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THE STEREOCHEMISTRY AND SYNTHESIS OF ACHILLIN

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Abstract—A synthesis of the guianolide Achillin (Ia) that determines the stereochemistry is reported. The difficulty of making stereochemical assignments in these systems from NMR coupling constants is noted.

ACHILLIN, the major guianolide from *Achillea lanulosa*[1] and *Achillea millifolium*[2] has been shown to have structure I, except for stereochemistry.[1] Recently, Smolenski *et al.*[2] have suggested the stereochemistry shown in II for achillin from a complete analysis of its NMR spectrum. We report here details of a synthesis[3] of achillin from O-acetylisophotosantonic lactone (III), which demonstrates that it actually has the stereochemistry represented in formula Ia.

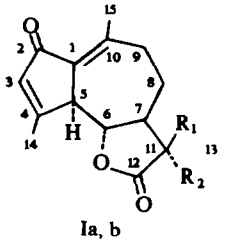
O-Acetylisophotosantonic lactone (III), of known absolute stereochemistry,[4] was converted to olefin Va by a sequence which has been reported previously.[3,5] Oxidation[3,5] of this compound with t-butyl chromate gives rise to desacetoxymatricarin (Ib),[6] a guianolide isomeric with achillin; it was established by studies with deuterated solvents that no epimerization had occurred during the synthesis.[3,5]

That achillin is epimeric with desacetoxymatricarin at least at C-11 was suggested by treating each compound with NaOH, which caused an eliminative lactone ring opening to yield trienone acids IVa[1] and IVb, respectively. Since achillin and desacetoxymatricarin did not give the same compound, they were shown to be epimeric at C-11, since C-7 is expected to be an epimerizable position under basic conditions. The isomers IVa and IVb are very similar in their spectral and optical properties and were difficult to differentiate, since only IVb could be obtained crystalline.

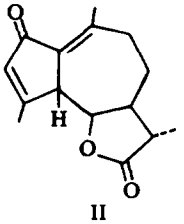
To modify our synthesis of desacetoxymatricarin[3,5] for a possible synthesis of compound Ia, it was necessary to epimerize the methyl group at C-11 at some stage in the sequence. Barton[7] has reported that epimerization at C-11 in the keto compound VIb could be effected in unspecified yield by KOBu-t in benzene, and that the resulting compound VIa was identical to one synthesized from β-santonin (C-11 β-methyl). Compound VIa could not be used in our synthesis of olefin VII, however, since the previous work[3,5] had shown that the alcohols derived from reduction of the C-3 ketone function could not be dehydrated if the C-4 methyl was in the more stable α-configuration.

Treatment of olefin Va with KOBu-t in refluxing t-butanol caused epimerization at C-11 and concurrent acetate saponification to give a ca. 1:1 mixture of hydroxy olefins Vb and VII. That epimerization had occurred at only C-11 was demonstrated by the use of t-butanol-O-d as solvent, under which conditions the compounds isolated were completely deuterated at C-11, since the NMR spectrum of each showed that the normal C-11 Me doublet centered at 8·78 τ had been replaced cleanly by a 3-proton singlet at this position. The C-6 proton signal appeared as the normal triplet,

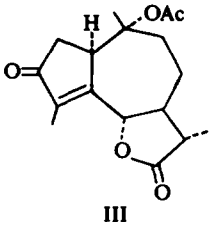
thus precluding deuterium incorporation at the asymmetric centers C-5, C-6 and C-7. The oily, less-polar isomer was identified as Vb since t-butyl chromate oxidation converted it into desacetoxymatricarin (Ib). The solid, more-polar isomer, therefore, can be assigned structure VII. Oxidation with t-butyl chromate converted it into achillin (Ia), identical in all respects with the natural compound. Gas chromatographic analysis of the total oxidation products showed that VII gave no desacetoxymatricarin and Vb gave no achillin. These results allow structure Ia to be assigned unambiguously to achillin.



