6-*O*-Demethylation of the Thevinols with Lithium Aluminium Hydride: Selective Demethylation of a Tertiary Alkyl Methyl Ether in the Presence of an Aryl Methyl Ether

by **Simon W. Breeden**, **Andrew Coop**, **Stephen M. Husbands**, and **John W. Lewis***

School of Chemistry, Cantock's Close University of Bristol, Bristol BS8 1TS, England

In the pursuit of ring-constrained analogues of buprenorphine, we wished to prepare 6-*O*-demethylated analogues of the thevinols and orvinols. Previously it had been disclosed that lithium aluminum hydride (LAH) in THF containing a chlorinated solvent could achieve this transformation. Here we report the results of our work with LAH in the non-coordinating solvent toluene. In refluxing toluene, the selective 6-*O*-demethylation of thevinols could be achieved with no 3-*O*-demethylation being observed. It appears that a C(20)–OH or C(20)–NH_2 group is needed on the substrate for this hydrogenolysis to proceed.

Introduction. – Although initially introduced as a clinical analgesic, the unique pharmacological profile of buprenorphine (**1a**) has led to its increasing use as a pharmacotherapy for opioid abuse. We have long been interested in ring-constrained analogues of buprenorphine (**1a**), particularly those having the furanomorphide structure (see **2**) [1][2]. To this end, we were interested in methods that would allow the selective 6-*O*-demethylation of the orvinols and thevinols (see **4**). For the thevinols, this required the selective dealkylation of an alkyl ether in preference to an aryl ether. This general process has been achieved previously with, *e.g.*, $AlCl_3$/NaI/MeCN or Me_3SiI, but only examples of primary and secondary alkyl ethers were reported [3]; in the thevinol structure the 6-OMe group is a tertiary alkyl methyl ether. The only reported examples of selective 6-*O*-demethylation were the conversion of **3a** and **4d** by lithium aluminium hydride (LAH) in THF containing a chlorinated solvent to give **3b** and **5d**, respectively [4]. We here report an expanded investigation of the effects of LAH on a range of thevinols, orvinols and related structures.

Results and Discussion. – As expected, LAH in refluxing THF was without effect on thevinol **4a**, but when it was refluxed with LAH in dioxane solution, a 42% yield of a *ca.* 1:1 mixture of the 3- and 6-*O*-demethylated products was obtained. In our extensive investigations of the thevinols, LAH-induced 3-*O*-demethylation had not previously been encountered, but an example of phenolic ether demethylation in 1,2-dimethoxyphenyl derivatives has been reported [5]. When the solvent was changed to toluene, a non-coordinating solvent that should increase the coordination of the lithium to the 6-OMe, 6-*O*-demethylation of **4a** was selectively achieved in 78% yield. Using this general procedure other thevinols, **4b** and **4c**, the orvinol buprenorphine (**1a**), thevinone (**6b**) and thevinal (**6a**) were similarly selectively demethylated, the latter two compounds with reduction of the carbonyl group (*Table*).

