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ACID CATALYSED REARRANGEMENTS OF IRIDOID AGLYCONES—II

TETRACYCLIC ACETAL FROM ASPERULOSIDOL, A NON NATURAL ASPERULOSIDE DERIVATIVE[1]

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"Dedicated to Prof. Luigi Panizzi on his Seventieth Anniversary"

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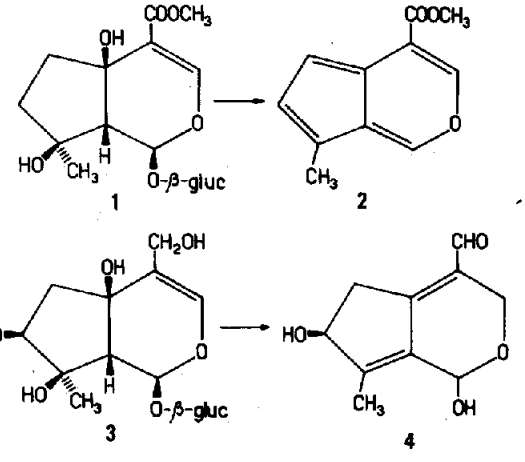
Abstract—The acid catalysed rearrangement of asperulosidol **5** leads to the tetracyclic acetal **7** whose structure and configuration has been determined by ^{1}H-NMR and ^{13}C-NMR spectroscopy, as well as by the Li/NH_3 reduction of **7** to the cyclopententriol **10**. The reaction course has been clarified by reacting **5** with DCl and formation of the monodeutero derivative **9**.

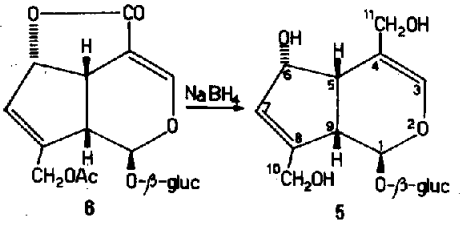
Recent research on iridoid aglycones showed the dependence of their acid catalysed rearrangements on the substituent at C-4. In fact the pseudoazulenic compound **2**,[2] obtained from ipolamiide **1** ($COOCH_3$-4), was responsible for the blue-green colour which **1** showed in acidic medium while lamiidol **3** (CH_2OH-4) afforded the colourless product **4**[1] in which the hemiacetal function involves the hydroxymethyl group.



In this paper a new iridoid, asperulosidol **5**, which we obtained by reducing asperuloside **6**,[3] has been investigated in acid conditions.

Complete evidence for structure **5** was achieved by comparing the ^{1}H-NMR and ^{13}C-NMR (Table 1) spectra of **5** and **6** as well as their UV and IR spectra. The bands typical of conjugated lactone functions are lacking in **5**.

On treatment with dilute HCl **5** gave the stable and crystalline compound **7** (~35% yield) with



$[\alpha]_D = +61°$ (−8° in **5**) and molecular formula $C_{10}H_{12}O_4$ differing from that of the aglycone of **5** ($C_{10}H_{14}O_5$), by one molecule of water.

The ^{1}H-NMR spectrum (D_2O) of **7** compared with that of the parent iridoid **5** showed absence of the olefinic H-3 and of glucosylic protons signals, while the chemical shifts of the H-7, 2H-11 and 2H-10[4] were practically unchanged, the latter appeared as a broad singlet (double doublet in **5**). The field region between δ 5.6−4.8 of **5** showed the signals of the H-6 and of the acetal H-1 as doublets at δ 4.87 and 4.94 respectively, whereas in the same region **7** revealed three one-proton signals—a sharp doublet at δ 5.51, a broad singlet at δ 5.22 and a doublet of doublets at δ 5.11—two of which corresponded to the resonances of **5** and the other probably to the aldehydic H-3 involved in an acetal function.

The aliphatic region of **5** which showed distinct triplets for the H-5 (δ 3.03) and H-9 (δ 2.70) protons, appeared greatly modified in **7** which showed broad signals at δ 3.22 (2H) and at δ 2.61 (1H), namely a proton more than in **5** which ought to be linked to C-4, now sp^3 hybridised.

