Chinese Chemical Letters Vol. 12, No. 12, pp 1057 – 1060, 2001
http://www.imm.ac.cn/journal/ccl.html

Reactions of Podophyllotoxin with DDQ

Qian Rong LI[1]*, Ting Hu ZHANG[1], Robert S.WARD[2]

[1]Structure Research Laboratory, University of Science and Technology of China, Hefei 230026
[2]Chemistry Department, University of Wales Swansea, Singleton Park,Swansea SA2 8PP UK

Abstract: Podophyllotoxin **1** reacts with DDQ in acetic acid to give podophyllotoxone **2** at 75°C and the naphthol **3** at 90°C, and in TFA to give the naphthalene **4**. 4′-*O*-Benzyl-epipodophyllotoxin **5** reacts with DDQ in acetic acid at 70°C to give the acetate **8**. The structural elucidation of these products is described.

Keywords: Podophyllotoxin, oxidation, DDQ.

Introduction

2, 3-Dichloro-5, 6-dicyanobenzoquinone (DDQ) can react with lignans of the mono-arylidene-butyrolactone[1], aryltetralin[2], dibenzylbutane[3] and aryltetralin-butyrolactone[4,5] series. We have studied the reactions of this reagent with podophyllotoxin **1**, which is a well-known natural product on account of its long history of use in folk medicine and the biological activity of its many derivatives[6]. In particular, derivatives of 4′-demethyl epipodophyllotoxin are used in cancer chemotherapy[7]. As a result, there is much interest in devising new approaches to the synthesis of podophyllotoxin derivatives, for study their chemical modification. Furthermore, the possible involvement of quinone or quinone-methide intermediates of these compounds in the biological mode of action[8] led to the preparation of the derivatives of this type[4].

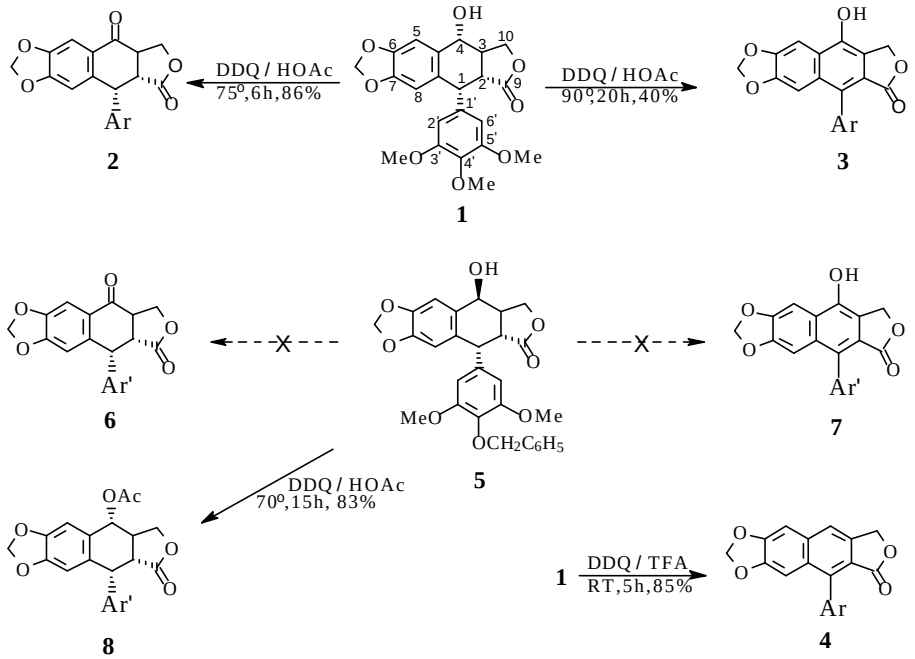
Results and Discussion

When podophyllotoxin **1** was treated with 1.5 equivalents of DDQ in acetic acid at 75°C, oxidation reaction occurred at C-4 to give podophyllotoxone **2**[9] in 86% yield. The product had showed two carbonyl signals at δ 173.3 and 192.7 ppm in its ^{13}C-NMR spectrum, and signals at 1764 and 1780 cm^{-1} in its IR spectrum. The structure of **2** was confirmed by the lack of a signal for H-4 in its ^{1}H-NMR spectrum and by comparison with the literature data for this compound. The same product was obtained in comparable yield when used $CHCl_3$ or MeOH as solvent. The direct conversion of **1** to **2** is an efficient method for the preparation of the podophyllotoxone.

