Selective Hydroxymethylation of Emodin

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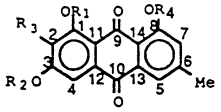
Synopsis. Electrochemical oxidation of 1,3,8-trihydroxy-6-methylanthraquinone, emodin, in dry alkaline methanol under a constant current of 0.05 A for 10 h under an applied potential difference of 15 V at room temperature resulted, for the first time, in an efficient and selective hydroxymethylation at C-2. The structure of the product was established from the detailed spectral analyses of its trimethyl ether and tetraacetylated derivative.

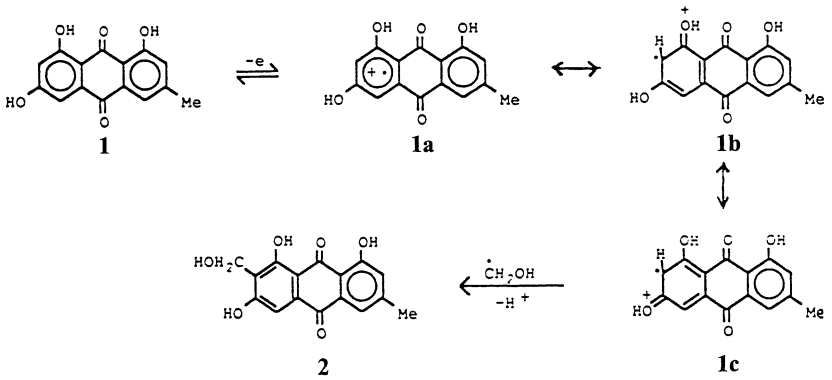
The field of electrochemistry, so far added many incredible routes to various electroorganic syntheses. Oxidative phenol coupling reaction has also enjoyed its applicabilities when tried with a number of simple substituted phenols,[1-4] though in some cases they ended with usual oxidation products,[5,6] The electrooxidative coupling of phenols has also been extended towards the synthesis of the alkaloidal skeletons.[7-9] Compared with other oxidation routes, electrooxidation appears to be more sensitive to steric factors and the tendency towards the specific formation of the single isomer on electrooxidation is rationalized as arising from a surface reaction, presumably on or near the electrode surface. In spite of the synthetic utility of such an oxidation procedure phenolic polyaromatic quinones, however, remained totally unexplored, though many of them can be used as dyes,[10] and bear clinically important antitumor activities, [11] and indicator properties.[12]

Our primary target was therefore to dimerize 1,3,8-trihydroxy-6-methylanthraquinone, emodin (**1**) an uniquely functionalized phenolic anthraquinone by electrochemical means simulating its chemical transformation.[13,14]

In this report, we wish to present our findings on the electrochemical reaction on emodin (**1**) in dry alkaline methanolic solution, which resulted in the isolation of the hydroxymethylated emodin (**2**) as the sole product (ca. 38%). Anodic oxidation of phenols in methanol has been reported to be a viable route to methoxylation



1: $R_1=R_2=R_3=R_4=H$
2: $R_1=R_2=R_4=H$; $R_3=CH_2OH$
3: $R_1=R_2=R_4=Me$; $R_3=CH_2OH$
4: $R_1=R_2=R_4=Ac$; $R_3=CH_2OAc$
5: $R_1=R_2=R_4=Me$; $R_3=H$
6: $R_1=R_2=R_4=Ac$; $R_3=H$



1 **1a** **1b** **2** **1c**

$$\mathbf{1a} + MeOH \longrightarrow \mathbf{1} + MeOH^{+\cdot}$$

$$MeOH^{+\cdot} \xrightarrow{-H^+} \dot{C}H_2OH$$

Scheme 1.

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in many cases.[15–18] However, here a hydroxymethylated product was isolated from this type of reaction. The most interesting feature of the product isolated from the reaction in methanol involved the incorporation of the solvent and that too through the formation of a C–C bond, instead of a C–O bond. So this type of hydroxymethylation reaction may have a potential to be used for the synthesis of several important naturally occurring anthraquinonoid compounds like ferruginol,[19] lucidin,[20] tritisporin,[21] asperthecin[22] etc.

The reaction apparently seems to proceed through the formation of a radical cation (**1a**—**c**) followed by the solvent incorporated addition via hydrogen abstraction (Scheme 1). Such type of hydroxymethylation is well known in photochemistry.[23] However, generation of carboxymethyl[24] or nitromethyl[25] radicals by electrolysis of acetic acid and nitromethane in presence of some inorganic or organic mediators are possible, which speaks in favor of the formation of hydroxymethyl radical from methanol. Thus the introduction of hydroxymethyl group in the product isolated seems to be rather unusual though not improbable. The formation of the sole product is the outcome of the balance of the steric and stereoelectronic factors of the radical cation. The other way, the reaction can be rationalized as a hydroxymethylation caused by formaldehyde in-cell generated from the oxidation of methanol in presence of alkali. Such an electrooxidation of methanol to formaldehyde is well documented during the industrial preparation of glycol.[26] In that case also the selective orientation of hydroxymethyl group, as reflected in the product **2**, occurs most efficiently. In this context it is worthwhile to mention that when emodin was allowed to react with formaldehyde in presence of alkali at room temperature, it gave three products, the minor one isolated being authenticated as **2**.

