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Regioselective Demethylation of Aconitine

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Abstract: **The regioselective demethylation of aconitine has been achieved with Lewis acids. Me_3SiI afforded first 18-*O*-desmethyl- and then 16,18-di-*O*-desmethylaconitine, but $AlCl_3$/NaI gave 16-*O*-desmethylaconitine first. The acetate and benzoate esters survived throughout these procedures. Aconitine decomposed on treatment with BBr_3.**

There are hundreds of norditerpenoid alkaloids from *Aconitum*, *Consolida* and *Delphinium* species.[1,2] These natural products display diverse biological activities,[3] and many of them are highly toxic to mammals[4] as well as to insects.[5] Aconitine (wolfsbane, monkshood) (**1**), which is still used in traditional Chinese medicine,[6] is a norditerpenoid alkaloid and potent neurotoxin isolated from various *Aconitum* species.[2,7] Aconitine (**1**) produces both central and peripheral effects in mammals. It markedly slows the inactivation of sodium channels, inducing a steady depolarisation due to the increase in sodium ion permeability and also decreasing the ion channel selectivity. Lycoctonine (**2**) C-18 esters display significantly different pharmacology from that of aconitine (**1**). For example, lycaconitine (**3a**) and methyllycaconitine (**3b**), from *Delphinium brownii*[8] or *D. elatum*,[9] and not from *Aconitum* species (despite the trivial names), are competitive nicotinic acetylcholine receptor antagonists.[10] These *Delphinium* alkaloids are not potent modulators of voltage-sensitive sodium channels. We wanted to esterify lycoctonine- and aconitine-type alcohols,[11] derived from readily available norditerpenoids, to prepare novel hybrid alkaloids. Therefore, we have investigated the regioselective demethylation of (**1**) and we report, in this *Letter*, our results with Lewis acids.

The rigorous work of Pelletier and colleagues on the chemistry[12] and spectroscopy[13] of *Aconitum* and *Delphinium* alkaloids has included a recent study[14] on the demethylation of delphinine (**4**) and related norditerpenoid alkaloids with HBr in acetic acid. However, to our knowledge, there are no literature data on the demethylation of (**1**). In reports of the demethylation at C-8 in delvestine (**5a**)[15] and delvestidine (**5b**)[16], effected with 3M sulfuric acid at 90°C for 17 h, solvolysis possibly occurs, i.e. exchange of the oxygen atom as well as the methyl group under mild acid hydrolysis.[17] There are also literature precedents for the facile cleavage of the analogous methylenedioxy functional group at C-7-C-8[18] and of C-8 acetate solvolysis.[19]

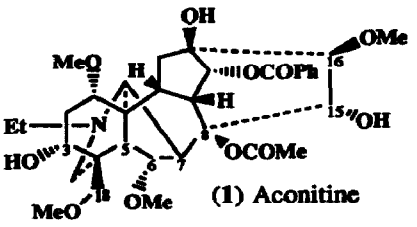
The demethylation of (1) presents the challenge of regioselective bond cleavage in the presence of acetate and benzoate esters. Also present in (1) are a tertiary and two secondary alcohols together with an *N*-ethyl tertiary amine. Under the conditions we chose to employ for *O*-demethylation, no side-reactions should occur at these functional groups. Furthermore, the Lewis acids should not catalyse Wagner-Meerwein type bond migrations or elimination-addition reactions[15,17] such as the alcoholysis of the C-8 acetate in (1).[19]

We anticipated that treatment of (1) with HBr in acetic acid would both demethylate and then acetylate at C-18 and also at C-16 in accordance with Pelletier's observations[14] that (4) gave (6) and (7). Under similar reaction conditions, we found that (1) gave essentially (8) and (9) in equal amounts after isolation by reverse phase HPLC (10%). This result was surprising given the close similarity in structure between delphinine (4) and aconitine (1). We propose that the α-C-3 hydroxyl group present in (1), but not in (4), undergoes ready acetylation in HBr in acetic acid, and that this acetate[11] promotes an intramolecular displacement of the C-18 methoxy functional group by the oxygen atom of the *O*-methyl ether at C-6. Displacement of C-6 methoxy by C-18 methoxy would probably occur with inversion of configuration at C-6. The ^{1}H NMR spectrum shows that H-5 (1.96 ppm, d, 6.4 Hz) is coupled to H-6 (4.45 ppm, d, 6.4 Hz) and H-6 shows no other cross-peak in the COSY-90 spectrum, therefore $J_{H6\text{-}H7} \approx 1$ Hz. We believe that the stereochemistry at C-6 is preserved, as the coupling constant of the H-6 proton, coupled to H-5, is 6.4 Hz which is similar to that found in aconitine (1): H-5 (2.10 ppm, d, 6.7 Hz), H-6 (4.05 ppm, dd, 6.7 and 1.3 Hz) and H-7 (2.84 ppm, d, 1.3 Hz) with C-6-α-OMe in (1). Pelletier and co-workers have reported[14] a cyclic ether of this type with a C-6 α-configuration whilst others have not assigned the stereochemistry of the tetrahydrofuran.[20,21,22] The novel tetrahydrofurans (8) and (9) will also be useful in SAR studies of aconitine (1) and related norditerpenoid alkaloids.

