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REDUCTION OF IRIDOID AGLYCONES—III

REACTIVITY OF LAMIOLGENIN TOWARDS $NaBH_4$[1,2]

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[Dedicated to Prof. Luigi Panizzi on his Seventieth Anniversary]

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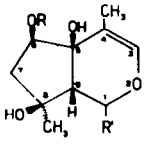
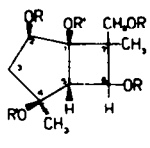
Abstract—The reaction which occurs when lamiolgenin 2 is treated with an excess of $NaBH_4$ is unusually complex owing to an intramolecular aldolic condensation which leads to a bicyclo[3.2.0]heptane derivative 4. The mechanism of this reduction has been investigated by using $NaBD_4$. Spectral data (IR, ^1H NMR, ^{13}C NMR) of the products are presented.

Recently,[1,2] we described the first results obtained in the reduction of iridoid aglycones with $NaBH_4$ in aqueous solution. We have ascertained that the substitution pattern of the dihydropyrane ring plays an important role in the reduction path. In fact aglycones with an unsubstituted dihydropyrane ring undergo the simple reduction of the aldehydic functions[1] while in aglycones with $COOCH_3$-4 and OH-5, the reduction is accompanied by a facile C-4, C-5 dehydration.[2] In order to investigate the influence of C-4 substituents on the course of this reaction, we examined the behaviour of the aglycone of lamiol 1 (lamiolgenin 2), still having the OH-5 but a Me group instead of the $COOCH_3$-4.

We obtained 2, up to now not isolated because of its instability, hydrolysing 1 with β-glucosidase. Owing to the low hydrolysis rate (48 h, 37°), a partial racemization of the C-1 centre occurred with formation of small quantities of the α aglycone **2a**, besides the more stable β epimer **2b**. Both the aglycones were isolated and characterised as diacetyl derivatives (their ^1H NMR spectra were in perfect agreement with the structure **3a** and **3b** respectively). The different yields of **2a** and **2b** confirm the absolute stereochemistry of the C-1 centre of 1, previously deduced[3] by comparing the M_D values of a series of corresponding derivatives of 1 and of harpagide (11-norlamiol). In accordance with this stereochemical approach, the M_D value of **2b** is highly negative (−249°), as in the pentaacetate of 1 (−700°), while that of **2a** is highly positive (+165°).





1 R=H, R'=(β)O-β-Glc
2 R=H, R'=OH
2a R=H, R'=(α)OH
2b R=H, R'=(β)OH
3a R=Ac, R'=(α)OAc
3b R=Ac, R'=(β)OAc

4 R=R'=H
5 R=Ac, R=H
6 R=R'=Ac

The reduction of 2 in aqueous solution with a marked excess of $NaBH_4$ at room temperature afforded 4 as the only product, with molecular formula $C_{10}H_{18}O_5$ which is transparent in the UV region and shows in the IR spectrum OH absorption and lack of bands attributable to C=C functions.

The ^1H NMR spectrum of 4 (Fig. 1) is greatly modified with respect to the resonance pattern of the aglycone unit of 1. The region of the olefinic and hemiacetalic resonances is empty; in agreement with this, the signal of the vinylic Me-4 of 1 (δ 1.66, d, J = 1.3 Hz) resonates at higher field (δ 1.20) surprisingly becoming a sharp singlet. Two new signals appear: a singlet (2H) at δ 3.52 and a doublet (1H) at δ 3.46 (J = 5.7 Hz).[4] Both spectra on the contrary contain, at near identical field position, the singlet of a Me geminal with OH (δ 1.27 in 1, δ 1.35 in 4), the signal multiplicity (although with different splitting pattern) of an ABX system[5] and lastly the signal of one proton appearing in 1 as a singlet (H-9, δ 2.58) and in 4 as a double doublet (δ 2.38, J_1 = 5.7, J_2 = 1.7 Hz) with one coupling constant identical with that of the doublet at δ 3.46.

The chemical shift similarity between the protons of the cyclopentane ring of 1 and some proton resonances of 4, indicates the presence of a cyclopentane moiety in 4, which is evidently not affected by the reaction, as previously described for other aglycones.[1,2]

The acetylation of 4 under mild conditions gives the triacetate 5 still showing an OH band in the IR spectrum. Its ^1H NMR spectrum, compared with that of 4, indicates the presence of one primary (δ 3.52→δ 4.09) and two secondary (δ 4.18→δ 5.21, δ 3.46→δ 4.31) alcoholic functions, the first of which is geminal to the X part of the ABX system.