Conversion of emodin (**1**) into **2** was accomplished by carrying out the electrolysis of a dry alkaline methanolic solution of emodin with Pt electrodes for 10 h. The product was established unambiguously to be 2-(hydroxymethyl)emodin (**2**) by a detailed comparative study of the ^{1}H NMR spectral data of the trimethyl ether (**3**) and the tetraacetylated derivative (**4**) of the product with those of the emodin trimethyl ether (**5**)[13] and emodintriacetate (**6**)[27] respectively.

Thus the absence in the ^{1}H NMR spectrum ($CDCl_3$) of **3** of a one proton signal at δ=6.72 corresponding the readily identifiable most upfield aromatic proton signal for H-2 in **5** and the appearance of the proton signal at δ=7.50 as a very sharp singlet, which can be attributed to H-4 of **3** in analogy with H-4 (δ=7.30) of emodin trimethyl ether (**5**), clearly indicates the hydroxymethylation has taken place at C-2. The remaining two aromatic protons appear as two separate doublets at δ=7.10 and 7.67 and can be recognized as H-7 and H-5 respectively when compared with H-7 (δ=7.02) and H-5 (δ=7.57) of trimethyl ether (**5**) of emodin. The coupling (2.0 Hz), however, while lower than is typical for *meta*-standing protons, is not outside the range of some examples, e.g., phthalic acid (0.5 Hz), isophthalic acid (1.6 Hz) and catechol (1.3 Hz). The three aromatic methoxyls in **3** resonated at expected positions (δ=4.0, 3H, s and 4.07, 6H, s). The aromatic methyl appeared at δ=2.50 (3H, s). The presence of two benzylic protons adjacent to a hydroxyl group in **3** is revealed by the appearance of a two proton singlet at δ=4.8.

Table 1. Carbon-13 NMR Spectral Data of Emodin Trimethyl Ether (**5**) and the Trimethylated Derivative of the Product (**3**)

Carbon atoms	Chemical shifts (δ values)	
	5	**3**
C-1	159.76 (s)[a]	161.67 (s)[a]
C-3	161.67 (s)[a]	160.04 (s)[a]
C-8	163.67 (s)[a]	159.88 (s)[a]
C-2	105.26 (d)	129.93 (s)
C-5	118.97 (d)	118.96 (d)
C-6	144.58 (s)	145.13 (s)
C-7	119.56 (d)	119.75 (d)
C-9	181.70 (s)[a]	181.46 (s)[a]
C-10	184.34 (s)[a]	183.70 (s)[a]
C-12	136.39 (s)[b]	135.33 (s)[c]
C-13	134.4 (s)[b]	134.47 (s)[c]
C-4	101.87 (d)	104.28 (d)
C-11	118.39 (s)	122.22 (s)[d]
C-14	121.52 (s)	121.12 (s)[d]
6-Me	22.04 (q)	22.07 (q)
0-Me	55.81 (q)[a]	56.53 (q)[a]
	56.43 (q)[a]	56.25 (q)[a]
	56.45 (q)[a]	54.85 (q)[a]
Ar-$\underline{C}H_2OH$	—	63.23 (t)

a) In the absence of adequate data of appropriate model compounds definite assignments were not made. b)—d) Values are interchangeable.

A very interesting feature of the ^{1}H NMR spectrum of the tetraacetyl derivative of **2** is the extraordinary upfield shift of one of the acetoxymethyl groups (δ=2.03) and the other three appeared at δ=2.40, 2.46, and 2.53, which clearly indicates the presence of one aliphatic and three aromatic acetoxyl groups. The benzylic protons appeared at δ=5.30 (2H, s). The aromatic protons resonated at δ=7.35 (1H, d, J=2 Hz; H-7) and δ=8.15 (2H, d, J=2 Hz; H-5) [the signal of H-4 was embedded in the signal of H-5] could also be rationalized when compared with the ^{1}H NMR spectrum[27] of emodintriacetate (**6**).

