Electrochemical Synthesis of Heterocyclic Compounds. XII (1). Anodic Oxidation of Catechol in the Presence of Nucleophiles

Ibro Tabaković*, Zdravko Grujić and Zlatko Bejtović

Faculty of Technology, "Djuro Pucar Stari" University,
78000 Banjaluka, Yugoslavia

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The electrochemical synthesis of coumestan derivatives and some related heterocyclic system (**2a-11a**) by anodic oxidation of catechol (**1**) in the presence of various nucleophiles **2-11** is described. Products were obtained in good yields and purity. The mechanism of oxidation was deduced from voltammetric data and by coulometry at controlled potential.

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We have shown (2) that the anodic oxidation of catechol, using controlled potential electrolysis in the presence of 4-hydroxycoumarin and dimedone provides a simple preparative route to the corresponding coumestans and benzofuran derivatives. In order to widen the scope of the reaction, some extensions of the basic procedure were thought valuable.

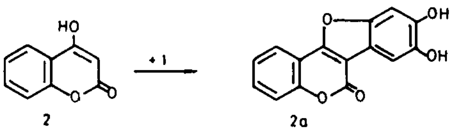
The compounds known as coumestans (3), 6*H*-benzofuro[3,2-*c*][1]benzopyran-6-one, have the basic structure of many natural products such as wedelolactone, medicagol, psoraldin, isopsoraldin, erosnin and the estrogenic coumestrol, show interesting physiological activities (4-6). Several methods for the synthesis of 6*H*-benzofuro[3,2-*c*][1]-benzopyran-6-ones have been reported (7-18). The present communication describes the electrochemical synthesis of these and some related heterocyclic systems.

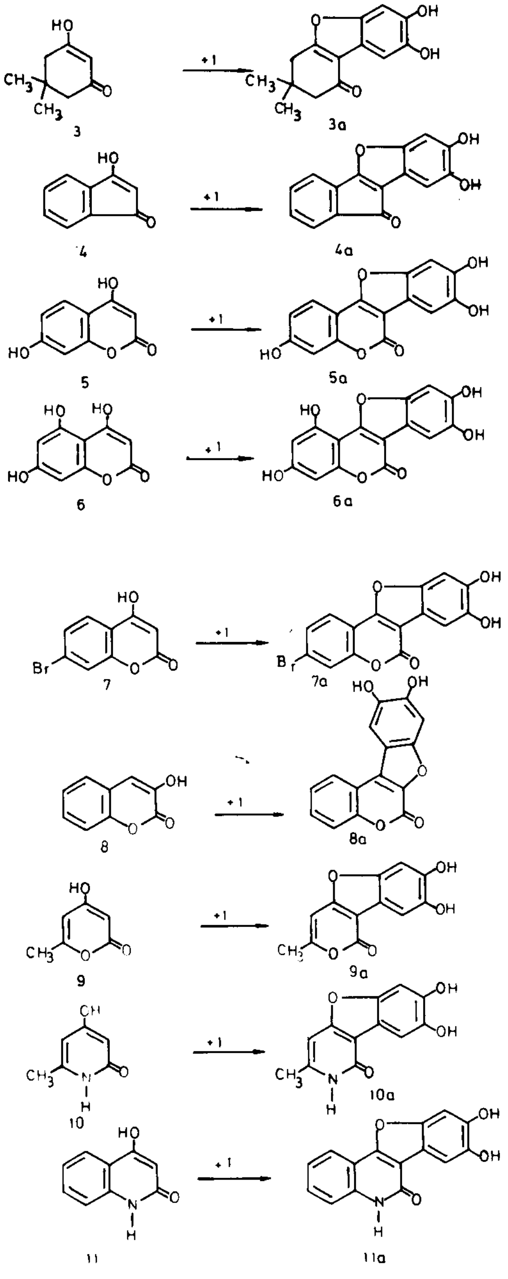
Results and Discussion.

Synthetic Aspects.

