Pergamon

Tetrahedron Letters, Vol. 35, No. 20, pp. 3371-3374, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(94)E0520-8

Regioselective Anthranoylation of Demethylated Aconitine: Novel Analogues of Aconitine, Inuline and Methyllycaconitine

David J. Hardick, Ian S. Blagbrough*, Susan Wonnacott¶ and Barry V. L. Potter

Department of Medicinal Chemistry, School of Pharmacy and Pharmacology, and ¶School of Biology and Biochemistry, University of Bath, Claverton Down, Bath BA2 7AY, U.K.

Abstract: **The regioselective acylation of 18-*O*-desmethylaconitine has been achieved with isatoic anhydride to afford the corresponding anthranilate ester, an analogue of inuline. The aniline nitrogen was then incorporated into an *S*-methylsuccinimide moiety, to afford a novel methyllycaconitine/aconitine hybrid alkaloid.**

Many naturally occurring[1,2,3] norditerpenoid alkaloids display important biological activities and semi-synthesis has been used to prepare several analogues of these bases.[4,5,6] There is an urgent requirement to identify selective pharmacological responses to such alkaloids in order to delineate structure-activity relationships (SAR) and to dissect, wherever possible, toxic from beneficial activities. Thus, aconitine (**1**) is a potent neurotoxin[6], acting by modulating voltage-sensitive sodium channels, but the related norditerpenoid alkaloid methyllycaconitine (MLA) (**2**) is the most potent, non-proteinaceous, neuronal nicotinic acetylcholine receptor antagonist yet found.[7]

Using regioselectively demethylated (**1**)[8], we have prepared novel analogues of inuline (**3**) and then of MLA (**2**). In this *Letter*, we present an efficient entry to these analogues by regioselective anthranoylation of (**12**) with isatoic anhydride (**13**), and conversion of the corresponding aniline in anthranilate (**14**) into the homochiral *S*-methylsuccinimide (**20**). This protocol will also have application in the preparation of analogues of the imine anhweidelphinine and of the acetate nudicauline.[2,3]

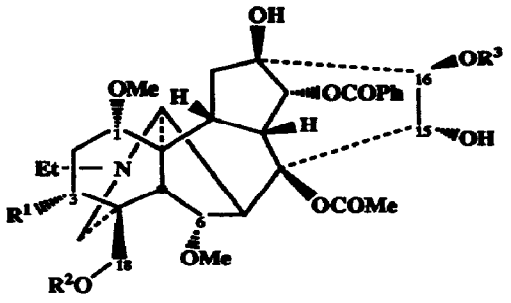
16,18-Di-*O*-desmethylaconitine (**4**)[8] was reacted with (**13**), in DMF at 70°C, to afford (45%) a mono-anthranoyl ester after column chromatography (SiO_2, 5% $MeOH/CH_2Cl_2$). However, detailed inspection of the ^1H NMR spectrum (270 MHz) revealed that the anthranilate was the ester (**5**) of the secondary alcohol at C-3 and not of the desired C-18 neopentyl alcohol. In particular, there was a characteristic doublet of doublets for H-3 at low field (5.10 ppm, 12.5 and 5.1 Hz) whilst H-18 was assigned to a multiplet at 3.11-3.25 ppm which also contained the methoxy signals (at 3.21 and 3.24 ppm) of C-1 and C-6.

Typically, the protons assigned to the AB pattern of the C-18 methylene group in (**14**), when it is anthranoylated, resonate at lower field (4.26-4.48 ppm) *vide infra*. The high reactivity of the C-3 secondary alcohol has previously been reported with respect to facile acetate ester formation[5], but we cannot entirely discount C-18 hydroxyl acetylation followed by 1,3 acyl group migration via a six membered ring. Such acyl transfers have precedent in sugar[9] chemistry and as 1,2-acyl transfers in inositol[10] chemistry.

