11: mp (dec.) 300 °C; $C_{10}H_5NO_3$ (m/e 187($M^+$)); $\nu_{max}$(KBr) 3430br., 2240, 1660, 1605, and 1560 $cm^{-1}$; $\delta(CD_3OD)$ 7.16(1H, br.d, J= 8Hz), 7.20(1H, td, J= 8, 1.5Hz), 7.50(1H, td, J= 8, 2Hz), and 7.88(1H, dd, J= 8, 1.5Hz). 12: mp (dec.)>300 °C; $C_{10}H_4N_2O_5$ (m/e 232($M^+$)); $\nu_{max}$(KBr) 2240, 1660, 1605, 1560, and 1530 $cm^{-1}$; $\delta(CD_3OD)$ 7.37(1H, d, J= 8Hz), 8.33(1H, dd, J= 8, 2.5Hz), and 8.73(1H, d, J= 2.5Hz).
8. In this case, a solution of 4 (1.5 mmol) in MeOH (150 ml) containing sat. $NaHCO_3$ and $LiClO_4$ (1.5 mmol) was electrolyzed at a controlled potential of +1200 mV vs. SCE.
9. K. Hashizume, S. Yamamura, and S. Inoue, Chem. Pharm. Bull. Jpn., 16, 2292 (1968).
10. These studies have been made according to the same method as previously reported [M. Iguchi, A. Nishiyama, Y. Terada, and S. Yamamura, Analytical Letters, 12(A10), 1079 (1979)].

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