Anodic oxidation of catechol (**1**), using controlled potential electrolysis (E = 0.9-1.1V *vs.* SCE), was typically performed in water solution containing sodium acetate (0.15 *M*) in the presence of various nucleophiles such as: 4-hydroxycoumarin (**2**), dimedone (**3**), 1,3-indandione (**4**), 4,7-dihydroxycoumarin (**5**), 4,5,7-trihydroxycoumarin (**6**), 4-hydroxy-6-bromocoumarin (**7**), 3-hydroxycoumarin (**8**), 4-hydroxy-6-methyl-α-pyrone (**9**), 4-hydroxy-6-methyl-2-pyridone (**10**) and 4-hydroxycarbostyrile (**11**). All electrochemical syntheses were carried out in an undivided cell at a graphite anode and Pt-cathode giving rise to high yield of coumestan derivatives and related heterocyclic systems (**2a-11a**) according to the Scheme 1.

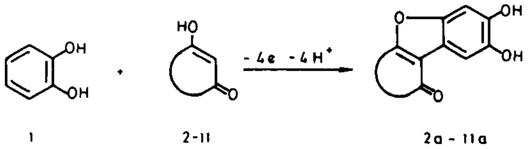
Scheme 1





Table

Electroanalytical and Preparative Data



Conversion	Cyclic (a) voltammatry results E_p (V *vs.* SCE)	Applied potential (V *vs.* SCE)	(b) n-value	Yield of product (%)	mp (solvent)	Molecular formula or lit mp	Elemental Analysis Calcd./Found %C	%H	%N
2 → **2a**	0.30 0.98	1.1	4.0	95	308-310° dec (ethanol-acetone)	310° dec (c) lit (2)			
3 → **3a**	0.44 0.95	1.1	4.1	90	280° dec (acetone)	280° dec (d) lit (2)			
4 → **4a**	0.50 0.75	0.9	4.2	96	145° (acetone)	$C_{15}H_8O_4$ (e) (252.11)	71.45 71.30	3.17 3.07	
5 → **5a**	0.45 0.86	1.0	3.9	92	>330° (acetone)	$C_{15}H_8O_6$ (f) (284.09)	63.41 63.18	2.81 2.80	
6 → **6a**	0.47 0.78	0.9	4.2	90	>330° (acetone)	$C_{15}H_8O_7$ (g) (300.08)	60.03 60.13	2.66 2.90	
7 → **7a**	0.40 0.97	1.1	3.9	95	>330° (acetone)	300° (h) lit (6)			
8 → **8a**	0.41 0.56	0.9	4.5	75	308° dec (methanol)	308° (i) lit (18)			
9 → **9a**	0.34 0.98	1.1	4.4	42	345° dec (methanol)	$C_{12}H_8O_5$ (j) (232.07)	62.10 62.50	3.44 3.12	
10 → **10a**	0.34 0.98	1.1	3.9	94	>330° (acetone)	$C_{12}H_9NO_4$ (k) (231.08)	62.36 62.40	3.89 3.91	6.05 5.99
11 → **11a**	0.47 0.95	1.1	3.8	89	>330 (acetic acid-water)	$C_{15}H_9NO_4$ (ℓ) 267.1)	67.44 67.58	3.36 3.12	5.24 5.15