The acetylation of **7** in mild conditions gave a crystalline monoacetate (peracetate) **8**, the ^{1}H-NMR spectrum ($CDCl_3$) of which showed a significant acetylation shift only for the allylic hydroxymethyl signal. The shift invariance observed for the signals of the 2H-11 and of the three protons of

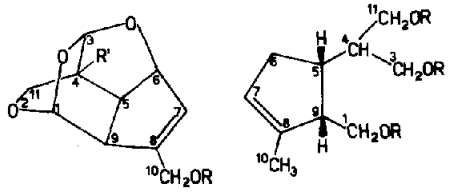
* In alphabetical order

Table 1. ^{13}C-NMR chemical shifts assignments

Compound (solvent)	C-1	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11
5 (D_2O)	99.64 d	142.59 d	114.46 s	42.59 d	74.62 d	129.29 d	150.60 s	46.49 d	61.04 t	61.54 t
6 (D_2O)*	93.75 d	150.69 d	105.48 s	36.73 d	87.04 d	128.91 d	142.97 s	44.26 d	62.22 t	174.51 s
7 (D_2O)	101.19[a] d	92.77[a] d	51.59[b] d	37.72[b] d	87.03 d	130.11 d	151.01 s	42.20[b] d	59.01[c] t	59.77[c] t

* our unpublished data

a, b, c these signal assignments may be reversed



7 R=R'=H
8 R=Ac, R'=H
9 R=H, R'=D

10 R=H
11 R=Bz

the δ 5.6–4.8 region indicated the presence in **7** of acetal functions involving all these protons.

These data show that the cyclopentene ring of **5**, unlike the dihydropyrane ring, was not affected by the reaction. In particular the two acetal protons present in **7** as well as the lack of the enol-ether function and of free formyl groups, the formation of ether-type linkages involving the OH-6 and the OH-11 and the acid-catalysed rearrangement described for **3** indicated the structure **7**[5] which in addition was confirmed by Dreiding models.

The comparison of the ^{13}C-NMR PND and SFORD spectra of **5** and **7** (Table 1) supported the proposed structure of **7**: (1) the presence of the only olefinic carbons C-7 and C-8 at near unchanged shift positions; (2) the two lines at δ 59.01 and 59.77 (both with triplet multiplicity) attributable to the oxymethylene carbons C-10 and C-11; (3) the presence of two acetal carbons C-1 and C-3 (δ 101.19 and 92.77); (4) a new methine carbon (C-4) in the aliphatic region which also contained the C-5 and C-9 resonances. The C-6 resonance appeared strongly deshielded in **7** ($\Delta\delta$ = 12.41) and is supported by the identity of the chemical shift (δ 87.03) with that (δ 87.04) observed in **6** in which this carbon is involved in two fused 5-membered cycles.

The structure proposed for **7** was confirmed by a detailed analysis of its ^{1}H-NMR spectrum in deuteropyridine[6] (Fig. 1) and corroborated by double resonance experiments. In fact the irradiation of the most shielded resonance at δ 2.26 (H-4, narrow multiplet) caused the contemporary simplification of: (1) the complex multiplet at δ 2.90 (H-5) into a doublet of doublets, (2) the sharp doublet at δ 5.50 (H-3, $J_{3,4}$ = 3.7 Hz) into a sharp singlet, (3) the narrow doublet at δ 4.03 (2H-11, $J_{4,2H\text{-}11}$ = 2.0 Hz) into a sharp singlet, which demonstrated the magnetic equivalence of these protons. Conversely, as expected, either the irradiation at δ 4.03 or δ 5.50 simplified the H-4 to a doublet of doublets ($J_{3,4}$ = 3.7 Hz, $J_{4,5}$ = 5.3 Hz) and an ill defined sextet respectively.

Double resonance at δ 2.90 (H-5) turned the doublet of doublets at δ 4.96 (H-6) into a small doublet ($J_{6,7}$ = 2.3 Hz) and the H-4 resonance into a simpler spin system. The irradiation at δ 4.96 (H-6)[7] was found to simplify the H-5 resonance into a doublet of doublets showing the coupling constants $J_{4,5}$ and $J_{5,9}$ (7.7 Hz). As expected by irradiating the olefinic H-7,[8] the H-6 resonance was reduced to a doublet ($J_{5,6}$ = 5.0 Hz), while the irradiation of the allylic CH_2OH-8 transformed the broad signal of the H-7 into a narrow doublet retaining the $J_{6,7}$ coupling.