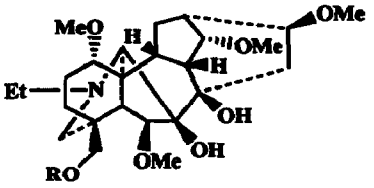
Treatment of (1) with Me_3SiI, in dichloromethane at 25°C, smoothly *O*-demethylated at C-18 to give (10) and then also at C-16 to give (11). This contrasts with the findings of Pelletier and co-workers demethylating (4),[14] who did not isolate any identifiable products from a comparable reaction with Me_3SiI. A ^{1}H NMR time-course study showed that the demethylation at C-18 in (1) was faster than that at C-16. Aliquots of the reaction mixture were removed and quenched with saturated aqueous sodium carbonate solution before extraction of the alkaloids into dichloromethane (60% of the total alkaloids recovered). The NMR spectrum of the crude alkaloid(s) indicated that, after 4 h, no starting material (1) remained. At this time, (10) was the predominant species with some (11) (the ratio was approximately 3:2 from ^{1}H NMR), but, after a further 20 h, (11) was the sole alkaloid product (60%) The acetate and benzoate were both intact.

On reaction of (1) with BBr_3, in anhydrous dichloromethane at either 25°C or -78°C, no identifiable products were isolated, although starting materials were consumed. The strategy of *O*-demethylation was then extended by using NaI with $AlCl_3$, in acetonitrile at 25°C. In this case, the Lewis acid $AlCl_3$ coordinates to oxygen, whilst the iodide attacks the methyl group. Akiyama and co-workers[23] have used NaI/$AlCl_3$ to demethylate an *O*-methyl ether in an inositol analogue, leaving intact ketal and benzoate protecting groups. In a similar manner, (1) gave two products (11) (42%) and (12) (22%) with the benzoate and acetate groups still present. 16-*O*-Desmethylaconitine (12) was not found in the demethylation products when Me_3SiI was used as a reagent and neither could the desired (10) be isolated from the reaction with NaI/$AlCl_3$ nor detected by tlc.

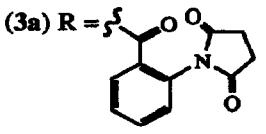
We conclude that, with NaI/$AlCl_3$, the order in which the C-16 and C-18 methoxy groups begin to be demethylated is reversed compared to that found with Me_3SiI. However, the di-*O*-desmethyl product (**11**) is always formed. The C-16 methoxy functional group has a characteristic low field resonance (3.76 ppm) in the ^1H NMR spectrum of these alkaloids, at significantly lower field than the other three methoxy groups whose proton resonances are close enough (3.17-3.30 ppm) to cross over as a function of small changes in the substitution pattern of the carbon skeleton. Therefore, it can be rapidly determined, by ^1H NMR spectroscopy, whether the C-16 methoxy group is still present in the molecule. The demethylation sequences provided by Me_3SiI and NaI/$AlCl_3$ provide convenient and practical synthetic methods for converting the unreactive *O*-methyl ethers of (**1**) into the alcohol functional groups with a degree of regiochemical control. However, with HBr/AcOH as the demethylating reagent, tetrahydrofuran formation accompanies acetylation and hydrolysis of the esters (**8**) and (**9**) is then required to produce the corresponding free alcohols. Control of the reaction time, when Me_3SiI was the Lewis acid, 4 h at 25°C, gave predominantly 18-*O*-desmethylaconitine (**10**) (34%) and (**11**) (25%) which will be useful in synthesizing new alkaloid derivatives.[11]



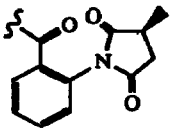
(**1**) Aconitine



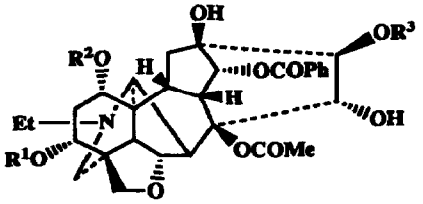
(**2**) R = H



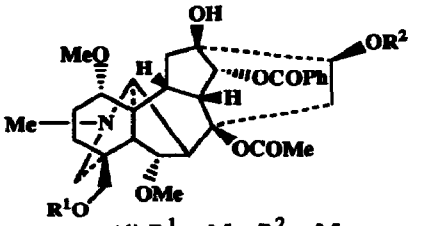
(**3a**) R =



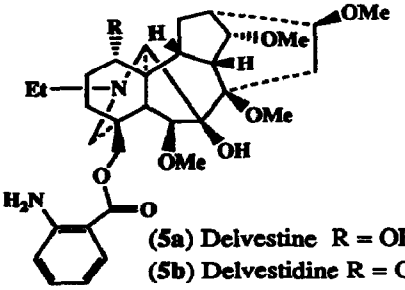
(**3b**) R =



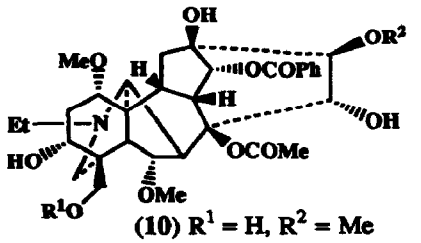
(**8**) R^1 = Ac, R^2 = Me, R^3 = Ac
(**9**) R^1 = Ac, R^2 = Ac, R^3 = Ac



(**4**) R^1 = Me, R^2 = Me
(**6**) R^1 = Ac, R^2 = Me
(**7**) R^1 = Ac, R^2 = Ac



(**5a**) Delvestine R = OH
(**5b**) Delvestidine R = OMe



(**10**) R^1 = H, R^2 = Me
(**11**) R^1 = H, R^2 = H
(**12**) R^1 = Me, R^2 = H

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