EFFICIENT SYNTHESIS OF A RANGE OF 1-HYDROXY-2-(1- ALKYLOXYMETHYL)-9,10-ANTHRAQUINONE DERIVATIVES

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ABSTRACT: *Five new 1- hydroxy-2- (1- alkyloxymethyl)-9,10- anthraquinones (9a-e) have been prepared. Selective nitration of 2- methyl-9,10-anthraquinone, reduction to the corresponding amine, diazotization and treatment by sulfuric acid solution afforded the 1- hydroxy-2- methyl-9,10-anthraquinone in good yield as the key intermediate. Reaction with dimethylsulphate/K_2CO_3 and subsequent monobromination with NBS/CCl_4 produced 1- methoxy-2- (bromomethyl)-9,10- anthraquinone. A mixture of HBr/AcOH was used for demethylation. Treatment of hydroxybromo derivatives with different alcohols afforded corresponding ethers in high yields.*

KEY WORDS : *1- Hydroxy-2- methyl-9,10- anthraquinone, 1- Hydroxy-2-(1- methoxymethyl)-9,10- anthraquinone.*

INTRODUCTION :

The chemistry of anthraquinone systems are important and interesting but the system is generally less studied than it might be if derivatives were more synthetically accessible. These compounds have been of long- standing interest to chemists because they are widely applied for mechanistic studies, such as electrochemical switching mechanisms [1-5].

A number of homologues of anthraquinone are of importance, especially 2- alkyl derivatives with alkyl chains ranging from one to five carbon atoms [7-9].

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In this paper a total synthesis of five new 1-hydroxy -2- (1- alkoxymethyl)-9,10- anthraquinone derivatives, is described.

RESULTS AND DISCUSSION :

Synthesis of 1- hydroxy-2- (1- alkoxymethyl)-9,10- anthraquinone derivatives *(9a-c)* outlined in Scheme 1 illustrates our general approach via selective nitration of 2- methyl 9,10-anthraquinone intermediates.

1- Nitro-2- methyl-9,10- anthraquinone *(2)* has been used for synthesis of various drugs and dyestuff intermediates [9]. This compound had previously been prepared by nitration of 2-methyl-9,10- anthraquinone *(1)* with anhydrous HF and potassium nitrate in an autoclave at 60°C [10] and also with a mixed of acid [10,12] in good yield. We have found that treatment of 1 with potassium nitrate in concentrated sulfuric acid afforded 2 in 97% yield as yellow crystals.

When compound 2 treated with a solution of sodium sulfide in boiling ethanol [13] for 10 minutes, 1- amino-2- methyl-9,10- anthraquinone *(3)* was obtained in 90% yield as red crystals. This compound is an important intermediate in the preparation of anthraquinone dyes [14].

There are two methods reported in the literature [15,16] for preparation of 1-hydroxy-2- methyl-9,10- anthraquinone *(4)*. The yields of these procedures are usually low and the preparation of starting materials are very difficult. We found out that treatment of compound *(3)* with $NaNO_2$ in concentrated sulfuric acid at 0°C and heated at 120°C for 10 minutes, gives 1- hydroxy-2- methyl-9,10-anthraquinone *(4)* in 95% yield as yellow crystals. ^{1}H-NMR of this compound showed a singlet at δ12.9 due to hydroxyl group peri to carbonyl.

The reaction of 1- nitro-, 1- amino-, and 1-hydroxy-2- methyl-9,10- anthraquinone with N-bromosuccinimide (NBS) and dibenzoyl peroxide (DBP) in dry carbon tetrachloride failed.

Treatment of compound *(4)* with dimethyl sulfate and potassium carbonate in dry acetone gave 1- methoxy-2- methyl-9,10- anthraquinone *(5)* in 90% yield as green- yellow crystals.

By refluxing compound *(5)* with N- bromo-succinimide and dibenzoyl peroxide in dry carbon tetrachloride, 1- methoxy-2- (bromo-methyl)- 9,10- anthraquinone *(6)* was obtained in 93% yield.

Treatment of 1- methoxy-2- (bromomethyl)-9,10- anthraquinone *(6)* with K_2CO_3 in methanol gave 1- methoxy- 2- (methoxymethyl)-9,10- anthraquinone *(7a)* and 1- methoxy-2-formyl-9,10- anthraquinone *(11)*. Finucane and Thompson [17] proposed that in moistured solvents, benzylic methylene groups were oxidized to carbonyls. Thus, when we used dry methanol, compound *(11)* was not produced.

