A Simple Synthesis of Eritadenine and its Homologues

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Summary Reaction of some tosylated sugars with adenine leads to the formation of the corresponding "reversed" nucleosides, oxidation of which with oxygen affords eritadenine and its homologues in good yields.

A PREVIOUS publication from our laboratories[1] has described a total synthesis of eritadenine (lentinacin) (III), a highly hypocholesterolaemic substance of *Lentinus edodes* ("Shiitake") from the amino-acid (I) *via* the pyrimidine (II).

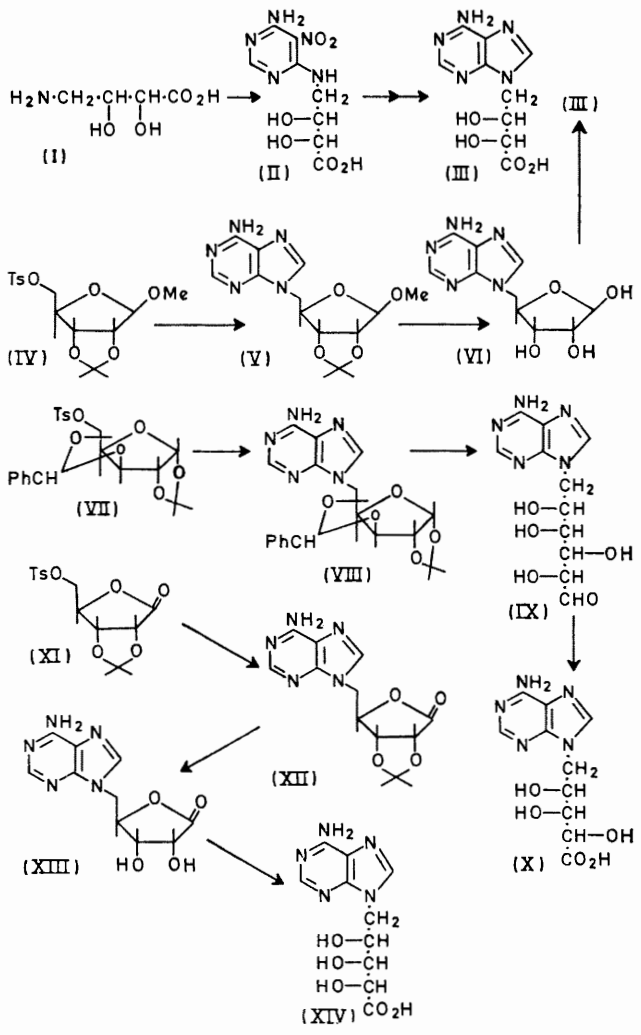
The amino-acid (I) is synthesized from D-erythronolactone,[2] but the yield of the lactone from D-glucose or D-ribose is not so good.[3] Hence, a synthetic method for eritadenine using the lactone appears uneconomical. We report a convenient synthetic route to eritadenine and its homologues.

Reaction of methyl 2,3-*O*-isopropylidene-5-*O*-tosyl-β-D-ribofranoside (IV)[4] with adenine in the presence of sodium in dimethylformamide afforded a "reversed" nucleoside (V) and the yield was (surprisingly) 90%.

Hydrolysis of (V) in dilute mineral acid gave (VI) in 80% yield. Oxidation of (VI) by oxygen in dilute alkali solution at room temperature gave (III) almost quantitatively. No other product was recognized on a thin-layer chromatogram of the reaction mixture.

Application of this method to other "reversed" nucleosides gave homologues of eritadenine. Reaction of 3,5-*O*-benzylidene-1,2-*O*-isopropylidene-6-*O*-tosyl-α-D-gluco-furanose (VII)[5] with adenine yielded (VIII) in excellent yield. Hydrolysis of (VIII) by dilute hydrochloric acid gave (IX) in 83% yield. Although the precise structure of the sugar moiety in (IX) was not examined, it presumably exists as a furanose or pyranose ring. Oxidation of (IX) by oxygen in a dilute alkali solution afforded 5-(6-amino-9*H*-purin-9-yl)-2(*S*),3(*R*),4(*R*)-trihydroxyvaleric acid (X) in 80% yield.

Furthermore, a homologue in which the three hydroxy-groups are all of *R*-configuration was obtained in a much easier way. Condensation of 2,3-*O*-isopropylidene-5-*O*-tosyl-D-ribonolactone (IX)[6] with adenine under milder conditions than in the case of the tosylated sugars gave



Physical constants of eritadenine homologues and their intermediates

	M.p.	$[\alpha]_D^{25}$	ν_{max} (Nujol) cm^{-1}	δ ppm (Me_2SO)
(V)	248—249°	−8·4 (MeOH)	3320, 3090, 1670, 1609, 1570	8·15 (s, 2H) 4·92 (s, H) 4·8—3·2 (m, 5H) 3·3 (s, 3H) 1·26 (s, 3H) 1·12 (s, 3H)
(VI)	168—169°	+32·3 (H_2O)	3300, 3220, 3100, 1668, 1609, 1572	
(VIII)	230—232°	+72·2[a]	3240, 3420, 3090, 1635, 1598, 1582	8·13, 8·10 (s, 2H) 7·22 (s, 5H) 1·40, 1·25 (S, 3H, 3H)
(IX)	230°(dec)	+60·0[a]	1677, 1650, 1611 1570	
(X)	224—225°	+26·5[b]	1695, 1610, 1575	
(XII)	192—193°	+31·7[a]	1774, 1647, 1605, 1582	8·42, 8·34 (s, 2H) 5, 6—4·6 (m, 5H) 1·52, 1·50 (s, 3H, 3H)
(XIII)	255°	+61·0 (H_2O)	1769, 1675, 1633, 1592	
(XIV)	225° (dec)	+40·6[b]	1695, 1645, 1610, 1581	

[a] Measured in Me_2SO solution.
[b] Measured in 1N-NaOH solution. All products exhibit the characteristic u.v. absorption spectrum of 9-substituted adenine (λ_{max} MeOH 262 nm at pH 7; 260 nm at pH 2; 263 nm at pH 11).

(XII) in 60% yield. Treatment of (XII) with hydrochloric acid gave (XIII), which was easily converted into the acid (XIV).

Studies of structure–activity relationship of these eritadenine homologues (involving exchange of the purine and acid moieties) are in progress.

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