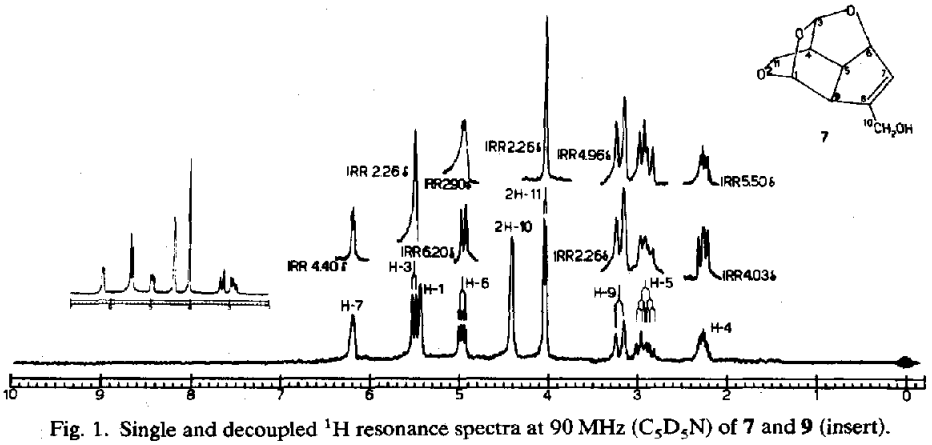


Fig. 1. Single and decoupled ^{1}H resonance spectra at 90 MHz (C_5D_5N) of **7** and **9** (insert).

In order to obtain additional information on the course of the reaction we treated **5** with dilute DCl and obtained the crystalline compound **9** (~32% yield) in which complete monodeuteration at C-4 had taken place. It is therefore evident that the formation of **7** occurred through the dialdehydic form of the aglycone of **5**.

The ^{1}H-NMR spectrum of **9** (Fig. 1) displayed the total absence of the H-4 resonance with consequent simplification of the H-3 and 2H-11 signals into sharp singlets and the complex multiplet of H-5 into a doublet of doublets (loss of $J_{4,5}$ but retaining of $J_{5,6}$ and $J_{5,9}$). As the lack of the H-4 produced multiplicity changes equivalent to those previously observed by double resonance of the same proton, the irradiation of the H-6 reduced the doublet of doublets of the H-5 to a simple doublet showing the residual $J_{5,9}$ coupling (7.7 Hz).

Regarding the stereochemistry of **7**, the chiral centres C-5 and C-9, not involved in the acid-catalysed rearrangement, obviously retained the configuration of the corresponding centres of **5**. For the centre C-1, the remarkable decrease of the coupling constant $J_{1,9}$ (9.0 Hz in **5** → < 1.0 Hz in **7**) confirmed the inversion of the OH-1, now in α-configuration. The stereochemistry of the other centres C-3, C-4 and C-6 is univocally fixed by the stereochemical requirements occurring for the closure of the acetal cycles which, according the Dreiding models, can take place in an easy way only if these chiral centres assume the configuration depicted in **7**. This implies a *cis*-arrangement among H-3, H-4, H-5 and H-6. The dihedral angles calculated with the Karplus relationship from the values of the coupling constants $J_{3,4}$, $J_{4,5}$ and $J_{5,6}$ are in accordance with the angles measured on the Dreiding model: (a) $J_{3,4}$ (3.7 Hz, $\Phi_{KAR} \simeq 50°$, $\Phi_{DR} \simeq 50°$), (b) $J_{4,5}$ (5.3 Hz, $\Phi_{KAR} \simeq 40°$, $\Phi_{DR} \simeq 45°$), (c) $J_{5,6}$ (5.0 Hz, $\Phi_{KAR} \simeq 42°$, $\Phi_{DR} \simeq 30°$). In addition the $J_{4,2H\text{-}11}$ (2.0 Hz, $\Phi_{KAR} \simeq 60°$) shows that the C(4)-H(4) linkage is the bisecting line of the angle between the 2H-11 protons ($\Phi_{DR} \simeq 55°$).