When 1- methoxy-2- (bromomethyl)-9,10-anthraquinone *(6)* in the presence of more than one molar equivalent of potassium carbonate was refluxed in dry methanol 1- methoxy-2-(dimethoxymethyl)-9,10- anthraquinone *(12)* was obtained in 80% yield as orange- yellow crystals. When this reaction was takes place in the presence of less than one molar equivalent of K_2CO_3 or in the absense of it, but in a longer period of time giving 1- methoxy- 2- (methoxy methyl)- 9,10- anthraquinone *(7a)* in 96% yield.

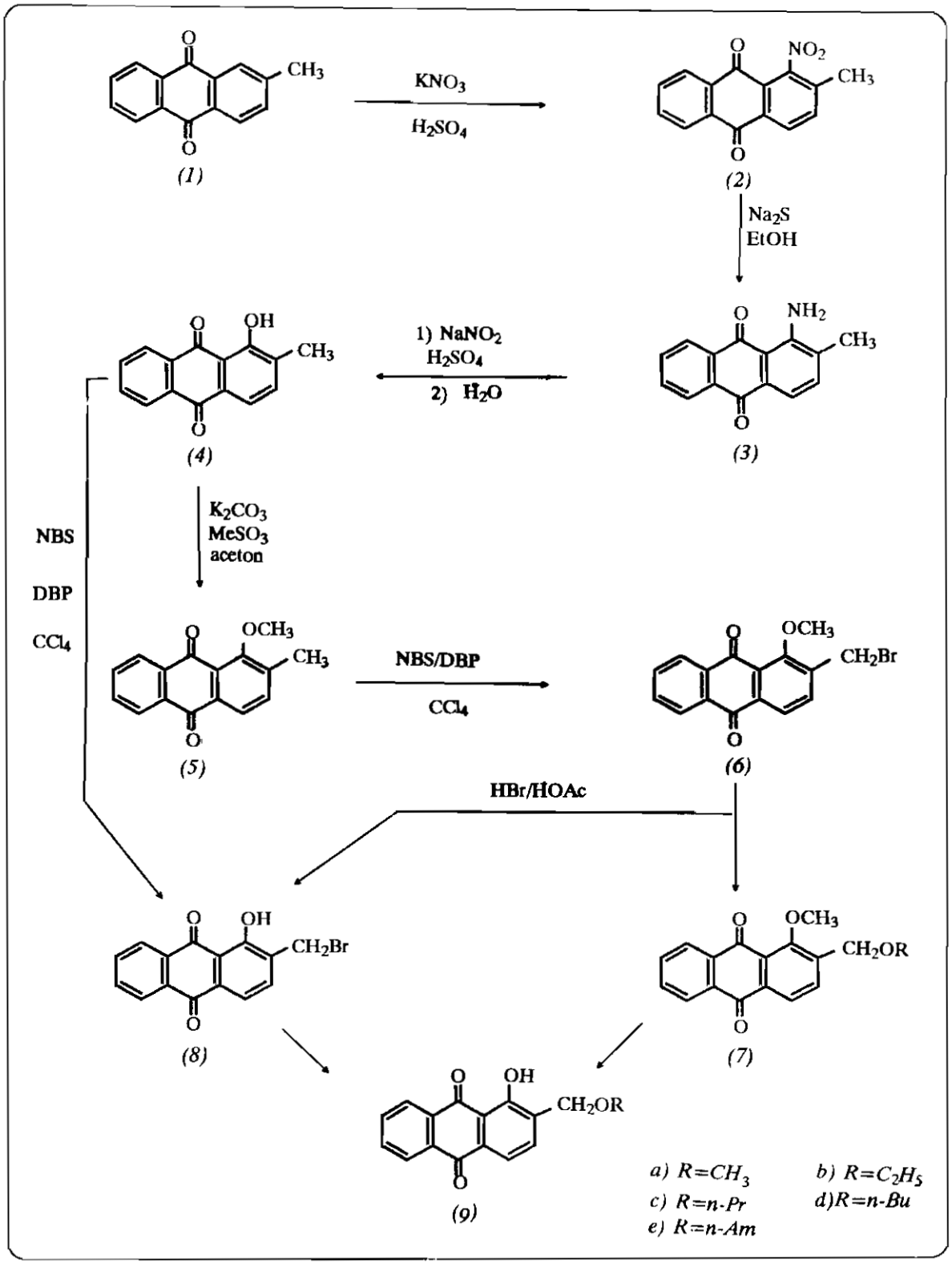
Treatment of compound *(6)* with several alcohols in the presence of K_2CO_3 produced new derivatives of corresponding ethers *(7a-e)* as outlined in Scheme 1.