(a) Pyrolytic graphite anode (2r = 0.6 cm); substrate concentration 10^{-3} molar; 0.15*M* aqueous sodium acetate; 0.4 V/s. (b) Determined by coulometry at controlled potential. (c) ir (potassium bromide): ν max = 3350, 1700, 1640, 1470, 1350, 1270, 1240, 1200, 1085 cm^{-1}; ms: m/e (relative intensity): 268 (100), 250 (15), 240 (4.0), 222 (6.3), 212 (25), 194 (4.3), 178 (3.9), 147 (25), 134 (7.9), 120 (6.1), 92 (2). (d) ir (potassium bromide): ν max = 3470, 2950, 1650, 1580, 1295, 1150, 1110, 1050 cm^{-1}; ms: m/e (relative intensity) 246 (5.7), 238 (17), 222 (4), 208 (2), 192 (3.7), 190 (5.2), 178 (100), 162 (5.7), 152 (8.1), 119 (7.0), 103 (6.7), 89 (8.5), 76 (11.3). (e) ir (potassium bromide): ν max = 3380, 2930, 1680, 1615, 1590, 1350, 1250, 835, 740 cm^{-1}; ms: m/e (relative intensity) 252 (7.1), 186 (100), 171 (52), 168 (11), 158 (21), 157 (22), 143 (17.7), 130 (14.5), 129 (27), 128 (17), 115 (52), 105 (51), 104 (20), 89 (11.4), 77 (21), 76 (28). (f) ir (potassium bromide): ν max = 3360, 1700, 1625, 1600, 1470, 1365, 1155, 1070, 1010, 850, 815, 770 cm^{-1}; ms: m/e (relative intensity) 284 (100), 236 (106), 231 (43.6), 210 (6.7), 202 (9.7), 196 (9), 190 (7), 186 (14.5), 181 (24), 162 (8.2), 142 (13.5), 136 (15), 135 (14), 121 (13), 115 (11), 107 (53), 106 (23), 105 (15.5), 104 (11), 92 (16.5), 77 (23), 76 (13). (g) ir (potassium bromide): ν max = 3330, 1710, 1620, 1500, 1270, 1150, 1020, 830, 750 cm^{-1}; ms: m/e (relative intensity) 300 (35.4), 272 (4), 241 (6.2), 224 (5), 196 (39), 182 (14), 181 (100), 166 (12.5), 162 (8), 132 (20), 121 (16.6), 119 (60), 91 (63), 85 (31), 79 (18.7), 77 (17), 73 (14.5), 71 (20). (h) ir (potassium bromide): ν max = 3410, 1700, 1610, 1400, 1370, 1120, 1100, 1050, 760 cm^{-1}. (i) ir (potassium bromide): ν max = 3350, 3300, 1705, 1610, 1570, 1460, 1335, 1290, 1260, 1110, 940, 850, 805, 750 cm^{-1}; ms: m/e (relative intensity) 268 (100), 241 (2), 240 (4), 212 (4.3), 199 (5), 184 (11.4), 149 (5.4), 139 (8.6), 120 (4), 92 (5). (j) ir (potassium bromide): ν max = 3480, 3300, 2930, 1700, 1640, 1610, 1600, 1570, 1460, 1305, 1230, 1120, 1050, 830 cm^{-1}; ms: m/e (relative intensity) 232 (100), 231 (5.6), 217 (17), 204 (8), 203 (16), 190 (3.4), 189 (6), 162 (11.3), 161 (4), 116 (6.8), 109 (5), 81 (6), 81 (6), 69 (7.9). (k) ir (potassium bromide): ν max = 3420, 3300, 2920, 1660, 1600, 1440, 1310, 1105, 970, 880 cm^{-1}; ms: m/e (relative intensity) 231 (100), 230 (18.8), 213 (3.5), 203 (6.7), 202 (13), 185 (14), 181 (16), 175 (4.8), 157 (6), 121 (3.1), 115 (12), 110 (4), 76 (4.8). (ℓ) ir (potassium bromide): ν max = 3280, 1670, 1600, 1450, 1310, 1150, 915, 870, 820, 745 cm^{-1}; ms: m/e (relative intensity) 267 (13), 266 (3), 236 (2), 235 (3.5), 162 (15), 161 (100), 133 (9.5), 132 (5.3), 120 (26.5), 119 (53), 105 (7.4), 104 (6), 92 (22), 77 (4), 76 (3).

Voltammetric and preparative data for the anodic oxidation of equimolar solution of catechol (**1**) and added nucleophile (**2-11**) are given in the Table. All voltammograms exhibited two irreversible peaks in the range of sweep rates (0.02-1.0V/s) studied. The current functions, $i_p/v^{1/2}C$, obtained by cyclic voltammetry generally decreases for the first peak, while that for the second peak increases with $v^{1/2}$. Coulometry at the applied potential, showed that the overall electrode reaction was a four-electron oxidation in all cases examined. The oxidation products (**2a-11a**) were precipitated during the reaction and after recrystallization their elemental analysis, ir and mass spectra were in agreement with the assigned structures.

Our present electrochemical method gives the products (**2a-11a**) in good yields ranging from 42 to 95% and with high purity. In certain cases, the electrochemical method is superior to other methods. Thus, we obtained 7,11,12-trihydroxycoumestan (**5a**), having the basic structure of natural medicagol, in 92% yield as an analytically pure compound. Livingston and coworkers (19) were not able to isolate compound **5a** in the pure state using the procedure of Wanzlick (13). The electrochemical synthesis of the heterocyclic compounds **2a-11a** can also be performed by means of constant current electrolysis (*ca.* 5 mA/cm^2) using an undivided cell and sodium acetate-water as a solvent-supporting electrolyte system, which would improve the applicability of the procedure.