When **1** was treated with 2.5 equivalents of DDQ in acetic acid at 90°C, a mixture of two products was obtained from which the naphthol **3**[10], mp 247-249°C, was isolated

in 40% yield. The ^{1}H-NMR spectrum showed no signals for H-1, H-2, H-3 and H-4, and all of the remaining signals were shifted downfield by comparison with those of the

Scheme 1



Ar =3,4,5-trimethoxyphenyl, Ar' = 4-benzyloxy-3,5-dimethoxyphenyl

starting material. The assignment was confirmed by the ^{13}C-NMR spectrum, in which the signals for C-1, C-2, C-3 and C-4 had moved downfield, and in IR spectrum, the band for the lactone carbonyl group shifted from 1764 cm^{-1} to 1750 cm^{-1}, due to conjugation with the aromatic ring. The another product was probably the compound **2** according to TLC.

When the epipodophyllotoxin derivative **5** was treated with 1.5 equivalents of DDQ in acetic acid at 70°C, neither the ketone **6** nor the naphthol **7** was obtained, but acetate **8**, mp 209-211°C, was isolated in 83% yield. This product had molecular formula $C_{30}H_{28}O_9$ (Requires: M^{+}532.1733, EI found: 532.1728) and showed two ^{13}C-NMR signals due to carbonyl groups at δ 173.4 and 171.1 ppm, as well as the signal at δ 20.8 ppm for the methyl carbon of the acetoxy group, which was consistent with the singlet at δ 2.17 ppm (3H) in the ^{1}H-NMR spectrum. In view of the large coupling constant (9.2 Hz)between H-3 and H-4, it was deduced that the configuration at C-4 had been inverted.

Table 1 ^{1}H-NMR spectra ($CDCl_3$ δ_{ppm}) (J Hz)

Proton	2	3	4	5	8
H-5	7.56s	7.49s	7.21s	6.88s	6.77s
H-8	6.71s	7.10s	7.12s	6.55s	6.54s
H-2′,6′	6.38s	6.52s	6.55s	6.31s	6.42s
OCH_2O	6.10AB(1.3)	6.10s	6.09s	5.98AB(1.1)	5.99AB(1.3)
H-4	-	-	7.70s	4.86d(3.1)	5.88d(9.2)
H-1	4.85d(4.1)	-	-	4.65d(5.0)	4.63d(4.1)
H-10	4.57t(8.4)	5.37s	5.38s	4.37m	4.39t(8.1)
	4.36t(9.8)				4.20t(9.9)
4′-OMe	3.82s	3.95s	3.97s	-	-
3′,5′-OMe	3.75s	3.84s	3.84s	3.68s	3.71s
H-2	3.29dd(4.1,15.1)	-	-	3.30dd(5.1,14.1)	2.94dd(4.3,14.6)
H-3	3.53m	-	-	2.81m	2.81m
CH_2-Ph	-	-	-	7.42d,7.35m	7.43d,7.36m
CH_2-Ph	-	-	-	5.26s	5.27s
$COCH_3$	-	-	-	-	2.17s

Table 2 ^{13}C-NMR spectra[a] (δ_{ppm})

