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ON THE C-16 HYDROXYL CONFIGURATION OF PROTOPRIMULAGENIN A AND PRIMULAGENIN A

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Recently, Segal and Taube reported[1] that the 16-OH configuration of quillaic acid(1) should be revised from α to β on the basis of the diacetonide(2c) formation of its tetraol derivative (2) and as a result suggested that the 16-OH configuration of the following Δ^{12}-oleanene triterpenoids should be revised from α to β(albigenic acid, cyclamiretin, primulagenin A(3), and echinocystic acid) and from β to α(cochalic acid, gummosogenin, longispinogenin(9), maniladiol, chichipegenin, and myrtillogenic acid). In the structure elucidation of these triterpenoids, 3 and 9 have functioned as the key compounds of both groups respectively.

Since the 16α-OH of protoprimulagenin A(8), a genuine sapogenol of the root of Primula sieboldi E. Morren, was determined on the basis of its ready conversion with acid to 3[2], the above report has prompted us to re-investigate the 16-OH configuration concerned. This paper deals with the PMR evidence taking advantage of the solvent shift which supports the previous assignment rather than the claim by Segal and Taube.

Among the tertiary methyls of Δ^{12}-oleanene triterpenoids, 14α-CH_3 is observed at the lowest field due to its homoallylic disposition, in case no anisotropic function attached nearby[3,4c,d,e]. If 16α-OH presents, 14α-CH_3 experiences additional deshielding effect due to their 1,3-diaxial relation whereas, in the case of 16α-OAc, the downward shift is somewhat reduced[4]. On the other hand, it has been shown in the PMR spectra of the hydroxylic compounds that the protons locating at the 1,3-diaxial proximity of the hydroxyl are observed at 0.2 -0.4 ppm deshielded in d_5-pyridine as compared with in $CDCl_3$[5].

In order to re-investigate the stereochemical correlation of 14α-CH_3 and 16-OH of the Δ^{12} -oleanenes in question, the PMR study utilizing the d_5-pyridine induced solvent effect on some

Δ^{12}-oleanene derivatives including 4~7a(16α-OH being rigorously established[4c,d,e]) has been carried out. As shown in Table, in the presence of 16α-OH, 14α-CH_3 is observed markedly deshielded in d_5-pyridine($\Delta \approx \sim 0.4$ ppm), while 14α-CH_3 of a compound having 16α-OAc, 16β-OH, 16β-OAc, or no substituent at C-16 appears at the ordinary position. Therefore, the 1,3-diaxial correlation of 14α-CH_3 and 16-OH in 2 and 3 is reconfirmed, thus proving correctness of the previous assignments of 16α-OH in 1 and 8, 16β-OH in 9 and other related triterpenoids. 16-epi-Protoprimulagenin A(8c), prepared from a 16-keto derivative of 8a by Na-EtOH reduction, is readily converted with acid to 9 quantitatively. Taking into consideration of slightly deformed but rigid conformation of the D-ring in 8~8d due to the presence of 13β,28-oxide ring[2], the 16-H signal patterns in 8~8d are in good accord with the respective assignments.

Next, the diacetonide(2c) prepared by the method(2,2-dimethoxypropane-acetone-p.TsOH) of Segal and Taube[1] has been examined. It has been found that 3 also yields a similarly labile 16,28-acetonide(3c) by the same method but much less effectively under the milder conditions($CuSO_4$-acetone, p.TsOH-acetone). It should be noted here that the 16,28-acetonide was shown to be formed even in the 16α-OH compounds under the strong reaction conditions[6]. As shown in Table, the coupling patterns of 16-H in 3c and 3d reveal the deformed D-ring conformation(concomitant E-ring deformation being participated as discussed in the acetyl migration of 3a[7]). On the other hand, in the compounds having the ordinary D-ring chair conformation(vid. 5c), the signals due to 16β-H are observed as a broad singlet($W_{\frac{1}{2}} = 7 \sim 9$ Hz) while 16α-H in 9a as a doublet of doublet as anticipated.

Although several 16β-OH compounds(e.g. myrtillogenic acid[8a] and 9[8b]) were reported not to form the 16,28-acetonide, 9 has been noticed in our hands to be readily converted under the mild conditions to its acetonide, which is quite labile and readily reconverted to 9 during the isolation procedure. It is therefore concluded that the 16,28-acetonide formation could not be a criterion for the determination of 16-OH configuration. Furthermore, the recent synthesis of 3[9] also involves in the synthetic pathway the chemical support of 16α-OH in 3.