Mechanistic Rationalization.

The oxidation of the catechol (**1**) in the presence of 4-hydroxycoumarin (**2**), as a nucleophile, was studied in some detail. The cyclic voltammogram of catechol exhibits the anodic wave at 0.25 V *vs.* SCE [Figure 1 (a)] corresponding presumably to the formation of *o*-quinone, which is reduced in the cathodic sweep at 0.05 V *vs.* SCE. The cathodic counterpart of the anodic peak disappears, when a sufficient amount of 4-hydroxycoumarin was added, and a second irreversible peak at 0.95 V *vs.* SCE appeared [Figure 1 (b)]. The anodic shift of the peak of 1, in the presence of 4-hydroxycoumarin (curve b), is probably due to the formation of a polymeric film, as already reported during the anodic detection of phenolic compounds (23). The reaction product, 11,12-dihydroxycoumarin (**2a**), is oxidized at a lower potential than the starting catechol (E_p = 0.18V *vs.* SCE). However overoxidation of **2a** was circumvented during the preparative reaction because of the insolubility of the product in water-sodium acetate media.

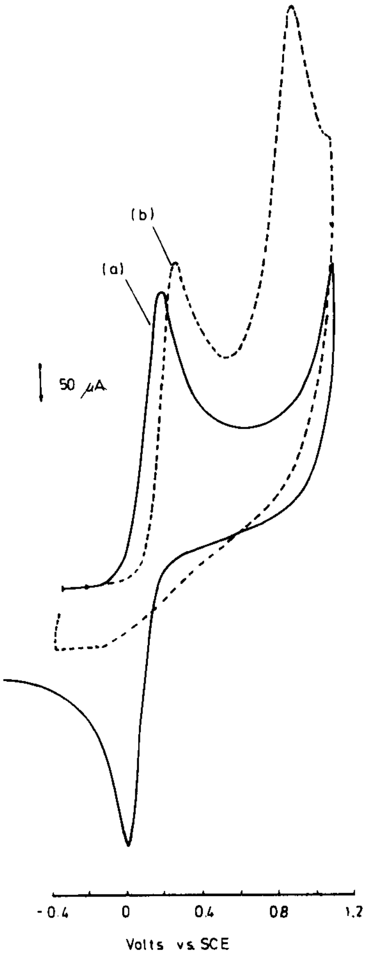


Figure 1. Cyclic voltammograms of 1 × 10^{-3} *M* catechol in 0.15 *M* aqueous sodium acetate solution at pyrolytic graphite anode (curve a) and plus 1 equivalent of 4-hydroxycoumarin (curve b). Scan rate: 150 mV/s. Pyrolytic graphite anode (2r = 6 mm).

Controlled potential electrolyses were performed at 0.4 and 1.0 *vs.* SCE. At both potentials the same product **2a** was isolated in greater than 90% yields. Cyclic voltammograms with constant conditions were obtained as a function of the charge passed and the results indicated that for constant potential electrolysis both waves decreased at a rate corresponding to the consumption of 4 F mol^{-1} (Figure 2).

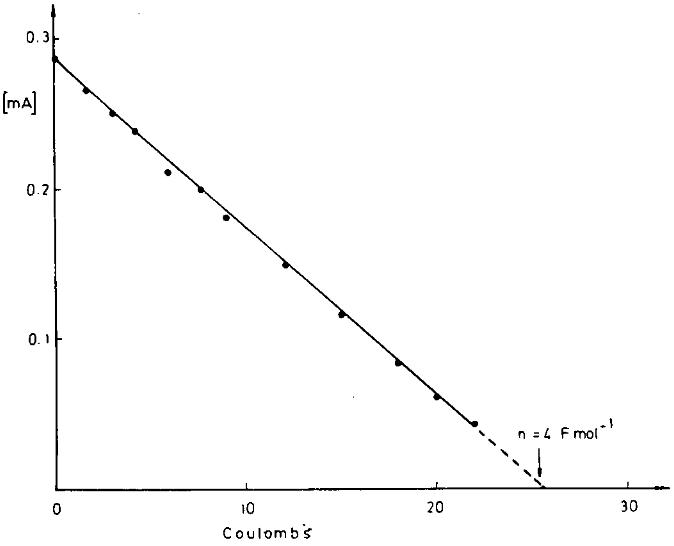
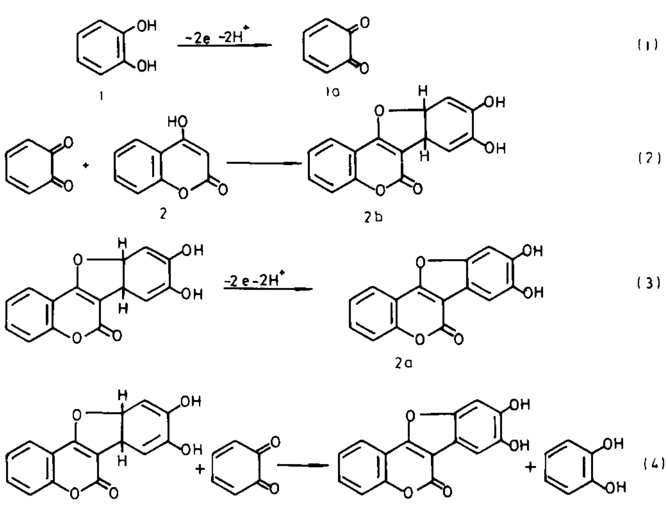