On these grounds it is possible to state that the formation of **7** from the aglycone (dialdehyde) of **5** needs well defined sterical requirements present only at the C-4 of the S-epimer.

An unequivocal confirmation, on chemical grounds, of the proposed structure was achieved by treating **7** with Li/NH_3. This reductive system permitted either the initial allylic hydrogenolysis at C-6 and C-10 or the successive reduction of the hemiacetal functions consequently formed, producing the unique cyclopententriol **10**.[9] Its structure is well supported by the ^{1}H-NMR spectrum (D_2O) in which are clearly recognisable: (a) the broad singlet at δ 5.62 of the unique olefinic proton; (b) the complex signals pattern between δ 4.0–3.5 (6H) corresponding to the resonances of the three hydroxymethyl groups; (c) the broad signal at δ 2.18 of the allylic 2H-6, counterpart of the H-6 resonance (δ 5.11) of **7**; (d) the broadened singlet of the allylic Me group at δ 1.74.

The benzoylation of **10** under mild conditions afforded the tri-O-benzoyl derivative (perbenzoate) **11**. Its ^{1}H-NMR spectrum ($CDCl_3$) compared with that of **10** showed the expected paramagnetic shifts for the resonances of the three hydroxymethyl groups ($\Delta\delta \simeq 0.8$).

We are investigating the behaviour of iridoids differently substituted at C-4 in acidic medium.

EXPERIMENTAL

Column chromatography: Silica gel 70–230 mesh (Merck); tlc: Silica gel Stratochrom SIF_{254} (Carlo Erba) plates; visualisation: 2N H_2SO_4 and heating for 2–3 min at 120°. ^{1}H-NMR *spectra*: Perkin–Elmer R32 (90 MHz) spectrometer; internal references: TMS and HDO (δ 4.70 from TMS). Spin decoupling experiments performed using frequency sweep mode; chemical shifts expressed in δ and coupling constants in Hz. Multiplicity legend: bd = broad doublet, bdd = broad double doublet, bs = broad singlet, bsg = broad signal, bt = broad triplet, d = doublet, dd = double doublet, m = multiplet, nd = narrow doublet, nm = narrow multiplet, s = singlet. ^{13}C-NMR spectra: Varian CFT-20 spectrometer; original data measured relative to dioxane and converted to TMS scale using $\delta_{DIOXANE}$ = 67.4 ppm. IR spectra: Perkin–Elmer 257 spectrophotometer. UV spectra: Perkin–Elmer 356 spectrophotometer. Optical rotations: Perkin–Elmer 141 instrument. M. ps (uncorrected): Kofler equipment.

Asperulosidol **5.** Asperuloside **6** (200 mg) dissolved in H_2O (6 ml) was treated with $NaBH_4$ (200 mg, ~10 times molar excess) for 2 hr at 5°. Excess $NaBH_4$ was decomposed by bubbling CO_2 until pH ~7 then decolorising charcoal (5 g) was added and the suspension stratified on a gooch funnel. The charcoal layer was washed with H_2O, then eluted with MeOH affording a residue (180 mg) which was crystallised from EtOH giving pure **5** (150 mg) as prisms, m.p.183–184°. $[\alpha]_D^{25} = -8°$ (H_2O, $c = 3.2\%$). UV(MeOH): $\lambda_{max} = 206$ nm ($lg\epsilon = 3.6$). IR (KBr) υ_{max} = 3280, 2900, 1655, 1455 cm^{-1}. ^{1}H-NMR (D_2O) of **5**: δ 6.66 (H-3, bs), 6.07 (H-7, bs), 4.94 (H-1, d, $J_{1,9} = 9.0$), 4.87 (H-6, bd), 4.43 (2H-10,dd, $J_{AB} = 15.0$), 4.17 (2H-11, bs), 3.03 (H-5, bt, $J_{5,6} = 6.6$, $J_{5,9} = 7.7$), 2.70 (H-9, bt, $J_{1,9} = 9.0$, $J_{5,9} = 7.7$). ^{1}H-NMR (D_2O) of **6**: δ 7.44 (H-3, d, $J_{3,5} = 2.0$), 6.00 (H-1, d, $J_{1,9} = 1.3$), 5.86 (H-7, bs), 5.76 (H-6, bd, $J_{5,6} = 6.7$), 4.82 (2H-10, bs), 3.6–3.1 (H-5, H-9). (Found: C, 50.81; H, 6.51. Calc. for $C_{16}H_{24}O_{10}$: C, 51.06; H, 6.43%).

