Carbohydrate Research, 190 (1989) c11–c13
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

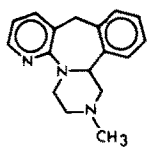
Preliminary communication

Synthesis of a novel carbamate-glucuronide

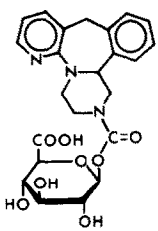
FRANS M. KASPERSEN, CONSTANT A. A. VAN BOECKEL, LEON P. C. DELBRESSINE, ANNEMIEK KOTEN, PETER L. JACOBS, AND CAREL W. FUNKE
Akzo Pharma Division, Organon International BV, P.O. Box 20, 5340 BH Oss (The Netherlands)
(Received January 23rd, 1989; accepted for publication, March 24th, 1989)

Glucosiduronic acids (glucuronides) are well known as phase II metabolites of xenobiotics, usually of phenols, alcohols, and acids, whereas those of hydroxylamines[1] and tertiary amines[2] (quaternary *N*-glucosiduronic acids) have been isolated more recently. In studies of the metabolism of tetracyclic compounds such as Org 3770 (**1**) in the mouse, a new type of glucuronide[3] was identified on the basis of n.m.r. (^1H, ^{13}C), i.r., and f.a.b.-m.s. data as the carbamate **2**. A similar glucuronide (**4**) has been isolated by Straub *et al.*[4] from the urine of dogs treated with SKF 86466 (**3**).

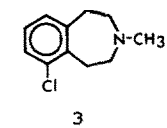
As part of a program on the development of routes of synthesis for glucuronides[5,6], we now report the synthesis of **2**.



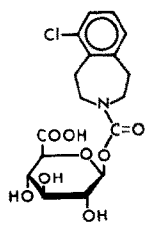
1



2



3



4

Reaction of racemic 1,2,3,4,10,14b-hexahydropyrazino[2,1-a]pyrido[2,3-c]benzazepine (**5**) with 1,1-dicarbonyldi(1,2,4-triazole) (2 equiv.) in tetrahydrofuran at room temperature for 1 h gave **6** in quantitative yield, m.p. 75° (dec.). ^1H-N.m.r. data ($CDCl_3$): δ 8.85 and 8.00 (triazole H-3 and H-5). E.i.-mass spectrum: *m/z* 346 ($M^{+\cdot}$). Reaction of **6** with methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranuronate[7] in the presence of NaH (1 equiv.) in CH_2Cl_2 at room temperature for 48 h gave <3% of the glucuronides. However, reaction of **6** with benzyl 2,3,4-tri-*O*-benzyl-α,β-D-glucopyranuronate (**9**) in the presence of NaH (1 equiv.) in

