PYRIDINDOLOL ANALOGUES. SYNTHESIS OF 3-HYDROXY-METHYL-1-(POLYHYDROXYALKYL)-β-CARBOLINES

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Abstract - Peracetylated (D)-glucose, (D)-galactose, (D)-ribose, (L)-arabinose and (D)-xylose have been subjected to a Pictet-Spengler cyclisation with methyl tryptophanate to give β-carboline derivatives which have been converted to a series of pyridindolol analogues.

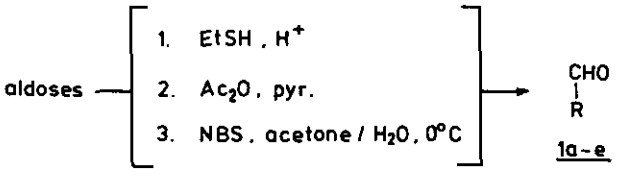
The biological properties and the natural occurrence of β-carboline derivatives such as pyridindolol[2] (a β-galactosidase inhibitor), ethyl β-carboline-3-carboxylate[3a,b] (a potent inhibitor of the specific binding of ^{3}H-diazepam to its brain receptor) and the 1-furanyl-β-carboline derivatives flazin[4a-e] and YS[5] - in the Japanese soy sauce - stimulates interest in the synthesis and biological activity evaluation of new β-carboline derivatives possessing analogous structures. Of particular interest as target compounds in this connection, appeared to be pyridindolol analogues in which the C(1)-position was substituted by polyhydroxylalkyl residues. In this communication we report an approach to the synthesis of this class of compounds.

The synthesis of pyridindolol has been achieved via a scheme which, in the critical step, involves the coupling of a tryptophan derivative with a hydroxylated three carbon aldehyde[6] or its equivalent[7]. The construction of the β-carboline system by a Pictet-Spengler reaction bears analogy to the related step in the biosynthesis of a variety of alkaloids[8]. In view of this, we envisioned the synthesis of the desired pyridindolol analogues via a biomimetic approach utilizing the Pictet-Spengler condensation of tryptophan with suitably protected aldoses.

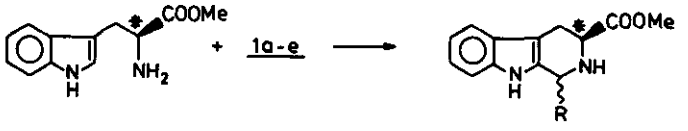
The required protected aldoses 1a - e, which have been described earlier, were prepared from the respective carbohydrates in three steps[9] (Scheme I). It should be mentioned that in our hands the regeneration of the aldehyde function from the thioacetal proceeded better upon treatment of the latter with N-bromosuccinimide[10].

Although the application of the Pictet-Spengler reaction to the syntheses of β-carbolines has been well-documented, only few examples involving aldoses have been reported. Classical reaction conditions employing acid catalysis frequently result in low yields of the desired β-carbolines; the reaction being accompanied by extensive, elimination and rearrangement processes[11]. MacLean[12] has recently shown that dopamine hydrochloride reacts with D-glucose and 2,5-anhydro-D-mannose to give the expected esoquinoline derivatives. On the other hand, tryptamine hydrochloride and histamine, while undergoing a Pictet-Spengler condensation with 2,5-anhydro-D-mannose, do not react with D-glucose. Cook et al.[6] have demonstrated that acidic conditions are not-essential for Pictet-Spengler cyclizations and have taken advantage of this in their synthesis of pyridindolol[6].

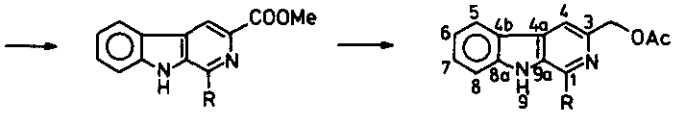
The reaction of aldoses 1a - e with methyl tryptophanate 2, in the absence of acid, was found to be critically dependent upon the nature of the solvent. Orientation experiments showed that whereas benzene or tetrahydrofuran were not ideal solvents for reaction for the whole series of carbohydrates 1a - e; it was found that a mixture of benzene and tetrahydrofuran (1 : 1) was able to affect the cyclization reaction in all cases to give the corresponding Pictet-Spengler products 3a - e[13] in practical yields (∿ 45%). Although 3a - e could be readily oxidized to crystalline 4a - e (DDQ, THF,