By prolonged acetylation at room temperature 5 is completely transformed into the pentaacetate (peracetate) 6[6] which proves the presence in 4 of two tertiary OH functions.

As the shift induced by this acetylation for the Me at δ 1.28 geminal to a tertiary OH group ($\Delta\delta$ = 0.26) and moreover for the X part (δ 5.21, $\Delta\delta$ 0.42) of the ABX system are smaller than that of the proton at δ 2.60 ($\Delta\delta$ = 0.74),[7] the latter must be identified as the counterpart of the H-9 of 1, vicinal to both tertiary OH groups.

The PND and SFORD ^{13}C NMR spectra of 4 (Fig. 1), which definitively exclude the presence of olefinic and hemiacetal carbons, show ten signals, four in the alipha-

†In alphabetical order.

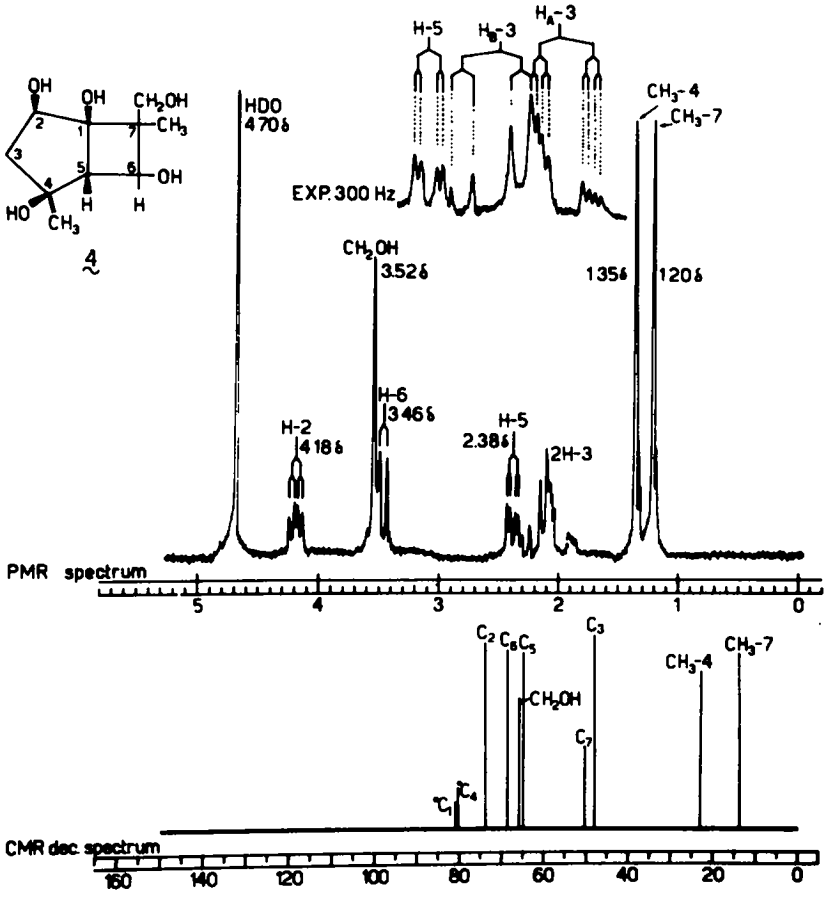
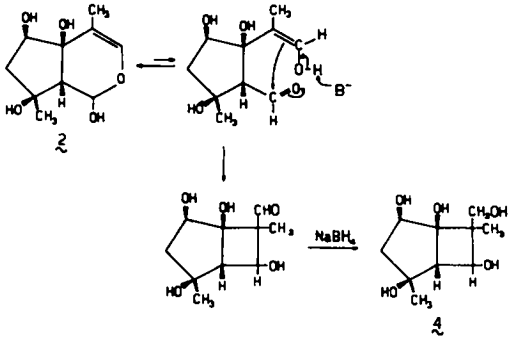


Fig. 1. ^1H NMR (D_2O) and ^{13}C NMR (D_2O) spectra of 4.