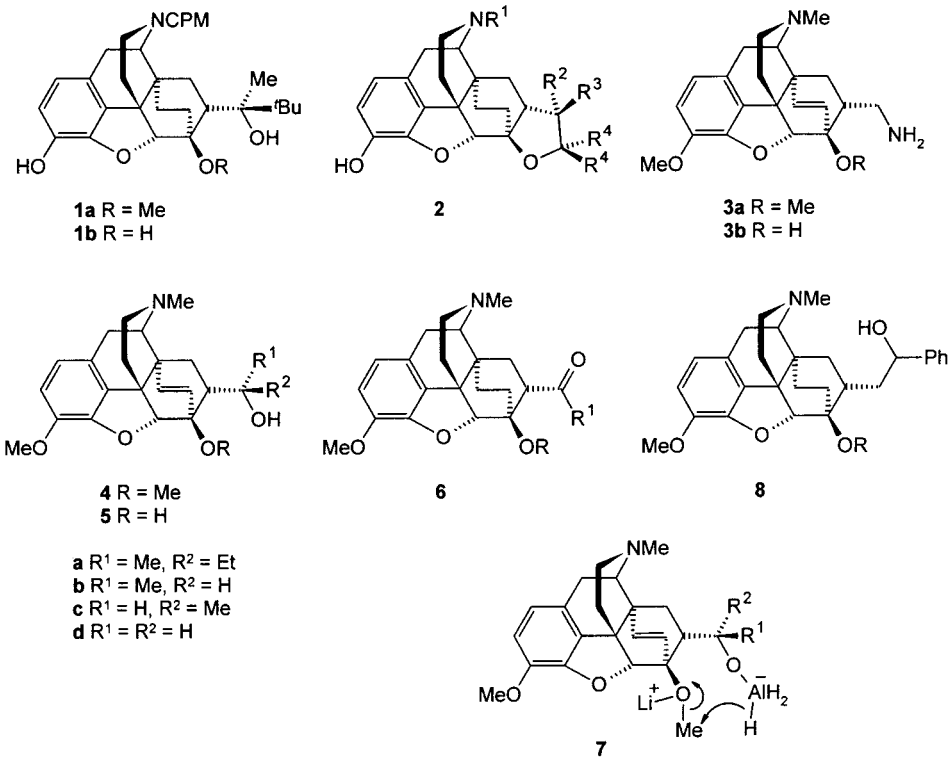

Table 1. *Yields of 6-O-Demethylated Products on Treatment with LAH*

Starting material	Product	Yield/%
1a	**1b**	31 (+ 40% recovered **1a**)
4a	**5a**	78
4b	**5b**	64
4c	**5c**	81
6a	**5d**	66 (+ 21% **4d**)
6b	**5b** + **5c**	76[a])
4b[b])	**5b**[b])	8

[a]) As a 1 : 1 mixture of epimers. [b]) MeO replaces OH.

It was suggested that a heteroatom associated with the 7α-substituent is necessary for 6-*O*-demethylation [4]. Since the 20-methyl ether of **4b** was recovered mostly unchanged from LAH/toluene, it appears that an alkoxy aluminum hydride species **7** is involved with a Li^+-activated complex with the 6-OMe group, from which hydrogenolysis of the MeO group can proceed *via* a cyclic mechanism as shown in **7**. The geometry of the transition state for such a mechanism is sensitive to ring size since the 21-OH analogue **8** of the thevinols did not undergo 6-*O*-demethylation under these conditions.

Thus, the utility of LAH in toluene has been demonstrated for selective 6-*O*-demethylation in the presence of the 3-OMe moiety in the thevinols.

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Experimental Part

General Procedure. To a soln. of the 6-*O*-methyl ether in toluene (10 ml/mmol) was added $LiAlH_4$ (6 equiv.), and the resulting suspension refluxed for 16 h. The cooled soln. was diluted with THF (10 ml/mmol) and $Na_2SO_4 \cdot 10\,H_2O$) (7 equiv.) added. After stirring for 1 h, filtration through *Celite* and removal of solvent left the crude product which was purified *via* column chromatography to give the 6-*O*-demethylated compound.

6-O-*Demethylbuprenorphine* (**1b**). *Buprenorphine* (**1a**) was treated as described above to give both recovered **1a** (80 mg: 40%) and **1b** (60 mg, 31%). R_f (AcOEt/hexane 1:1) 0.1. IR: 3278 (OH). ^{1}H-NMR (300 MHz, $CDCl_3$): 1.03 (*s*, *t*-Bu); 1.42 (*s*, Me); 4.16 (*s*, H−C(5)); 6.48 (*d*, $J = 8.0$, H−C(1)); 6.72 (*d*, $J = 8.0$, H−C(2)). ^{13}C-NMR: 3.27; 4.13; 9.48; 19.77; 22.82; 26.26; 30.04; 33.25; 35.24; 36.35; 40.37; 43.21; 43.79; 45.34; 58.44; 59.61; 75.59; 81.26; 96.49; 116.79; 119.48; 127.70; 132.82; 137.53; 145.77. MS: 453 (30, M^+), 435 (72, [$M - H_2O$]$^+$), 378 (100, [$M - H_2O - {}^t$Bu]$^+$).

20-Ethyl 6-O-*demethylthevinol* (**5a**). Compound **4a** was treated as described above to yield **5a** (78%). R_f (MeOH/CH_2Cl_2 1:9) 0.51. IR ($CHCl_3$): 3364 (OH). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.97 (*t*, *Me*CH_2); 1.41 (*m*, MeC*H*$_2$); 1.04 (*s*, Me−C(20)); 2.37 (*s*, MeN); 3.83 (*s*, MeO); 4.37 (*d*, H−C(5)); 5.32 (*d*, H−C(19)); 5.69 (*d*, H−C(18)); 6.53 (*d*, H−C(1)). 6.62 (*d*, H−C(2)). ^{13}C-NMR: 22.41; 24.09; 30.38; 33.25; 33.57; 43.13; 43.24; 43.62; 45.53; 46.73; 52.36; 56.47; 60.03; 75.41; 78.73; 98.13; 112.92; 119.52; 128.38; 130.29; 134.45; 136.64; 141.76; 148.13. MS: 397 (68, M^+), 324 (100, [M − EtC(Me)OH]$^+$). HR-MS: 397.2248 ($C_{24}H_{31}NO_4^+$; calc. 397.2253).