1a-e



2 3a-e



4a-e 5a-e

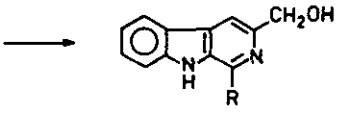
a R = 1'-OAc, AcO-2', 3'-OAc, 4'-OAc, 5'-OAc

b R = AcO-, AcO-, OAc, OAc

c R = OAc, OAc, OAc, OAc

d R = AcO-, OAc, OAc

e R = AcO-, AcO-, OAc



6a-e

a R = HO-, OH, OH, OH

b R = HO-, HO-, OH, OH

c R = OH, OH, OH, OH

d R = HO-, OH, OH

e R = HO-, HO-, OH

RT), after isolation, it was experimentally advantageous to oxidize the mixtures containing 3a - e, without isolation of the reduced β-carbolines. This procedure provided 4a - e in an overall yield of 50-60%. The structures of 4a - e are assigned on the basis of their characteristic ^{1}H NMR spectra (Table I, vide Experimental).

Reduction of the ester function in 4a - e was achieved by reaction with $LiBH_4$ (RT) and the thereupon formed boron complexes were most conveniently worked up by consecutive treatment with (i) acid (aq. HCl), (ii) methanol (repeated addition and evaporation of the solvent) and (iii) reacetylation (Ac_2O, pyridine) to yield polyacetates 5a - e. Hydrolysis of 5a - e (NaOMe/MeOH, RT) provided the pyridindolol analogues 6a - e (∿ 60%) as amorphous solids. The structures of these products were attested by MS, ^{1}H-NMR and ^{13}C-NMR spectra (Table II and III). In particular the ^{13}C-NMR spectra were characteristic and highly informative. Results on the activity of the synthesized analogues towards β-galactosidase will be presented elsewhere.

EXPERIMENTAL

β-Carboline Esters 4a - e. General Procedure

In a typical experiment, a mixture of the peracetylated aldose (1a, 8 mMol) in dry benzene (100 ml) and methyl tryptophanate (prepared from the corresponding hydrochloride, 2.00 g, 7.85 mMol) in dry THF (100 ml) was refluxed for 12 h. After evaporating the solvents the residual diastereomer mixture (3a) was dissolved in dry THF (200 ml) and allowed to react with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 3.93 g, 17.3 mMol) by stirring for 2 days at room temperature. After evaporating the solvent, the oily product was dissolved in EtOAc (250 ml) and treated with ammonia (100 ml, 25%) by stirring for 5 min. Subsequently, the organic layer was separated, washed with water (2x 50 ml), dried over Na_2SO_4 and the solvent evaporated. Chromatography of the residue on silica gel column (eluents: EtOAc/Pet. ether 60-80°C, 7/3) yielded the β-carboline derivative 4a.

Pyridindolol analogues 6a - e. General Procedure

Illustrative example: the β-carboline derivative 4a (0.59 g, 1.15 mMol) was added to a solution of $LiBH_4$ (0.25 g, 11.5 mMol) in dry THF (50 ml) and the mixture stirred for 1.5 h at room temperature. After quenching the reaction with MeOH (5 ml), the solvents were removed, the residue dissolved in MeOH and the solution acidified (5% HCl) to pH $\leq$ 5. Thereafter, the solvent was evaporated and the resulting product subjected repeatedly (5x) to dissolution in MeOH (15 ml), stirring (1 min) and removal of the solvent. Following this treatment, the residue was dried (1 h, 50°C, 0.1 mm Hg) and subsequently acetylated to 5a by stirring with Ac_2O (1.27 ml), pyridine/p-dimethylaminopyridine (15 ml/catalytic amount) for 16 h at room temperature. After evaporation of the solvents, EtOAc (150 ml) was added, the organic layer washed consecutively with sat. $NaHCO_3$ (3x 25 ml) and sat. NaCl (25 ml) and then dried over Na_2SO_4. Removal of the solvents and chromatography of the residue on silica gel yielded 5a as an oil. Treatment of the latter (0.93 g, 1.8 mMol) with MeOH (5 ml) containing a catalytic amount of sodium (stirring overnight, RT) yielded 6a as an amorphous product which was washed with ether and dried.

Table I. Data on β-carboline esters 4a - e.