tic region and six in the region between 60 and 80 ppm characteristic of the ether-type carbons. The first set of signals is attributable to one quaternary carbon (δ 49.91, singlet), to the cyclopentane methylene carbon (δ 47.67, triplet) and to two Me's (δ 13.58 and 22.37, quartets), the more deshielded geminal with the OH group. In the second group, are present: the low intensity signals of two carbons bearing tertiary OH functions (δ 80.65 and 80.16, singlets), the signals of two carbons bearing secondary alcoholic functions (δ 73.64 and 68.26, doublets, the first[10] relative to the cyclopentane ring) and, lastly, the signal of the carbon bearing the primary alcoholic function (δ 65.45, triplet). As these five resonances account for all the OH groups of 4, the sixth and more shielded line at δ 64.36 (doublet) must be attributed to a nonoxygenated methine carbon, evident counterpart of the so far undetected C-9 of 1.

On the basis of all above data it is clear that one primary and one secondary alcoholic function as well as one Me bearing nonoxygenated quaternary carbon are formed in the reaction. This excludes that the reduction of 2 follows a route analogous to that previously reported[1,2] and suggests that a cyclization occurs. As in the ^1H NMR spectra of 4 and its derivatives the more shielded Me resonates as a sharp singlet and the CH_2OH as a singlet or an ABX system, both must be linked to the new nonoxygenated quaternary carbon. At this point it is evident that the cyclization occurs through an intramolecular aldolic condensation, evidently faster than the simple reduction of the dialdehydic functions, between the aldehydic function C-1 and the C-4 of 2 and therefore the structure of 1,2,4,6 - tetrahydroxy - 4,7 - dimethyl - 7 - hydroxymethyl bicyclo[3.2.0]heptane may be postulated for 4.



The detailed analysis of the ^1H NMR spectrum of 4 and spin decoupling experiments corroborate the proposed structure. On expanded scale (300 Hz) (Fig. 1) it is possible to diagram the splitting pattern of the AB part (δ 2.4–1.8) of the ABX system. The A part (H_A-3) is surprisingly splitted in eight lines, showing a further doublet splitting (J = 1.7 Hz) readily identifiable as a long range coupling (W type) with H-5. In fact the irradiation of the double doublet at δ 4.18 (H-2, X part) simplifies the complex AB pattern into a simpler AB system (δ 2.4–1.8, J_{AB} = 14.0, J_{AX} = 3.0, J_{BX} = 5.0 Hz) whose high field lines

(H_A-3) retain the W coupling with H-5. These findings point out a conformationally rigid system[11] to which H-5 and H_A-3 (methylene proton in β configuration) belong. By irradiating the H-5 proton (δ 2.38) the doublet at δ 3.46 (J = 5.7 Hz) collapses to a singlet and may be assigned to the H-6 proton.[12] This confirms that the OH bearing methine H-6 is adjacent to the quaternary carbon formed in the reduction and that it is corresponding to the hemiacetalic H-1 of 4.

In order to achieve experimental evidence for the mechanism involved in the formation of 4, the reduction of 2 was repeated using $NaBD_4$ in D_2O. The reaction afforded as sole product 7 in which, as expected, a monodeuteration label has taken place. In fact its ^1H NMR spectrum is superimposable on that of 4 apart the singlet at δ 3.52 (CH_2OH-7) whose integral value now corresponds to only one proton (CHDOH).

Regarding the stereochemistry of 4, the centres C-1, C-2 and C-4 obviously retain the same configuration as 1, as well as the C-5 centre owing to its lack of deuteration.

The stereochemistry of the chiral centres C-6 and C-7, although the cyclization occurs in a stereospecific way leading to a sole stereoisomer, has not yet been experimentally ascertained owing to the temporary lack of 4.

EXPERIMENTAL

Column chromatography: silica gel 70-230 mesh (Merck); thin layer chromatography: silica gel SIF_{254} (Carlo Erba) plates; visualization: 2N H_2SO_4 and heating for 2–3 min at 120°.

^1H NMR *spectra.* Perkin–Elmer R-32 (90 MHz) spectrometer: internal references: TMS and HDO (δ 4.70 from TMS); external reference: TMS. Spin decoupling experiments performed using frequency sweep mode; chemical shifts expressed in δ and coupling constants in Hz.