Our attempts in obtaining 1- hydroxy-2-(alkoxymethyl)-9,10- anthraquinones *(9a-e)* from 1- methoxy- 2- (alkoxymethyl)-9,10- anthra-quinones *(7a-e)* in a mixture of HBr/AcOH proved unsuccessful and compound *(8)* was obtained in all cases.

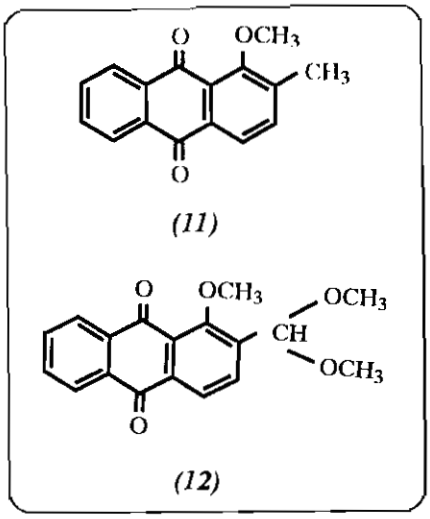
By refluxing compound *(6)* with hydrobromic acid in glacial acetic acid, 1- hydroxy-2-(bromomethyl)-9,10- anthraquinone *(8)* was obtained in 90% yield as fine orange- yellow needles.

Treatment of compound *(8)* with different alcohols in the presence of K_2CO_3 afforded corresponding ethers *(9a-e)* in excellent yields. It

should be noted that when compound *(8)* was treated with methanol even in the presece of excess K_2CO_3 and elongation of reaction time, only compound *(9a)* was obtained.



Scheme 1



EXPERIMENTAL :

Chemical materials were obtained from *Merck* (*Darmstadt*, Germany) and *Fluka* (Switzerland).

Melting points were determined in open capillary tubes in a *Buchi*-510 circulating oil melting point apparatus and are uncorrected. IR spectra were recorded on a *Perkin Elmer*. 157-G and 781 spectrophotometers. NMR spectra were recorded on a R-248 60MHz (*Hitachi*, Japan) spectrometer using tetramethylsilane (TMS) as an internal standard. Mass spectra were determined on GCMS-QP 1000EX at 70ev (*Shimadzu*, Japan). Ultraviolet spectra were recorded on a UV/vis spectrometer PU 8750. Thin-layer chromatography were carried out on silica gel 60F 254 analytical sheets obtained from *Merck*. Column chromatography was carried out on short columns of silica gel 60, *Merck* (230-400 mesh) in glass columns (2 or 3 cm Φ) using 15-30 grams of silica gel per one gram of crude mixture.

1-Nitro-2- methyl- 9,10- anthraquinone (2)

2- Methyl- 9,10- anthraquinone *(1)* (22.2g, 0.1mmol) was dissolved in concentrated sulfuric acid (200mL) and finely ground potassium nitrate (20.2g, 0.2mol) was added in portions during one hour period at 0-5°C. The mixture was stirred for one hour at this temperature and then crushed ice was added. The separated solid was filtered off and washed with warm water (3×300mL) to give a yellow crystalline solid which was recrystallized from acetic acid to give 1- nitro-2- methyl- 9,10- anthraquinone *(2)* in 97% yield (25.8g) as yellow needles, m.p: 270°C (lit. [18], 272-273°C).

^{1}H-NMR($CDCl_3$): δ2.40 (s, 3H, CH_3), 7.60-8.50 (c, 6H, ArH) ppm.

IR(Nujoul): ν_{max} 1675(m,CO),1595(m, Ar)cm^{-1}.

UV(chloroform): λ_{max}(log ε) 209(4.25), 230(4.36), 258(4.63), 330(3.66) nm.