Tetracyclic acetal **7.** Compound **5** (100 mg) was treated with 2N HCl (2 ml) for 10 min at 20°. The soln was extracted with EtOAc (50 ml × 5 times) and the collected extracts, evaporated *in vacuo* at room temp, gave a residue (40 mg) which chromatographed on silica gel (4 g) in EtOAc-MeOH (97:3) afforded pure **7** (18 mg, ~35% yield) which crystallised from acetone, m.p. 158–159° (needles). $[\alpha]_D^{25} = +61°$ (H_2O, $c = 2.8\%$). UV (MeOH): $\lambda_{max} = 204$ nm ($lg\epsilon = 3.7$). IR (KBr): ν_{max} = 3360, 2975, 2920, 2900, 1650, 1465 cm^{-1}. ^{1}H-NMR (D_2O: δ 6.15 (H-7, bsg), 5.51 (H-3, d, $J_{3,4} = 3.7$), 5.22 (H-1, bs), 5.11 (H-6, dd, $J_{5,6} = 5.0$, $J_{6,7} = 2.3$), 4.29 (2H-10, bs), 4.18 (2H-11,bs), 3.22 (H-5, H-9, bsg), 2.61 (H-4, bsg). ^{1}H-NMR (C_5D_5N): δ 6.20 (H-7, bsg), 5.50 (H-3, d, $J_{3,4} = 3.7$), 5.43 (H-1, bs), 4.96 (H-6, dd, $J_{5,6} = 5.0$, $J_{6,7} = 2.3$), 4.40 (2H-10, bs), 4.03 (2H-11, nd, $J_{4,2H\text{-}11} = 2.0$), 3.20 (H-9, bd, $J_{5,9} = 7.7$), 2.90 (H-5, m, $J_{4,5} = 5.3$, $J_{5,6} = 5.0$, $J_{5,9} = 7.7$), 2.26 (H-4, nm, $J_{3,4} = 3.7$, $J_{4,5} = 5.3$, $J_{4,2H\text{-}11} = 2.0$). (Found: C, 60.97; H, 6.25. Calc. for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17%).

Monoacetate **8.** Compound **7** (30 mg) dissolved in pyridine (0.3 ml) was treated with Ac_2O (0.6 ml) for 1 hr at room temp. After addition of MeOH (2 ml) the soln was left for 20 min and then evaporated to dryness, the residue dissolved in EtOAc (50 ml) was washed with H_2O (1 ml) and finally evaporated *in vacuo* to give crude **8** (35 mg). This residue was chromatographed on silica gel (3.5 g) in benzene-Et_2O (1:1) giving pure **8** (27 mg) which was crystallised from EtOH: m.p. 125–126° (needles), IR

($CHCl_3$): υ_{max} 2950, 2880, 1735, 1650 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 6.15 (H-7, bs), 5.40 (H-3, bd, $J_{3,4}$ = 3.7), 5.10 (H-1, bs), 4.95 (H-6, bsg), 4.70 (2H-10, bs), 4.10 (2H-11, nd, $J_{4,2H\text{-}11}$ = 2.0), 3.05 (H-5, H-9, bsg), 2.37 (H-4, bsg). ^{1}H-NMR (C_5D_5N): δ 6.13 (H-7, bs), 5.48 (H-3, d, $J_{3,4}$ = 3.7), 5.35 (H-1, bs), 4.90 (H-6, dd, $J_{5,6}$ = 6.7, $J_{6,7}$ = 2.3), 4.62 (2H-10, bdd, J_{AB} = 14.0), 4.00 (2H-11, d, $J_{4,2H\text{-}11}$ = 2,0), 3.08 (H-9, bd), 2.90 (H-5, m), 2.25 (H-4, bsg).