	4a	4b	4c	4d	4e
mp	190-194°C	204-207°C	oil	120°C	oil
yield	55%	52%	61%	49%	58%
δ $^1H(CDCl_3)$					
H-4	8.85 s	8.79 s	8.81 s	8.83 s	8.82 s
H-5	8.17 d	8.14 d	8.16 d	9.15 d	8.16 d
	(7.8)	(8.0)	(7.9)	(7.9)	(7.8)
H-6	7.4 m	7.3 m	7.4 m	7.3 m	7.4 m
H-7	7.6 m	7.6 m	7.6 m	7.6 m	7.6 m
H-8	7.6 m	7.6 m	7.6 m	7.6 m	7.6 m
H-9	9.46 s	9.10 s	9.74 s	9.41 s	9.22 s
H-1'	6.50 d	6.52 d	6.53 d	6.54 d	6.63 d
	(7.5)	(2.9)	(4.4)	(7.8)	(3.9)
H-2'	6.26 dd	5.84 dd	5.82 dd	6.12 dd	5.91 dd
	(3.6, 7.5)	(2.9, 9.7)	(4.4, 6.1)	(4.0, 7.8)	(3.9, 8.4)
H-3'	5.30 dd	5.63 dd	5.5 m	5.1 m	5.4 m
	(3.7, 7.0)	(2.0, 9.7)			
H-4'a	5.2 m	5.3 m	4.23 dd	4.11 dd	4.12 dd
			(5.8, 12.3)	(6.6, 11.7)	(5.3, 12.4)
H-4'b	-	-	4.48 dd	4.34 dd	4.30 dd
			(2.9, 12.4)	(5.1, 11.7)	(2.8, 12.4)
H-5'a	4.0 m	3.86 dd	-	-	-
		(7.6, 11.3)			
H-5'b	4.22 dd	4.30 dd	-	-	-
	(3.4, 12.8)	(5.0, 11.5)			
$\underline{OCH_3}$	4.02 s	4.02 s	3.99 s	4.00 s	4.03 s
OAc	2.0 m	2.0 m	2.0 m	2.0 m	2.0 m

IR ($CHCl_3$) spectra of all the compounds, show strong bands in the region ∿ 1740 cm^{-1}.

Table II. Data on pyridindolol analogues 6a - e[a].

	6a	6b	6c	6d	6e
Yield	71%	65%	46%	65%	60%
MS (E.I.)	348	348	318	318	318
δ $^1H(D_6$-DMSO)					
H-4	8.03 s	8.02 s	7.97 s	7.93 s	8.03 s
H-5	8.19 d (7.7)	8.22 d (7.8)	8.13 d (7.8)	8.10 d (7.8)	8.21 d (7.8)
H-6	7.2 m	7.2 m	7.0 m	7.0 m	7.2 m
H-7	7.5 m	7.5 m	7.4 m	7.3 m	7.5 m
H-8	7.63 d (8.0)	7.64 d (8.2)	7.55 d (8.1)	7.53 d (8.2)	7.66 d (8.1)
H-9	-	11.1 s	-	-	-
H-1'	5.12 d (5.2)	5.34 s	5.29 d (4.9)	5.23 d (5.7)	5.31 s
H-2'	4.12 d (5.0)	3-5 m	3-4.5 m	3.72 dd (2.3, 5.7)	3-4 m
H-3'	3.6 m	3-5 m	3-4.5 m	3.4 m	3-4 m
H-4'	3.6 m	3-5 m	3-4.5 m	3.4 m	3-4 m
H-5'	3.3 m	3-5 m	-	-	-
Ø$\underline{CH_2}$O	4.69 s	4.72 s	4.71 s	4.72 s	4.72 s

[a] Products were amorphous solids which did not exhibit defined melting points.

IR (KBr) spectra of all compounds exhibit bands in the region 3000-3600, 2850 and 2900 cm^{-1}. Carbonyl bands were absent.

Table III. ^{13}C Chemical shifts of 6a - e.

	6a	6b	6c	6d	6e
$\delta(D_6$-DMSO)					
C-1	132.67	132.80	138.45	139.91	132.88
C-3	140.87	140.78	144.78	144.96	140.79
C-4	109.85	109.49	110.04	110.04	109.52
C-4a	129.11	128.85	128.61	128.48	128.89
C-4b	120.44	120.47	121.45	121.73	120.42
C-5	118.85	118.78	116.46	115.64	118.74
C-6	121.35	121.35	121.10	120.94	121.33
C-7	127.79	127.69	126.20	125.64	127.68
C-8	112.18	112.02	114.29	114.97	112.10
C-8a	144.75	146.27	145.08	144.96	146.06
C-9a	148.77	148.63	146.13	147.83	148.68
C-1'	76.39*	73.42*	75.73*	75.02*	74.54*
C-2'	72.41*	72.40*	72.61*	73.95*	72.65*
C-3'	71.80*	69.96*	72.39*	71.66*	71.55*
C-4'	71.31*	69.60*	63.47	62.70	63.56
C-5'	63.39	63.23	-	-	-
$\emptyset\underline{CH_2}O$	64.47	64.58	64.90	65.00	64.56

* Individual assignments of the carbon shifts has not yet been established.

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13. Although compounds 3a - e represent diastereomeric mixtures, the trans diastereomer could be isolated as a crystalline product in each case.

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