Figure 2. Coulometry for oxidation at +0.4V of catechol (1.5 × 10^{-3} *M*) and 4-hydroxycoumarin (1.5 × 10^{-3} *M*) in 0.15 *M* aqueous sodium acetate solution at graphite anode (15 × 4 cm).

The data available are limited but do allow main features of the reaction pathways to be formulated. The results indicate that at 0.32 V and 0.95 two distinct oxidative processes were occurring, both of which resulted in the same products. The most likely mechanism which would fit the observed electrochemical properties can be described in the form of the Scheme 2.

The electrochemical oxidation of catechol leads to the corresponding *o*-quinones followed by hydroxylation with prolonged oxidation in acidic media (20,21). Papouchado, Scheme 2



Petrie and Adams (20) claimed that more quantitative electrochemical studies at the intermediate *p*H values were difficult because of secondary dimerization reactions and filming of the electrode surface.

However, according to our results, it seems that the intermolecular and intramolecular 1,4 (Michael) addition of 4-hydroxycoumarin (**2**) to *o*-quinone (**1a**) formed (eq. 2) is faster than other secondary reactions, leading presumably to the intermediate dihydrocoumestan derivative **2b**. The compound **2b** is oxidized at a higher potential (E_p = 0.95V) to the product **2a**. It can be seen from the mechanism written that as the chemical reaction (eq. 2) occurs, the catechol (**1**) is regenerated through homogeneous oxidation (eq. 4) and hence can be reoxidized at the electrode surface. Thus as the chemical reaction takes place, the apparent number of electrons transferred increases from the limits of n = 2 to n = 4 F mol^{-1}.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra (potassium bromide pellets) were recorded on a Perkin-Elmer M-377 spectrophotometer, the nmr spectra were recorded on a Perkin-Elmer R 12A spectrometer using tetramethylsilane as an internal standard, and mass spectra were recorded on a Hitachi Perkin-Elmer RMV-6L mass spectrometer. The apparatus and celles for voltammetry, coulometry and preparative electrolysis have been described earlier (22).

General Procedure for Electrochemical Preparation of Heterocycles **2a-11a**.

An undivided electrolytic cell with the graphite anode (3 × 12 cm), Pt-cathode (2 × 5 cm) and SCE as a reference electrode was used. During the electrolysis an electronic integrator was used to record the quantity of electricity passed.

In a typical procedure, catechol (0.002 mole) and nucleophile **2-11** (0.002 mole) are dissolved in 100 ml of 0.15 *M* aqueous sodium acetate solution. The potential was maintained at a fixed value (see Table) with initial currents generally 300-500 mA. Electrolysis was usually discontinued when the current dropped to 20-40 mA which generally took 2-4 hours. When constant current electrolysis (*ca.* 5 mA cm^{-2}) was used the reaction ended after 4 F mole^{-1} had been transferred. The process was interrupted several times during the electrolysis and the graphite anode was washed in acetone in order to "activate" it.

To the solution after electrolysis a few drops of acetic acid was added and the solution was placed in the refrigerator for 1-3 hours. The precipitated solid was collected by filtration and recrystallized from an appropriate solvent (see Table).

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