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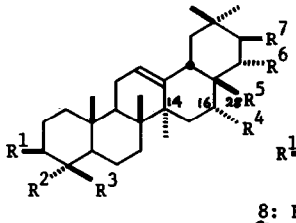
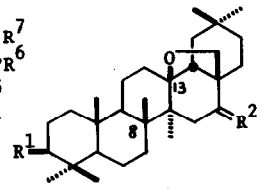
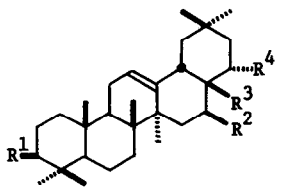


1 ~ 7a



8: R^1= OH, R^2= α-OH, β-H
8a: R^1= OAc, R^2= α-OH, β-H
8b*: R^1= OAc, R^2= α-OAc, β-H
8c*: R^1= OH, R^2= β-OH, α-H
8d*: R^1= OAc, R^2= β-OAc, α-H



9: R^1= R^2= OH, R^3= CH_2OH, R^4= H
9a: R^1= R^2= OAc, R^3= CH_2OAc, R^4= H
10[4e]: R^1= R^4= OH, R^2= H, R^3= CH_2OH

	R^1	R^2	R^3	R^4	R^5	R^6	R^7	ref.
1	OH	CHO	CH_3	OH	COOH	H	H	
1a	OH	CHO	CH_3	OH	$COOCH_3$	H	H	1)
2	OH	CH_2OH	CH_3	OH	CH_2OH	H	H	1)
2a	$OC(CH_3)_2$-OCH_2		CH_3	OH	CH_2OH	H	H	*
2b	$OC(CH_3)_2$-OCH_2		CH_3	OAc	CH_2OAc	H	H	*
2c	$OC(CH_3)_2$-OCH_2		CH_3	$OC(CH_3)_2$-OCH_2		H	H	1)
3	OH	CH_3	CH_3	OH	CH_2OH	H	H	2)
3a	OAc	CH_3	CH_3	OH	CH_2OAc	H	H	2)
3b	OAc	CH_3	CH_3	OAc	CH_2OAc	H	H	*
3c	OH	CH_3	CH_3	$OC(CH_3)_2$-OCH_2		H	H	*
3d	OAc	CH_3	CH_3	$OC(CH_3)_2$-OCH_2		H	H	*
4	OH	CH_3	CH_3	OH	CH_2OH	OH	H	4c)
4a	OH	CH_3	CH_3	OAc	CH_2OH	OH	H	*
5	OH	CH_3	CH_3	OH	CH_2OH	OH	OH	4c)
5a	OAc	CH_3	CH_3	OH	CH_2OAc	OAc	OAc	4c)
5b	OAc	CH_3	CH_3	OAc	CH_2OAc	OAc	OAc	4c)
5c	OAc	CH_3	CH_3	OH	$CH_2O(CH_3)_2$-O		OAc	4c)
6a	OAc	CH_2OAc	CH_3	OH	CH_2OAc	OAc	OAc	4c)
7a	OAc	CH_3	CH_2OAc	OH	CH_2OAc	OH, OAc		4d)

* Experimental details of the new compounds will be published elsewhere.

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	14α-CH_3 (90 MHz, δ)*				16-H (δ, J in Hz)*		
	i)CCl_4	ii)$CDCl_3$	iii)d_5-pyridine	Δ(iii-i) and/or (iii-ii)	i)CCl_4	ii)$CDCl_3$	iii)d_5-pyridine
1a		1.36	1.72	+0.36		4.50(br.s)	4.94(br.s)
2			1.74				4.56(br.s)
2a		1.40 (or 1.34)	1.80	+0.40 (or +0.46)		4.00(br.s)	4.62(br.s)
2b		1.29				5.19(br.s)	
2c	1.36 ~1.22						
3			1.76				4.53(br.s)
3a	1.36		1.73	+0.37	3.93(br.s)		4.35(br.s)
3b	1.24		1.39	+0.15	5.02(br.s)		5.43(br.s)
3c	1.30 (or 1.25)				3.53(d.d,4.5,12.5)		
3d	1.31 (or 1.26)		1.48 (or 1.35)		3.54(d.d,4.5,12.5)		3.77(d.d,4,12)
4			1.80				
4a		1.35	1.47	+0.12		5.71(br.s)	6.17(br.s)
5			1.73				4.91(br.s)
5a	1.40	1.43	1.76	+0.36 +0.33	4.13(br.s)	4.20(br.s)	4.48(br.s)
5b	1.27	1.30	1.45	+0.18 +0.15	5.03(br.s)	5.24(br.s)	5.62(br.s)
5c	1.39 (or 1.33)	1.41	1.74	+0.35(or +0.41) +0.33	4.74(br.s)	4.82(br.s)	5.13(br.s)
6a	1.41	1.43	1.76	+0.35 +0.33	4.14(br.s)	4.19(br.s)	4.43(br.s)
7a		1.42	1.78	+0.36		4.20(br.s)	4.54(br.s)
8			1.51				5.91(d,4.5)
8a	1.16	1.21	1.54	+0.38 +0.33	3.92(d,4.5)	3.98(d,5.4)	5.98(d,4.5)
8b		1.15**				5.05(d,5.4)	
8c			1.40				
8d		1.19**				5.38(d.d,6.3,10)	
9			1.32				
9a	1.28		1.36	+0.08	5.43(d.d,5.4,11)		5.83(d.d,5.4,12.6)
10			1.29				

* Blank column: not measured due to less solubility, or unclear due to overlapping.

** These lowest methyl signals might be due to 8β-CH_3 rather than 14α-CH_3.

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