Monodeutero derivative **9.** Compound **5** (100 mg) was treated several times with D_2O then with 2N DCl (2 ml) and worked up as described for **7.** The monodeutero derivative **9** (17 mg, ~32% yield), was crystallised from acetone m.p. = 158-159°. ^{1}H-NMR (C_5D_5N): δ 6.20 (H-7, bs), 5.50 (H-3, s), 5.43 (H-1, bs), 4.96 (H-6,dd,$J_{5,6}$ = 5.0, $J_{6,7}$ = 2.3), 4.40 (2H-10, bs), 4.03 (2H-11, s), 3.20 (H-9, bd, $J_{5,9}$ = 7.7), 2.90 (H-5, dd, $J_{5,6}$ = 5.0, $J_{5,9}$ = 7.7).

Cyclopententriol **10.** Compound **7** (100 mg) was dissolved in liquid NH_3 (100 ml) adding abs EtOH (1 ml). The reaction vessel was kept at −45° and Li (200 mg, ~10 times molar excess) was added during 2 hr in small portions. After the last addition, Li excess was decomposed with EtOH (2 ml), and NH_3 was left to evaporate. The residue was dissolved in H_2O (50 ml) and continuous extracted with EtOAc (200 ml). The organic soln was evaporated *in vacuo* to give a residue (50 mg) which, chromatographed on silica gel (5 g) in $CHCl_3$-MeOH (9:1) afforded pure **10** (25 mg) as colourless viscous oil. $[\alpha]_D^{25}$ = −23° (MeOH, c = 0.8%). UV (MeOH) λ_{max} = 204 nm (lgϵ = 3.5). ^{1}H-NMR (D_2O): δ 5.62 (H-7, bs), 4.0–3.5 (2H-1, 2H-3, 2H-11), 2.46 (H-9, bsg), 2.3–1.7 (H-4, H-5), 2.18 (2H-6, bsg), 1.74 (3H-10, bs).

Tribenzoate **11.** Compound **10** (25 mg) was dissolved in pyridine (0.2 ml) and treated with 0.8 ml of a mixture pyridine-BzCl (10:4) for 2 hr at room temp. After H_2O (2 ml) addition, the mixture was stirred for 30 min and extracted with benzene, washing successively the organic layer with sat $NaHCO_3$, 2N HCl and H_2O. The soln was evaporated *in vacuo* leaving a residue (40 mg) which was chromatographed on silica gel (4 g) in benzene-Et_2O (95:5) giving pure **11** (25 mg) as colourless viscous oil. ^{1}H-NMR ($CDCl_3$): δ 5.56 (H-7, bs), 4.8–4.3 (2H-1, 2H-3, 2H-11), 2.88 (H-9, bsg), 2.7-2.2 (H-4, H-5, 2H-6), 1.84 (3H-10, bs).

REFERENCES

[1]A. Bianco, C. C. Bonini, M. Guiso, C. Iavarone and C. Trogolo, *Tetrahedron Letters* 4829 (1978).

[2]A. Bianco, M. Guiso, C. Iavarone, R. Marini-Bettolo and C. Trogolo, *Gazz. Chim. Ital.* **106,** 733 (1976).

[3]A. Bianco, M. Guiso, C. Iavarone, P. Passacantilli and C. Trogolo, *Ibid.* **108,** 13 (1978).

[4]This signal has been assigned by irradiating the H-7 resonance.

[5]In order to simplify the NMR data comparison of **7** and related iridoids, we maintained for **7** the iridoid skeleton numbering instead of the correct IUPAC nomenclature 2-hydroxymethyl-5,9,12-trioxa-tetracyclo [5.3.1.$1^{6,10}$.$0^{4,11}$] dodec-2-ene.

[6]In this solvent the resonances appear greatly modified, as signals shape and multiplicity, resulting particularly suited for analysing the splitting patterns and making unambiguously the chemical shift assignments reported in the experimental.

[7]This irradiation simplifies also the signal of the olefinic H-7.

[8]The same irradiation sharpens the broad singlet (δ 4.40) of the 2H-10 and the broad doublet of the H-9, both allylic.

[9]For this compound too was maintained, for comparison reasons, the parent iridoid numbering.