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ACID-CATALYZED REARRANGEMENTS OF IRIDOID AGLYCONES. I - BEHAVIOUR OF LAMIIDOL, A NON NATURAL LAMIIDE DERIVATIVE

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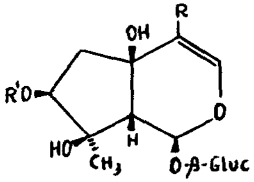
The high instability of iridoid aglycones in acid medium(1) has for a long while thwarted a study of their reactivity. Lately, we have initiated research in this area by examining the acid-catalyzed rearrangements of iridoid glycosides with different substituents at C-4. In this paper, we report the behaviour of the synthetic iridoid lamiidol 1 obtained by reduction of lamiide 2 with an excess of $NaBH_4$ in aqueous solution(2).



1 R = CH_2OH, R' = H

2 R = $COOCH_3$, R' = H

3 R = $COOCH_3$, R' = p-OH(C_6H_4)CH=CHCO-

On treatment with 0.2N HCl (2.0 ml) for 2 h at room temp., 1 (0.5 g) is completely transformed (silica gel TLC in EtOAc:MeOH 9/1) into a single product 4 . This was isolated in 38% yield after neutralization,extraction with EtOAc and purification on silica gel using EtOAc:MeOH 95/5. 4 ($[\alpha]_D^{20}$ = - 45°,MeOH,c= 0.45%) is an amorphous but reasonably stable compound whose UV (MeOH, λ_{max} = 297 nm, lgε = 4.3) and IR (KBr, ν_{max} 2830,2720,1660,1620 cm^{-1}) spectra suggest the presence of a highly conjugated aldehydic group.

The acetylation of 4 with Ac_2O and pyridine for 2 h at room temp. gives the amorphous peracetate 5, a diacetate, which reacts immediately with 2,4 DNP as does 4 . The elemental analysis and mass spectrum of 5 ($M^{+\cdot}$= 280) agree with the molecular formula $C_{10}H_{12}O_4$ for 4 which thus differs from the aglycone of 1 in lacking the elements of two water molecules.

The ^{1}H-NMR spectrum of 4 (Table), when compared to that of 1 , lacks the signals of the olefinic H-3,H-9 and all glucosylic protons but retains the signal for the hemiacetal proton. In addition, a new signal due to a formyl proton is present. The resonances of the ABX system (AB = 2H-6, X = H-7) are slightly modified, and like that of the CH_3-8 (now weakly split), appear more downfield as a result of the deshielding due to the allylic nature of all these protons. The field position of the allylic CH_2O signal is however unchanged in both spectra.

Table - 90 MHz ^{1}H-NMR ASSIGNMENTS$^{(a)}$

Compound (solvent)	H-1 2H-1	H-3 2H-3	CH_2OH-4 CHO-4	2H-6	H-7	CH_3-8	H-9	CH_3CO
1 (D_2O)	5.71,bs	6.44,s	4.23,s	2.6-1.8 bo AB part	3.70* X part	1.19,s	2.66,bs	
4 ^ (CD_3COCD_3)	5.78,bs	4.28,bs	9.76,d J=2.0Hz	3.6-2.5 bo AB part	4.40,bd X part	1.98,d J~1 Hz		
5 ($CDCl_3$)	6.88,d J=2.3Hz	4.48,dd J_{AB}=18.0	9.77,d J=2.0Hz	3.8-2.6† bo AB part	5.81,bd J=7.3Hz X part	1.96,bs		2.10,s
6 (D_2O)	4.38,s +	4.44,s+	4.23,s+	3.3-2.2 bo AB part	~4.4 § X part	1.94,bs		
7 ($CDCl_3$)	4.81,s +	4.89,s+	4.67,s+	3.4-2.4 bo AB part	5.63,bd J=7.3Hz X part	1.96,bs		2.07,s 2.05,s

(a) bd=broad doublet, bo=broad octet, bs=broad singlet, d=doublet, dd=doublet of doublets, s=singlet

* Assigned by spin decoupling as partly submerged by glucosylic signals

^ **4** is sparingly soluble in D_2O

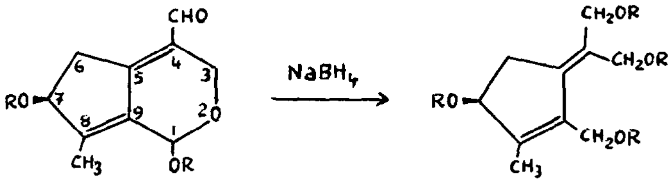
† δ_A= 2.72, δ_B= 3.48, J_{AB}= 18.0 Hz, J_{AX}= 2.5 Hz, J_{BX}= 7.3 Hz