Carbon	2	3[b]	4	5	8
C=O	173.28	169.98	169.87	174.78	173.36
C-6	153.40	148.98	148.92	148.31	147.92
C-7	153.25	149.38	150.22	147.34	147.46
C-3′,5′	148.31	146.03	140.65	151.28	151.35
C-4a	128.36	130.96	134.85	137.93	137.66
C-8a	132.32	131.49	137.91	134.78	134.81
C-1’	137.76	137.43	140.04	131.74	131.78
C-4’	141.71	153.03	153.19	152.90	152.89
C-5	109.85	98.66	103.97	110.29	109.54
C-8	106.28	103.20	103.86	108.84	106.88
C-2′,6′	107.74	108.39	107.51	107.44	107.36
OCH_2O	102.61	102.62	102.06	101.39	101.41
C-4	192.66	122.94	119.32	70.14	73.43
C-10	67.20	67.21	68.22	67.40	70.13
4′-OMe	60.98	60.69	61.23	-	-
3′,5′-OMe	56.45	56.52	56.37	55.99	55.92
C-1	46.86	31.49	130.55	43.74	43.54
C-2	44.84	119.70	118.91	38.02	38.41
C-3	43.64	125.23	130.55	40.24	45.38
CH_2-Ph	-	-	-	*	#
CH_2-Ph	-	-	-	66.41	71.15
CH_3C=O	-	-	-	-	171.14
CH_3C=O	-	-	-	-	20.83

[a]Solvent $CDCl_3$ unless indicated. [b]solvent d^6-DMSO.
*128.261,128.231,128.149,128.079. #128.269,128.243,128.097,127.996

Finally when **1** was treated with 1.5 equivalents of DDQ in trifluoroacetic acid (TFA) at room temperature the naphthalene **4**[11], mp 276-8°C, was obtained in 85% yield. The NMR spectra of this product are resembled to those of **3**, except the presence of a singlet at δ 7.70 ppm for H-4.

The detailed analysis data of the ^{1}H- and ^{13}C-NMR spectra are listed in **Table 1** and

Table 2, respectively. The ability of DDQ to bring about benzylic oxidation is well documented[12]. Both H-4 and H-1 of **1** are attacked by DDQ to form **3** and **4**, even though the latter attack is more difficult due to steric hindrance. However, if acetic acid was replaced by TFA as solvent, dehydration followed dehydrogenation of **1** took place also to give **4**. In case compound **5**, because both H-4 and H-1 are highly hindered, none of the benzyl positions are oxidized. Instead, the reaction proceedes by S_N2 displacement to give **8**.

Acknowledgment

We gratefully acknowledge the Natural Science Foundation of Anhui Province for financial suport (No.98541842).

References

1. S. Ghosal, S. Banerjee, *J. C. S. Chem. Comm*., **1979**, 165.
2. R. S. Ward, P. Satyanarayana, B. V. Gopala Rao, *Tetrahedron Letters*, **1981**, 3021. Pelter, R. S. Ward, R.Venkateswarlu, C.Kamakshi, *Tetrahedron*, **1991**, *47*, 1275.
3. A. Pelter, R. S. Ward, Q. R. Li, *J. Nat. Prod.*, **1993**, *56*, 2204.
4. Q. R. Li, *J. of China University of Science & Technology*, **1995**, *25*, 245.
5. D. C. Ayres, J. D. Loike, *Lignans: Chemical,Biological and Clinical Properties*, Cambridge University Press, Cambridge, **1990**, pp.85-137.
6. F. Issell, A. R. Rudolph, A. C. Louie, T. W. Doyle, *Etoposide (VP-16): Current Status and New Developments*, ed. by B. F. Issell, F. M. Muggia, S. K. Carter, Academic Press, New York, **1984**, Chap. 1 and 2.
7. J. Wozniak, B. S. Glisson, K. R. Hande, W. E. Ross, *Cancer Res.*, **1984**, *44*, 626.
8. P. M. Dewick, D. E. Jackson, *Phytochem.*, **1981**, *20*, 2277.
9. Kamal, Y. Damayanthi, *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 657.
10. A. Pelter, R. S. Ward, Q. R. Li, Jaroslav Pis, *Tetrahedron: Asymmetry*, **1994**, *5*, 909.
11. D. Walker, J. D. Hiebert, *Chem. Rev*., **1967**, *67*, 153.

Received 18 April, 2001