The most convincing evidence in support of the structure **2** for the product was provided by a comparison of the ^{13}C NMR spectral data of its trimethyl ether (**3**) with those of trimethyl ether (**5**) of emodin[13] (Table 1). The noise-decoupled spectrum of **3** displays 19 carbon signals. The degree of protonation of each carbon atom of the compound was determined by Attached Proton Test (APT) method[28] and the assignments of the carbon chemical shifts were made on the basis of the reported δ_c values of the appropriate anthraquinone monomers.[29]

Experimental

Mps reported are uncorrected. Silica gel (60—100 mesh) was used for column chromatography. TLC analyses were on silica gel plates with 0.2 mm thickness (E. Merck). In all cases of NMR measurements $CDCl_3$ was used as the solvent and TMS as the internal standard. IR spectra were run on a Beckman 20 spectrophotometer, ^{1}H and ^{13}C NMR spectra on a Varian EM-390 instrument operating at 90 MHz and Varian

LX300 (75 MHz) instrument respectively. MS was recorded in an instrument equipped with a direct inlet system and operating at 70 eV. All analytical samples were routinely dried over P_2O_5 for 24 h in vacuo. Na_2SO_4 was used for drying and petrol used had bp 60—80 °C.

Electrolysis and Product Analysis. Electrolysis of the dry methanolic solution (70 ml) of emodin (**1**, 0.14 g) in alkaline medium (pH 9.0 with respect to NaOH) was carried out at a constant current (0.05 A) for 10 h under an applied potential difference of 15 V at room temperature, using platinum plates with an area of 1 cm^2 as the electrodes. After the electrolysis, the electrolytic solution was acidified with 1 M (M=mol dm^{-3}) HCl and then extracted thrice with 30 ml portions of ether. The combined ether layers were dried over anhydrous Na_2SO_4, the solvent was evaporated and the residue was chromatographed.

Unconverted emodin (**1**, 0.06 g) was obtained from the earlier petrol–EtOAc (5 : 1) eluate and subsequent elution of the column with petrol–EtOAc (3 : 1) gave 2-(hydroxymethyl)emodin (**2**, 0.054 g) as an orange-red solid, mp>300 °C (petrol–EtOAc); TLC R_f 0.53 (silica gel, 1 : 1 petrol–EtOAc); IR (KBr) 3550 (OH) cm^{-1}; MS m/z 300 (M^+). Found: C, 64.30; H, 4.11%. Calcd for $C_{16}H_{12}O_6$: C, 64.00; H, 4.00%.

General Procedure for the Formation of the Trimethyl Ether of 2-(Hydroxymethyl)emodin. A solution of 2-(hydroxymethyl)emodin (**2**, 0.025 g) in dry acetone (100 ml) was heated under reflux with Me_2SO_4 (3 ml) over anhydrous K_2CO_3 (100 g) for 10 h. Usual work up and careful column chromatography of the reaction product yielded, along with the tetramethyl ether as a minor product,[12] the trimethyl ether **3** (0.018 g), mp 215 °C (petrol–EtOAc); TLC R_f 0.16 (silica gel, 1 : 1 petrol–EtOAc); ^1H NMR δ=2.50 (s, 3H, CH_3), 4.0 (s, 3H, OCH_3), 4.07 (s, 6H, OCH_3), 4.80 (s, 2H, CH_2O), 7.10 (d, 1H, J=2.0 Hz, 7-H), 7.67 (d, 1H, J=2.0 Hz, 5-H), 7.50 (s, 1H, 4-H); IR (KBr) 3500 (aliphatic OH) cm^{-1}; MS m/z 342 (M^+). Found: C, 66.80; H, 5.28%. Calcd for $C_{19}H_{18}O_6$: C, 66.66; H, 5.26%. As the major product in its petrol–EtOAc (5 : 1) eluate.

General Procedure of the Formation of the Tetraacetylated 2-(Hydroxymethyl)emodin (4). Usual acetylation of **2** (0.02 g) (Ac_2O/Py) yielded a tetraacetate **4** (0.016 g), mp 190 °C (petrol–EtOAc); TLC R_f 0.66 (silica gel, 1 : 1 petrol–EtOAc); ^1H NMR 2.03 (s, 1H, aliphatic $OCOCH_3$), 2.40 (s, 3H, $ArOCOCH_3$), 2.46 (s, 3H, $ArOCOCH_3$), 2.50 (s, 3H, Ar-Me), 2.53 (s, 3H, $ArOCOCH_3$), 5.30 (s, 2H, CH_2O), 7.35 (d, 1H, J=2 Hz, 7-H), 8.15 (d, 2H, J=2 Hz, 5-H) [the signal of 4-H was embedded in the signal of 5-H]; IR (KBr) 1740 (aliphatic $OCOCH_3$) and 1780 (aromatic $OCOCH_3$) cm^{-1}; MS m/z 468 (M^+). Found: C, 61.70; H, 4.29%. Calcd for $C_{24}H_{20}O_{10}$: C, 61.53; H, 4.27%.

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