0008-6215/89/$ 03.50

TABLE I

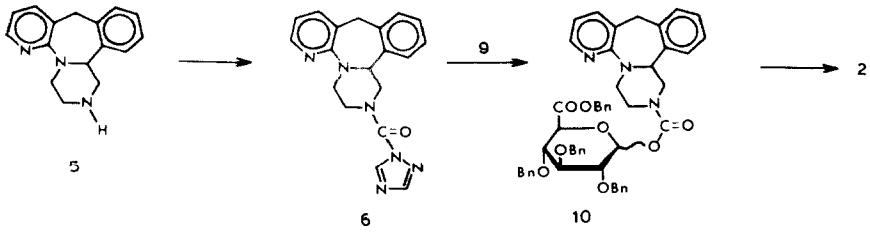
SPECTRAL PARAMETERS OF THE CARBAMATE-GLUCURONIDES **10** AND **2**

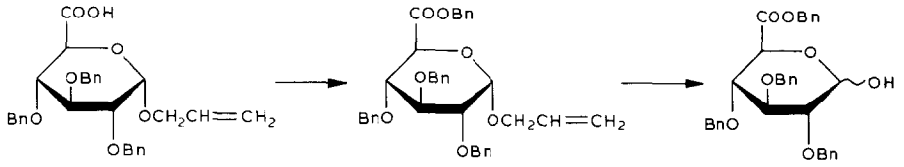
	10[a]	α**2**[b]	β**2**[b]
I.r. data (cm^{-1})			
Carbamate-carbonyl	n.m.[c]	1698	1698
Carboxylate-carbonyl		1620	1615
^{1}H-N.m.r. (δ in p.p.m., J in Hz; CD_3OD)			
H-1	6.40 (α)	6.15 (3.4)	5.48 (7.5)
	5.75 (β)		
Pyridine protons	6.72	6.84	6.84
	~7.4	7.47	7.48
	8.10	8.07	8.07
F.a.b.-m.s.			
Positive mode (m/z)	832 $(M + H)^+$	494 $(M + Na)^+$	494 $(M + Na)^+$
		472 $(M + H)^+$	472 $(M + H)^+$
		296	296
		252	252
Negative mode (m/z)	n.m.[c]	470 $(M - H)^-$	470 $(M - H)^-$
		294	294

[a]Mixture of 4 diastereomers. [b]Mixture of 2 diastereomers. [c]Not measured.

CH_2Cl_2 at $-20°$ followed by slow heating to room temperature (total reaction time, 48 h) gave **10** (45%) with an $\alpha\beta$-ratio of 1:1.5. The spectral data are summarized in Table I. The glucopyranuronate **9** was synthesized as follows. Reaction of allyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranosiduronic acid[5] (**7**) with benzyl iodide (4 equiv.) and $KHCO_3$ (3 equiv.) in *N,N*-dimethylformamide for 1 h at room temperature gave **8** [e.i.-mass spectrum: m/z 503 (22%, $M^{+\cdot} - 91$)] which was converted without purification into **9** (65%) by reaction with sodium acetate (3 equiv.) and $PdCl_2$ (1.2 equiv.) in acetic acid for 16 h at room temperature under nitrogen. Compound **9** ($\alpha\beta$-ratio 7:3) had m.p. 130–132°, $[\alpha]_D$ +7.2° (*c* 1, dichloromethane); ν_{max} 3245 (OH) and 1732 cm^{-1} (C=O). D.c.i.(NH_3)-mass spectrum: m/z 572 $(M + NH_4)^+$.

The glucuronide derivative **10** was characterized by ^{1}H-n.m.r. and m.s. data (Table I). Transfer hydrogenation by reaction of **10** with Pd/C (10%, 1 equiv.) in refluxing ethanol–cyclohexene (1:2) gave **2**, in quantitative yield, which was separated into two pairs of diastereomeric α- and β-glucuronides by h.p.l.c. [phenyl





7 8 9

Bondapak with 0.1M ammonium acetate (pH 4.2)–acetonitrile]. The spectral data are summarized in Table I. The synthetic β-glucuronide **2** was identical in h.p.l.c. and spectral parameters to the metabolite isolated from the mouse.

REFERENCES

1 P. L. JACOBS, L. P. C. DELBRESSINE, F. M. KASPERSEN, AND G. J. H. SCHMEITS, *Biomed. Environ. Mass Spectrom.*, 14 (1987) 689–697.
2 J. P. LEHMAN, C. FENSELAU, AND J. R. DEPAULO, *Drug Metab. Dispos.*, 11 (1983) 221–225.
3 L. P. C. DELBRESSINE, M, E. G. MOONEN, AND H. M. VAN DEN WILDENBERG, unpublished results.
4 K. STRAUB, M. DAVIS, AND B. HUANG, *Drug Metab. Dispos.*, 16 (1988) 359–366.
5 C. A. A. VAN BOECKEL, L. P. C. DELBRESSINE, AND F. M. KASPERSEN, *Recl. Trav. Chim. Pays Bas*, 104 (1985) 259–265.
6 F. M. KASPERSEN AND C. A. A. VAN BOECKEL, *Xenobiotica*, 17 (1987) 1451–1471.
7 J. FIANDOR, M. T. GARCIA-LOPEZ, F. G. DE LAS HERAS, AND P. P. MENDEZ CASTRILLON, *Synthesis*, (1985) 1121–1123.