1-Amino-2- methyl-9,10- anthraquinone(3)

1-Nitro-2- methyl- 9,10- anthraquinone *(2)* (26.7g, 0.1mol) in boilling ethanol (1500mL) was added to a stirred solution of crystalline sodium sulfide (78g, 1mol) in water (900mL) at 70°C. The mixture was boiled for 10 minutes. Ethanol was evaporated and the residue was cooled to give red crystals which were then filtered off, washed with water (4×500mL), dried (water pump), and recrystallized from acetic acid to give 1- amino-2- methyl- 9,10- anthraquinone *(3)* in 90% yield (21.4g) as red crystals, m.p: 201°C (lit [18], 204-205°C).

^{1}H-NMR($CDCl_3$): δ2.23(s, 3H, CH_3), 6.62-8.45 (c, 6H, ArH) ppm.

IR(Nujoul): ν_{max} 1660(m, CO), 1610(m, CO), 1580(m, Ar) cm^{-1}.

UV(chloroform: λ_{max} (log ε) 211(4.32), 247(4.62), 470(3.90) nm.

1-Hydroxy-2-methyl-9,10-anthraquinone (4)

1- Amino-2- methyl-9,10- anthraquinone *(3)* (23.7g, 0.1mol) was dissolved in concentrated sulfuric acid (500mL) and then cooled to 0°C. A mixture of sodium nitrate (25g, 0.36mol) and concentrated sulfuric acid (250mL) was added and stirred at 0°C for 30 minutes. Water (700mL) was added to the diazonium solution and heated at 120°C for 10 minutes. The reaction mixture was added to crushed ice. The precipitate was filtered off and washed with water (500mL) and dried (water pump), to give a yellow crystalline solid which was recrystallized

from acetic acid to give 1- hydroxy-2-methyl-9,10- anthraquinone *(4)* in 95% yield (22.6g) as yellow needles, m.p: 180°C (lit. [19,20], 183°C).
^{1}H-NMR($CDCl_3$): δ2.40 (s, 3H, CH_3), 7.30- 8.50 (c, 6H, ArH), 12.95(s, 1H, OH)ppm.
IR(Nujoul): ν_{max} 1670(m, CO), 1635(m, CO), 1585(m, Ar) cm^{-1}.
UV(chloroform): λ_{max}(log ε) 254(4.53), 327(3.74), 414(3.95) nm.

1-Methoxy-2- methyl- 9,10- anthraquinone (5)

1- Hydroxy-2- methyl-9,10- anthraquinone *(4)* (11.9g, 50 mmol), finely ground potassium carbonate (20.7g, 150 mmol), dimethyl sulfate (8mL) were added in dry acetone (1000mL) and refluxed for 6 hours. The mixture was filtered off and the solution was evaporated. The resulting precipitate was dissolved in chloroform, washed with water (2×250mL), and dried ($CaCl_2$). The solvent was evaporated to give yellow crystalline solid which was recrystallized from acetic acid to give 1- methoxy-2- methyl- 9,10- anthraquinone *(5)* in 90% yield (11.3g) as green yellow needles, m.p.: 165°C (li. [20], 166.5-167°C).
^{1}H-NMR($CDCl_3$): δ2.34 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 7.30-8.30 (c, 6H, ArH)ppm.
IR(KBr): ν_{max} 1675(s, CO), 1580 (s, Ar) cm^{-1}.
UV(chloroform): λ_{max} (log ε) 203 (3.92), 257 (4.62), 346 (3.66) nm.

1-Methoxy-2-(bromomethyl)- 9,10-anthraquinone (6)

1- Methoxy-2- methyl-9,10- anthraquinone *(5)* (12.6g, 50mmol), N- bromosuccinimide (8.75g, 50mmol), and dibenzoyl peroxide (1g) in dry carbon tetrachloride (1500mL) were heated to reflux for 6 hours. The solvent was evaporated and the precipitate dissolved in chloroform (250mL) and washed with water (3×200mL), dried ($CaCl_2$) and the solvent was evaporated. The product was recrystallized from acetic acid to give 1- methoxy-2- (bromomethyl)-9,10-anthraquinone *(6)* in 93% yield (15.45g) as fine yellow needles, m.p: 190°C (lit. [20], 194.5-195.5°C).
^{1}H-NMR($CDCl_3$): δ4.00(s, 3H, OCH_3), 4.57(s, 2H, CH_2Br), 7.50-8.40(c, 6H, ArH) ppm.
IR(KBr): ν_{max} 1670(s, CO), 1585(m, Ar)cm^{-1}.
UV(chloroform): λ_{max} (log ε) 208(4.41), 229(4.53), 258(4.59), 318(3.79), 346(3.72) nm.