^{13}C NMR *spectra.* Varian CFT-20 spectrometer; internal reference: dioxane; chemical shifts expressed in δ (ppm downfield from TMS). IR spectra: Perkin–Elmer 257 spectrophotometer.

Analytical determination of amorphous products: the solution of each compound was filtered through Schleicher and Schüll blauband filter paper and dried *in vacuo* at 60° to constant weight.

Lamiol 1. The isolation of 1 from *Lamium amplexicaule* was carried out as previously described.[3] ^1H NMR (D_2O): δ 6.18 (H-3, d, J = 1.3 Hz), 5.69 (H-1, bs), 4.03 (H-6, m, partly covered by glucosylic signals), 2.58 (H-9, bs), 2.4–1.7 (2H-7, m), 1.66 (CH_3-4, d, J = 1.3 Hz), 1.27 (CH_3-8, s).

Lamiolgenin 2a *and* 2b*—acetate* 3a *and* 3b. 1 (200 mg) dissolved in H_2O (4 ml) was treated with β-glucosidase (100 mg, Fluka EC 3.2.1.21) at 37° for 16 hr. The soln was extracted with EtOAc (8 × 20 ml) and the collected extracts, evaporated *in vacuo* at 30° gave 54 mg of a crude mixture of 2a and 2b (tlc in H_2O sat BuOH) which was immediately acetylated with pyridine (0.4 ml) and Ac_2O (0.8 ml) for 2 hr at 25°. After addition of MeOH (3 ml) the soln was left for 20 min and afterwards evaporated *in vacuo* to give a residue (60 mg) which, chromatographed on silica gel (6 g) in EtOAc, afforded pure 3a (10 mg) and 3b (35 mg) as colourless viscous oils.

3a $[\alpha]_D^{25} = +55°$ (dioxane, $c = 0.7\%$). ^1H NMR ($CDCl_3$): δ 6.25 (H-1, d, $J_{1,9} = 3.7$ Hz), 6.01 (H-3, q, J = 1.4 Hz), 5.29 (H-6, X part of an ABX, $J_{6,7} = 5.0$, $J_{6,7'} = 9.3$ Hz), 2.6–1.7 (2H-7, AB part of an ABX, $J_{6,7} = 5.0$, $J_{6,7'} = 9.3$, $J_{AB} = 16.0$ Hz), 2.60 (H-9, d, J = 3.7 Hz), 1.60 (CH_3-4, d, J = 1.4 Hz), 1.28 (CH_3-8, s), 2.13, 2.11 (CH_3CO). (Found: C, 55.78; H, 6.80. Calc. for $C_{14}H_{20}O_7$: C, 55.99; H, 6.71%). 3b $[\alpha]_D^{25} = -83°$ (dioxane, $c = 1.8\%$). ^1H NMR ($CDCl_3$): δ 6.49 (H-1, d, $J_{1,9} = 2.0$ Hz), 6.11 (H-3, q, J = 1.3 Hz), 5.26 (H-6, t, $J_{6,2H\text{-}7} = 3.3$ Hz), 1.94 (2H-7, d, $J_{6,2H\text{-}7} = 3.3$ Hz), 2.64 (H-9, d, J = 2.0 Hz), 1.68 (CH_3-4, d, J = 1.3 Hz), 1.32 (CH_3-8, s), 2.15, 2.08 (CH_3CO). (Found: C, 55.83; H, 6.82. Calc. for $C_{14}H_{20}O_7$: C, 55.99; H, 6.71%).

$NaBH_4$ *reduction of* 2, *poliol* 4. Crude 2 (100 mg) dissolved in H_2O (5 ml) was treated with $NaBH_4$ (350 mg, ~30 times molar excess) for 45 min at 25°. $NaBH_4$ excess was decomposed by bubbling CO_2 until pH ~ 7, the soln was treated with decolorizing charcoal (1 g) and the suspension stratified on a gooch funnel. The charcoal layer was washed with H_2O, then with MeOH affording a residue (70 mg) which was chromatographed on silica gel (7 g) in H_2O sat BuOH giving pure 4 (50 mg) as colourless viscous oil. (Found: C, 54.80; H, 8.40. Calc. for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31%).