6-O-*Demethylthevinol* (**5b**). Compound **4b** was treated as described above to yield **5b** (64%). R_f (MeOH/CH_2Cl_2 1:9) 0.43. IR ($CHCl_3$): 3333 (OH). ^{1}H-NMR (300 MHz, $CDCl_3$): 1.11 (*d*, Me−C(20)); 2.40 (*s*, MeN); 3.83 (*s*, MeO); 4.19 (br. *q*, H−C(20)); 4.31 (*d*, H−C(5)); 5.39 (*d*, H−C(19)); 5.68 (*d*, H−C(18)); 6.54 (*d*, H−C(1)); 6.63 (*d*, H−C(2)). ^{13}C-NMR: 20.47; 22.50; 26.82; 33.34; 43.29; 43.58; 44.64; 45.59; 47.02; 53.62; 56.38; 60.16; 66.49; 76.61; 97.92; 112.76; 119.60; 129.77; 134.12; 135.74; 141.81; 148.11. MS: 369 (98, M^+), 324 (100, [M − MeCHOH]$^+$). HR-MS: 369.1953 ($C_{22}H_{27}NO_4^+$; calc. 369.1940).

7α-Ethyl-20-methoxy-6-O-*demethyl-6,14*-endo-*ethenotetrahydrothebaine* (**5b**). The C(20)-methyl ether of **4b** was treated as described above to yield **5b** (8%). R_f (MeOH/NH_3/CH_2Cl_2 10:1:89) 0.56. IR ($CHCl_3$): 3367 (OH). ^{1}H-NMR (300 MHz, $CDCl_3$): 1.06 (*d*, Me−C(20)); 2.39 (*s*, MeN); 3.23 (*s*, MeO−C(20)); 3.58 (*s*, MeO−C(3)); 3.60 (br. *q*, H−C(20)); 4.53 (*d*, H−C(5)); 5.34 (*d*, H−C(19)); 5.74 (*d*, H−C(18)); 6.46 (*d*, H−C(1)); 6.60 (*d*, H−C(2)). ^{13}C-NMR: 17.42; 22.41; 26.39; 33.56; 42.66; 43.58; 45.75; 47.32; 52.36; 56.51; 60.19; 73.91; 77.45; 80.55; 95.44; 116.12; 119.63; 127.16; 128.57; 133.11; 134.26; 137.43; 146.87. MS: 383 (100, M^+), 324 (46, [M − MeOCHMe]$^+$). HR-MS: 383.2107 ($C_{23}H_{29}NO_4^+$; calc. 383.2096).

6-O-*Demethylisothevinol* (**5c**). Compound **4c** was treated as described above to yield **5c** (81%). R_f (MeOH/CH_2Cl_2 1:9) 0.48. IR ($CHCl_3$): 3312 (OH). ^{1}H-NMR (300 MHz, $CDCl_3$): 1.14 (*d*, Me−C(20)); 2.41 (*s*, MeN); 3.83 (*s*, MeO); 3.64 (br. *q*, H−C(20)); 4.36 (*d*, H−C(5)); 5.42 (*d*, H−C(19)); 5.73 (*d*, H−C(18)); 6.54 (*d*, H−C(1)); 6.63 (*d*, H−C(2)). ^{13}C-NMR: 15.27; 20.65; 22.47; 29.96; 33.00; 42.84; 43.55; 45.08; 45.58; 46.19; 56.46; 60.14; 65.85; 70.58; 79.30; 97.42; 113.04; 119.64; 129.21; 136.40; 141.87; 147.94. MS: 369 (83, M^+), 324 (100, [M − MeCHOH]$^+$). HR-MS: 369.1921 ($C_{22}H_{27}NO_4^+$; calc. 369.1940).

7α-(Hydroxymethyl)-6-O-*demethyl-6,14*-endo-*ethenotetrahydrothebaine* (**5d**). Compound **6a** was treated as described above to yield a *ca.* 1:1 mixture of the reduction product **4d** (with analyses as described above) and **5d** (66%). R_f (MeOH/CH_2Cl_2 5:95) 0.32. IR ($CHCl_3$): 3328 (OH). ^{1}H-NMR (300 MHz, $CDCl_3$): 2.39 (*s*, MeN); 3.83 (*s*, MeO); 4.37 (*s*, H−C(5)); 5.40 (*d*, H−C(19)); 5.72 (*d*, H−C(18)); 6.55 (*d*, H−C(1)); 6.64 (*d*, H−C(2)). ^{13}C-NMR: 22.59; 28.84; 32.84; 39.95; 43.03; 43.52; 45.59; 46.41; 52.12; 56.43; 60.14; 65.31; 79.21; 97.47; 112.95; 119.66; 129.21; 134.06; 136.00; 141.92; 147.92. MS: 355 (100, M^+), 324 (76, [$M - CH_2OH$]$^+$). HR-MS: 355.1796 ($C_{21}H_{25}NO_4$; calc. 355.1783).

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