In order to prepare the corresponding MLA/aconitine hybrid analogues of (**2**) and (**3**), the C-3 hydroxyl of aconitine (**1**) needed to be temporarily protected or even removed. Formation of (**6**) and subsequent demethylation using Me_3SiI, in dichloromethane at 25°C, gave (**7**), (**8**) and (**9**) in a ratio 1:3:3 respectively. The C-3 acetate prevented the desired *O*-demethylation at C-18 which had previously been so facile[8] with a hydroxyl functional group at C-3. We therefore decided to remove completely the secondary alcohol from C-3 in (**1**). This reduction can be efficiently accomplished using a Barton radical (tin hydride) deoxygenation procedure[11], and 3-deoxyaconitine (**10**) was prepared by this protocol following the procedure of Pelletier and his co-workers.[12] Thus, the imidazole thiocarbamate (**11**), prepared in 1,2-dichloroethane, 4 h at 80°C, (85%), was treated with nBu_3SnH, in toluene at 80°C, to give (**10**) (76%).[12]

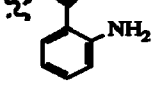
Regioselective demethylation of (**10**) was achieved smoothly with Me_3SiI, 10 h at 25°C, to reveal the desired substituted neopentyl alcohol in (**12**) (48%). Reaction with (**13**), 17 h at 75°C, gave the anthranilate (**14**) regioselectively (45%), a novel inuline (**3**) analogue, with no loss of acetate or benzoate. The ^1H NMR spectroscopic evidence (270 MHz) for this regioselective ester formation includes the H-18 methylene signals of (**14**) resonating at low field (4.26 ppm, d, 10.4 Hz) and (4.44-4.48, m, H-18 and H-15), whilst the comparable signals of aconitine (**1**) resonate at 3.50 and 3.63 ppm. The ^{13}C NMR spectrum was particularly useful in determining the site of demethylation, as there was a significant upfield shift of the carbon attached to the *O*-methyl ether. Thus, in 3-deoxyaconitine (**10**) C-18 resonates at 80.2 ppm in the *O*-methyl ether, whilst in the corresponding primary alcohol (**12**) this signal has moved upfield to 71.2 ppm. With respect to this primary alcohol, esterification at C-18 produced no appreciable change in chemical shift at C-18 as (**14**) also shows a chemical shift of 71.2 ppm which we assign to C-18. This consistency in the chemical shift of C-18 on esterification is comparable with the similar values of the methylene signals found in ethanol (58.2 ppm) and in ethyl acetate (60.3 ppm).

From the initial demethylation of (**10**), some (**15**) (19%) was also recovered which was reacted with an equivalent of (**13**) in the usual manner. From an inspection of the ^1H NMR spectrum, some dianthranoylation had also occurred to give (**16**). The low field signal at 5.38 ppm (d, 5.7 Hz), which resonated near to the other methine ester proton signal of H-14 (5.06 ppm, d, 4.9 Hz), was attributed to H-16 and not to H-15. The H-15 proton still resonated at 4.70 ppm (dd, 5.7 and 3.1 Hz) coupling through oxygen to the C-15-OH (d, 4.32 ppm, 3.1 Hz) and was similar to that seen in (**1**).[13] Furthermore, from our studies of the acetylation of (**4**), using two equivalents of acetic anhydride in dichloromethane and catalysed by 4-dimethylamino-pyridine, we know that the major product from this reaction is the C-16,18-diacetate.



(1) $R^1 = OH$ $R^2 = Me$ $R^3 = Me$

(4) $R^1 = OH$ $R^2 = H$ $R^3 = H$

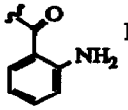
(5) $R^1 =$  $R^2 = H$ $R^3 = H$

(6) $R^1 = MeCOO$ $R^2 = Me$ $R^3 = Me$

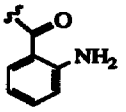
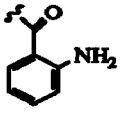
(10) $R^1 = H$ $R^2 = Me$ $R^3 = Me$