Triacetate 5. Compound 4 (40 mg) was treated with pyridine (0.2 ml) and Ac_2O (0.4 ml) for 1 hr at 25° and worked as previously described for 3a affording a residue (60 mg) which, chromatographed on silica gel (6 g) in EtOAc, gave 20 mg of pure 5 as viscous colourless oil. ^1H NMR ($CDCl_3$): δ 5.21 (H-2, dd, $J_{2,3} = 5.3$, $J_{2,3'} = 1.7$ Hz), 4.31 (H-6, d, $J_{5,6} = 5.7$ Hz), 4.09 (CH_2O-7, s), 2.60 (H-5, dd, $J_{5,6} = 5.7$, $J_{3,5} = 2.0$ Hz), 2.3–1.7 (2H-3), 1.28 (CH_3-4, s), 1.16 (CH_3-7, s), 2.05, 2.07, 2.10 (CH_3CO).

Pentaacetate 6. Triacetate 5 (20 mg) treated with pyridine (0.3 ml) and Ac_2O (0.6 ml) for 36 hr at 30° and worked up as previously described for 3a gave a residue (25 mg) which, chromatographed on silica gel (25 g) in Et_2O–EtOAc (1:1), afforded pure 6 (10 mg) as colourless viscous oil. (Found: C, 55.82; H, 6.77. Calc. for $C_{20}H_{28}O_{10}$: C, 56.07; H, 6.59%). ^1H NMR ($CDCl_3$): δ 5.63 (H-2, d, $J_{2,3} = 5.7$ Hz), 4.77 (H-6, d, $J_{5,6} = 5.7$ Hz), 4.26 (CH_2O-7, AB system, J = 12.0 Hz), 3.34 (H-5, dd, $J_{5,6} = 5.7$, $J_{3,5} = 2.3$ Hz), 2.9–2.1 (2H-3, AB part of an ABX system), 1.54 (CH_3-4, s), 1.04 (CH_3-7, s), 2.16, 2.08, 2.06, 1.99, 1.93 (CH_3CO).

$NaBD_4$ *reduction of* 2, *poliol* 7. Crude 2 (50 mg) dissolved in D_2O (3 ml) was treated with $NaBD_4$ (175 mg, ~30 times molar excess) and worked up as previously described for 5 giving a residue (40 mg) which, chromatographed in the same conditions as 5, gave pure 7 (21 mg) as colourless viscous oil. (Found: C, 54.46; H, 8.91. Calc. for $C_{10}H_{17}DO_5$: C, 54.78; H, 8.74%).

REFERENCES

[1]Note I. A. Bianco, M. Guiso, C. Iavarone, P. Passacantilli and C. Trogolo, *Tetrahedron* **33**, 851 (1977).

[2]Note II. A. Bianco, D. Budai, M. Guiso, C. Iavarone, R. Marini-Bettolo and C. Trogolo, *Gazz. Chim. Ital.* **109**, in press (1979).

[3]M. L. Scarpati and M. Guiso, *Tetrahedron* **23**, 4709 (1967).

[4]Spin decoupling experiments have shown that in glucosylic protons region (δ 3–4) of 1 only one aglycone signal (H-6, δ 4.03, m) appears.

[5]In 1 X = H-6, δ 4.03, m; AB = 2H-7, δ 2.3–1.7, m. In 4 X = δ 4.18, dd, $J_{AX} = 3.0$, $J_{BX} = 5.0$ Hz; AB = δ 2.4–1.8, m, (2H).

[6]The tertiary OH-5 of 1 may be acetylated in 4 most likely because of its proximity to the CH_2OH group formed in the reduction.

[7]A very similar deshielding value, owing to acetylation of both OH-5 and OH-8, was observed for the H-9 of harpagide ($\Delta\delta$ = 0.61)[8] and linarioside ($\Delta\delta$ = 1.14).[9]

[8]H. Lichti and A. von Wartburg, *Helv. Chim. Acta* **49**, 1552 (1966).

[9]I. Kitagawa, T. Tani, K. Akita and I. Yosioka, *Chem. Pharm. Bull.* **21**, 1978 (1973).

[10]This chemical shift value is practically identical to that of the corresponding carbon of 1 (unpublished data).

[11]In the more flexible iridoidic cyclopenta[c]pyrane ring such high value for a W coupling between the corresponding H-9 and H-7 of saturated cyclopentane ring had never been observed.

[12]The reverse irradiation modifies the H-5 resonance (doublet of doublets) into a narrow doublet ($J_{3,5} = J_W = 1.7$ Hz).