Preparation of 1- methoxy-2- (alkoxymethyl)- 9,10- anthraquinone (7a-e).

General Procedure: 1- Methoxy-2- (bromomethyl) -9,10- anthraquinone *(6)* (0.66g, 2mmol) and potassium carbonate (0.25g, 1.8mmol) in alcohol (100mL) were refluxed for 3-4 hours. The solvent was evaporated and precipitate was dissolved in chloroform (50mL), washed with water (2×50mL), and dried ($CaCl_2$). The residue was recrystallized to give 1- methoxy-2-(alkoxymethyl)-9,10- anthraquinone (7a-e) (Table 1).

1-Hydroxy-2- (bromomethyl) -9,10- anthraquinone (8)

1- Methoxy-2- (bromomethyl)-9,10- anthraquinone *(6)* (6.62g, 20mmol) in a mixture of hydrobromic acid (47%, 125mL) and glacial acetic acid (250mL) was refluxed for 10 minutes.

Table 1

Compound	m.p.(°C)	^{1}H-NMR	MS(M^+)	IR	Yield (%)
(7a)	145	3.40, 3.84, 4.51, 7.50-8.30	282	1680, 1595	96
(7b)	100	1.28, 3.55, 3.82, 4.52, 7.30-8.20	296	1675, 1595	98
(7c)	86-88	0.95, 1.70, 3.48, 4.57, 7.48-8.18	310	1680, 1600	90
(7d)	71-72	0.95, 1.20-1.80, 3.52, 3.87, 4.60, 7.50-8.30	324	1680, 1595	96
(7e)	46-47	0.70, 1.00-1.60, 3.30, 3.60, 4.30, 7.10-7.90	338	1680, 1590	96

Table 2

Compound	m.p.(°C)	^{1}H-NMR	MS(M^+)	IR	Yield (%)
(9a)	160-162	3.40,4.46,7.50-8.20,12.78	268	1675,1635,1595	96
(9b)	128-129	1.28,3.58,4.50,7.40-8.30,12.75	282	1675,1635,1595	93
(9c)	112-113	0.97,1.54, 3.45,4.47, 7.40-8.20, 12.73	296	1675,1630,1595	95
(9d)	102-103	0.97,1.16-1.90,3.49,4.44,7.40-8.30,12.76	310	1675,1635,1595	96
(9e)	96-97	0.92,1.05-1.85,3.54, 4.45,7.40-8.15,12.74	324	1675,1635,1600	95

Fine orange-yellow needles of 1- hydroxy-2-(bromomethyl)-9,10- anthraquinone *(8)* in 90% yield (5.7g) was formed, which were filtered off, washed with water (2×100mL), and dried under suction, m.p.: 191-192°C (lit. [21], 190-191°C).
^{1}H-NMR($CDCl_3$): δ4.58 (s, 2H, CH_2Br), 7.50-8.40(c, 6H, ArH), 13.20(s, 1H, OH) ppm.
IR(KBr): ν_{max} 1670(s, CO), 1650(s, CO), 1595(s, Ar) cm-^{1}.
UV(chloroform): λ_{max} (log ε) 224(3.38), 253(4.52), 336(3.50), 412(3.91) nm.

Preparation of 1- Hydroxy-2- (alkoxymethyl) -9,10- anthraquinone (9a-e)

General Procedure:1- Hydroxy-2-(bromomethyl)-9,10- anthraquinone *(8)* (3.17g, 10mmol) and potassium carbonate (1.7g, 12mmol) in alcohol (250mL) were refluxed for 3-4 hours. The solvent was evaporated and the residue was disolved in chloroform (200mL), washed with water (2×100mL), and dried ($CaCl_2$). The residue was recrystallized to give 1- hydroxy-2-(alkoxymethyl)- 9,10- anthraquinone (9a-e) (Table 2).

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