\+ These assignments may be reversed

§ This resonance, covered by CH_2OH signals, becomes partly visible in CD_3OD as broad doublet

Paramagnetic shifts observed in the ^{1}H-NMR spectrum of the diacetate **5** clearly indicate the presence of two secondary hydroxyl groups in **4** ; one belongs to the hemiacetal function and the other is geminal to the X proton of the ABX spin system. Since acetylation does not affect the signals of the allylic CH_2O, now appearing as an AB system, this group must be involved in an ether-type linkage.

This evidence, together with the presence of an extensively conjugated aldehydic function and the absence of a primary and two tertiary hydroxyl functions, point to the given structure for the acid-catalyzed rearrangement product of 1. 4 must arise from the aglycone of 1 by the formation of a hemiacetalic linkage between the C-1 aldehyde and the CH_2OH function which creates a new dihydropyran ring. It is important to note that the acid-catalyzed rearrangement of 1 to 4 involves the same reaction as the spontaneous formation of cyclic hemiacetals from 1,5-hydroxyaldehydes (ring chain tautomerism). The stabilization process of the iridoid aglycone(3) is obviously not influenced by the formation of the diene system.



4 R = H

5 R = Ac

6 R = H

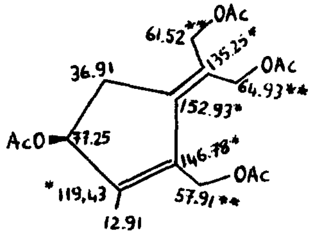
7 R = Ac

The proposed structure was unequivocally confirmed by reduction of 4 (80 mg) with an excess of $NaBH_4$ in aqueous solution which afforded, as main product, the expected cyclopententetrol 6(4). This was isolated in 70% yield by absorption of the neutralized solution on decolorizing charcoal, elution with methanol and chromatography on silica gel using $CHCl_3$:MeOH 7/3. Acetylation of 6 carried out as for 4 gave an amorphous tetraacetate(peracetate) 7(5) whose UV spectrum (MeOH, λ_{max} = 250 nm, lg ε = 4.2) showed that the diene system of 4 was not affected by the reaction; the formyl group of course was reduced. In fact, the λ_{max} value of the residual chromophore of 7 is in accordance with the figure (λ_{max}=249nm) calculated using the diene absorption rules(6).

The ^1H-NMR spectrum of 6(Table) still shows the signals assigned to the allylic CH_3 and ABX system(7); in addition, three methylene singlets attributable to allylic CH_2OH groups are present, arising from the reduction both of the free formyl group and of the hemiacetal function of 4 . The spectrum of 7 (Table) shows the expected paramagnetic shifts for these singlets and for the H-7 proton

In agreement with the above structure, the PND and SFORD ^{13}C-NMR spectra of

7 in $CDCl_3$ contain characteristically weak signals for four quaternary (sp^2) carbons, all singlets, and for three allylic hydroxymethyl carbons, all triplets.



7

Further research is in progress to establish the role of various substituents on the behaviour of iridoid glycosides in acid media.

References and notes

1. M.Bobbitt, "Cyclopentanoid Terpene Derivatives",(Edited by W.I.Taylor and R.Battersby) p.3 . Dekker,N.Y.(1969).
2. 1 was identical in all respects (NMR,UV,$[\alpha]_D$) with the product previously obtained from the reduction of 3 with $LiAlH_4$ in THF (A.Bianco,C.C.Bonini, M.Guiso,C.Iavarone,C.Trogolo,Gazz.Chim.Ital. 107, 67 (1977).
3. It is well known that 3,4-dihydroiridoid aglycones are more stable than their dehydro counterparts.
4. In order to make a more immediate comparison of spectral data, we did not use the IUPAC nomenclature for compound 6 but maintained the standard iridoid numbering.
5. A satisfactory elemental analysis was obtained for 7.
6. The λ_{max} value (298 nm) of the UV spectrum of 4 is also in accordance with the calculated value (297 nm).
7. The chemical shift value of the X-proton, H-7, which is masked by CH_2OH resonances, was established by a spin decoupling experiment.

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