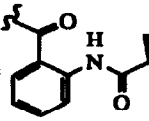
(11) $R^1 =$  $R^2 = Me$ $R^3 = Me$

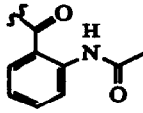
(12) $R^1 = H$ $R^2 = H$ $R^3 = Me$

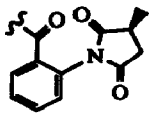
(14) $R^1 = H$ $R^2 =$  $R^3 = Me$

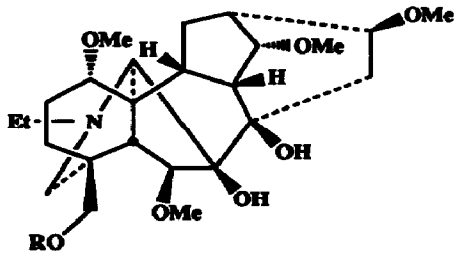
(15) $R^1 = H$ $R^2 = H$ $R^3 = H$

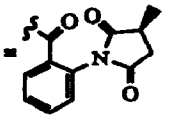
(16) $R^1 = H$ $R^2 =$  $R^3 =$ 

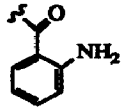
(18) $R^1 = H$ $R^2 =$  $R^3 = Me$

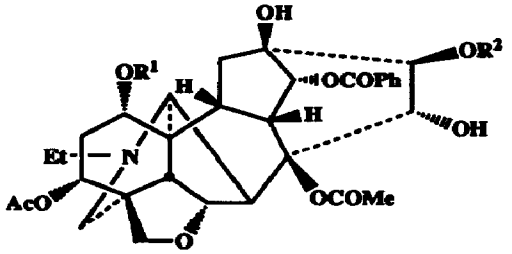
(19) $R^1 = H$ $R^2 =$  $R^3 = Me$

(20) $R^1 = H$ $R^2 =$  $R^3 = Me$



(2) R = 

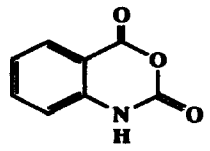
(3) R = 



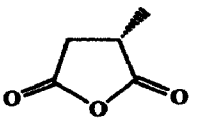
(7) $R^1 = Me$ $R^2 = Me$

(8) $R^1 = Me$ $R^2 = H$

(9) $R^1 = H$ $R^2 = H$



(13)



(17)

Reaction of (14) with homochiral *S*-(-)-methylsuccinic anhydride (17) (3.4 equiv.), in dichloromethane at 25°C, afforded the mixed half-acid amides (18) and (19) which were not isolated, but were both converted directly into the corresponding homochiral succinimide (20) on treatment with carbonyl diimidazole (2.8 equiv.) at 25°C. Purification on SiO_2 (5% MeOH/CH_2Cl_2) gave pure (20) (51%) as a colourless, amorphous solid (satisfactory ^1H, ^{13}C NMR and mass spectra). These novel semi-synthetic norditerpenoid alkaloids (14) and (20) should be useful in determining the respective role(s) of the anthranilate and the succinimide moieties for eliciting binding (haptophores) resulting in the selective biochemical pharmacology of aconitine (1) and MLA (2) at protein receptors. Such SAR studies are in progress in our laboratories.

Acknowledgements: We acknowledge the financial support of The Wellcome Trust (Project Grant 036214). We wish to express our gratitude to Dr MG Rowan and Ms PA Coates (University of Bath) and to Dr T Lewis (Zeneca Agrochemicals) for their helpful comments, advice and encouragement throughout these studies. BVLP is a Lister Institute Research Professor.

REFERENCES

1. Pelletier, S. W.; Mody, N. V.; Joshi, B. S.; Schramm, L. C. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W. Ed.; J. Wiley and Sons: New York, **1984**, *2*, pp. 205-462; Pelletier, S. W.; Joshi, B. S. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W. Ed.; Springer-Verlag: New York, **1991**, *7*, pp. 297-564.
2. Yunusov, M. S. *Natural Product Reports* **1991**, *8*, 499-526.
3. Yunusov, M. S. *Natural Product Reports* **1993**, *10*, 471-485.
4. Ross, S. A.; Pelletier, S. W. *Heterocycles* **1990**, *31*, 671-675.
5. Pelletier, S. W.; Ross, S. A. *Heterocycles* **1991**, *32*, 1307-1315.
6. Benn, M. H.; Jacyno, J. M. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S.W. Ed.; J. Wiley and Sons: New York, **1983**, *1*, pp. 153-210.
7. Wonnacott, S.; Albuquerque, E. X.; Bertrand, D. *Methods in Neurosciences* **1993**, *12*, 263-275.
8. Blagbrough, I. S.; Hardick, D. J.; Wonnacott, S.; Potter, B. V. L. *Tetrahedron Lett.* **1994**, *35*, preceding *Letter*.
9. Chaplin, D.; Crout, D. H. G.; Bornemann, S.; Hutchinson, D. W. *J. Chem. Soc. Perkin 1*, **1992**, 235-237.
10. Meek, J. L.; Davidson, F.; Hobbs, J. *J. Amer. Chem. Soc.* **1988**, *110*, 2317-2318.
11. Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc. Perkin 1* **1975**, 1574-1585.
12. Kulanthaivel, P.; Pelletier, S. W. *Tetrahedron* **1988**, *44*, 4313-4320.
13. Joshi, B. S.; Wunderlich, J. K.; Pelletier, S. W. *Can. J. Chem.* **1987**, *65*, 99-103.

(*Received in UK* 31 *January* 1994; *revised* 4 *March* 1994; *accepted* 10 *March* 1994)