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A Synthesis of Morphine-6-glucuronide

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Abstract: A practical synthesis of morphine-6-glucuronide from 3-acetylmorphine and methyl 2-α-bromo-3,4,5-tri-*O*-acetylglucuronate is described. Similar syntheses of codeine-6-glucuronide, codeine-6-glucoside and morphine-6-glucoside are also documented

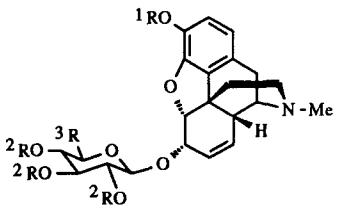
The morphine metabolite morphine-6-glucuronide (M6G, 1) is a more effective and longer lasting analgesic drug than morphine (2) with fewer side effects.[1] Unfortunately morphine is also metabolised to morphine-3-glucuronide (M3G, 3), a compound which antagonises the analgesic effect of morphine. Since M3G is formed in greater abundance than M6G, there is much interest in using the latter, rather than morphine, as a pain killing drug.[2]

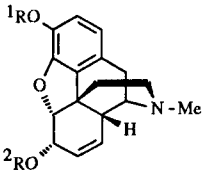
M6G has been obtained through the selective hydrolytic cleavage of morphine-3,6-diglucuronide (4), using β-glucuronidase as a catalyst,[3] but an efficient synthesis involving direct monocoupling between morphine, or codeine, and a glucuronic acid derivative has not yet been fully realised.

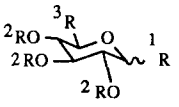
Syntheses of M6G and codeine-6-glucuronide (5) have been reported by Yoshimura *et al.*,[4] but we have been unable to reproduce the methods described and to obtain the final products in a pure form. Similarly, a patent application describes,[5] as the key step, a reaction between the imidate (6) and 3-acetylmorphine (7). The yield of the 'adduct glycoside' is claimed as 63%, and it is stated that this may be converted into M6G by treatment with 5% NaOH and crystallisation of the product from HOAc. However, although we can routinely prepare the adduct by this route in yields of 10-15%, the M6G obtained from it cannot be purified by crystallisation, as stated, and it is contaminated with NaOAc. The use of other bases presents similar difficulties and, since the glucuronide is highly water soluble, this constitutes a major problem if the method is to be adopted on a large scale.

We have significantly improved the coupling procedure by refluxing (7) (240 mg) in toluene (10 cm^3) with the 2α-bromoglucuronate (8) (600 mg) in the presence of silver carbonate on Celite (1:1)[6] (2.5 g), which was added in 0.5 g portions over 3h. This gives the 'adduct' (9) (210 mg, 45%), which can be successfully deprotected by either treatment with 0.1M NaOH aq., and then neutralising with HOAc (20mM), or by heating it in H_2O (20mM) with Amberlite IRA410 resin for 10 h., prior to treatment with 0.1M NaOH, and evaporation. In both cases the residue is redissolved in the minimum of 1% MeCN in H_2O and eluted through a Waters Sep-pak C-18 cartridge with this solvent mixture. Initial fractions are rich in inorganic salts and later ones give pure M6G in 85% yield.

This route has also been applied to the syntheses of the glycosides (5) [from codeine (10) and (8)], (11) [from (7) and 2α-bromo-tetra-*O*-acetylglucose (12)], and (13) [from (10) and (12)], in overall yields close to those for M6G. The weak point in our route is the use of Celite, which appears to promote the decomposition of the 'adducts'. We have tried many other supports and methods but, so far, without improvement, for example, a commonly recommended means of activating a pyranose is *via* the imidate derivative,[7] however, in our hands a reaction between cyclohexanol and the imidate (14) gives only a 69:31 α:β-selectivity and only a 12% combined yield of the corresponding 'adducts'. Furthermore, no coupling is observed between this activated sugar and codeine, whereas in the reaction of 2-[2,3,4,6-tetra--*O*-benzyl-α,β-glucopyranosyl]oxy 2-pyrimidine (15)[8] and codeine both α- and β-'adducts' are formed in equal amounts, and in only 35% yield.







1, ^1R=^2R=H;^3R=CO_2H

2, ^1R=^2R=H;^3R=CO_2Me

6, ^1R=OC(NH)CCl_3;^2R=$(Me)_2CHCO$

5, ^1R=Me;^2R=H;^3R=CO_2H

3, ^1R=β-D-glucuronyl;^2R=H

8, ^1R=α-Br; ^2R=Ac; ^3R=CO_2Me

9, ^1R=^2R=Ac;^3R=CO_2Me

4, ^1R=^2R=β-D-glucuronyl

12, ^1R=α-Br; ^2R=Ac; ^3R=CH_2OAc

11, ^1R=^2R=H;^3R=CH_2OH

7, ^1R=Ac;^2R=H

14, ^1R=OC(NH)CCl_3; ^2R=Bn; ^3R=CO_2Me

13, ^1R=Me;^2R=H;^3R=CH_2OH

10, ^1R=Me;^2R=H

15, ^1R=O-2-pyrimidate;^2R=Bn;^3R=CH_2OBn

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References:

1. Osborne, R.; Thompson, P; Joel, S.; Trew, D.; Patel, N.; Slevin, M; *Br. J. Clin. Pharm.*, 1992, *34*, 130.
2. Frances, B; Gout, R.; Monsarrat, B.; Cros, J.; Zajac, J-M.; *J. Pharm. Exp. Ther.*, 1992, *262*, 25.
3. Brown, R.T.; Carter, N.E.; Scheinmann, F.; Turner, N.J.; *Tetrahedron Letters*, 1995, *36*, 1117.
4. Yoshimura, H.; Oguri K.; Tsukamoto, H.; *Chem. Pharm. Bull.*, 1968, *16*, 2114.
5. Salford Ultrafine Chemicals and Research Ltd. PCT/GB92/01449 (1993).
6. Schneider, G.; Sembdner, G.; Schreiber, K.; Phinney, B.O.; *Tetrahedron*, 1989, *45*, 1355.
7. Schmidt, R.R.; Grundler, G.; *Synthesis*, 1981, 885.
8. Vankar, Y.D.; Vankar, P.S.; Behrendt.; Schmidt, R.R.; *Tetrahedron*, 1991, *47*, 9985.

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