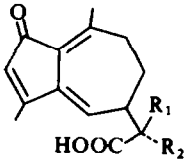
Ia, b



II

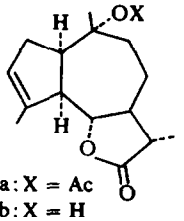


III

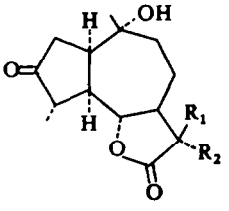


a: $R_1 = CH_3, R_2 = H$
b: $R_1 = H, R_2 = CH_3$

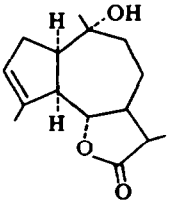
IVa, b



Va: X = Ac
b: X = H



VIa, b



VII

Therefore, the tentative assignment of structure II (or its optical antipode) by Smolenski, *et al.*,[2] to achillin is shown to be in error. Their assignment rests on the magnitude of the coupling constants between the protons on the four contiguous asymmetric centers. In particular, the 60 MHz spectrum in $CDCl_3$ showed three lines centered at 7·39 τ, which they assigned by double resonance techniques to the C-11 proton. This signal was interpreted as being part of a partially obscured quartet arising from a coupling of the adjacent Me group with the C-11 hydrogen (J = 7·4 Hz), and slightly broadened by a very small coupling to the C-7 proton. Smolenski, *et al.*, proposed that the dihedral angle between the C-7 and C-11 protons was near 90° to account for the low coupling constant. The observed 10·0 Hz coupling between C-6 and C-7 was assigned to a *cis* lactone fusion, although, as we have pointed out[3,5] a *trans* fusion in several of the achillin isomers (such as in Ia) is also consistent with this coupling, as judged from Dreiding models. Formula II allows the ca. 90° angle between the C-7 and C-11 protons in one conformation, while in either of the two

reasonable conformations of the more rigid isomer Ia, this angle is ca. 30°, for which the Karplus equation[8, 9] demands a coupling of ca. 7 Hz. We have, therefore, run the 100 MHz spectrum of achillin in $CDCl_3$, and can detect four lines of what is undoubtedly a 5-line pattern centered at 7·32 τ. In accord with this assignment, irradiation at 110 Hz (C-13 H position) collapses the signal to an unsymmetrical *doublet* at 7·32 τ, J = 7·5 Hz, not the singlet reported previously.[2] Thus this data, as well as the synthesis, supports structure Ia for achillin.

EXPERIMENTAL

Isomerization at C-11 *of olefin* Va. Olefin Va[5] (100 mg) and KOBu-t (100 mg) in t-BuOH (5 ml) was refluxed 2 hr under N_2, then cooled. Ether was added, the soln was washed with dil HCl and with H_2O, then dried. Removal of the solvent gave a brownish solid, which showed two well-resolved spots on TLC. Chromatography on silica gel (10 g) and elution with pet. ether–ether, 4:1, gave, in fractions 5–8 (50 ml), 38·5 mg (45%) of oily Vb $[\alpha]_D^{24}$ +26° (*c*, 1·0 in Chf), $\lambda_{max}^{CCl_4}$ 5·65 μ; NMR ($CDCl_3$), τ 4·53 (C-3 H, Hw = 5 Hz), 5·86 (C-6 H, t, J = 9·5 Hz), 8·15 (C-4 Me, Hw = 6 Hz), 8·78 (C-11 Me, d, J = 7 Hz), 8·85 (C-10 Me). Fractions 12–17 had 21·0 mg (25%) of crystalline VII, m.p. 151–153° (from ether); $[\alpha]_D^{24}$ +102° (*c*, 1·0 in Chf); $\lambda_{max}^{CHCl_3}$ 5·65 μ; NMR ($CDCl_3$), 4·53 (C-3 H, Hw = 7 Hz), 5·72 (C-6 H, t, J = 9·5 Hz), 8·17 (C-4 Me, Hw = 5 Hz), 8·81 (C-11 Me, d, J = 7 Hz), 8·88 (C-10 Me). (Found: C, 72·11; H, 8·41. $C_{15}H_{22}O_3$ requires: C, 71·97; H, 8·86%).

In another run, increasing the reaction time to 4 hr produced 19·5 mg (23%) of VII and 31·8 mg (37%) of Vb. In another run, in which t-BuOD was used as the solvent and the reaction time was 11 hr, 22·8 mg of 11-deutero-VII (27%) and 21·9 mg (25%) of 11-deutero Vb were isolated. These compounds had NMR spectra which were identical to those of the undeuterated materials, except the doublets centered at τ 8·78 and 8·81 respectively (C-11 Me) were replaced by 3-proton singlets at these positions.

Trienone acid IVa *from achillin* (Ia). Achillin (9·8 mg) was dissolved in 1·00 ml of 0·2N NaOH in MeOH in a flask fitted with a serum stopper and flushed well with N_2. The soln was transferred rapidly by syringe to a polarimeter cell and the change in rotation was followed with time. After 60 min, the value was constant at $[\alpha]_D^{24}$ +203°. The soln was diluted with H_2O, acidified with HCl aq and extracted with ether. Evap of the ether gave an oil showing one component detectable by TLC (no achillin remained), which could not be obtained crystalline. It had λ_{max}^{EtOH} 235, 243, 260, 320 mμ; $\lambda_{max}^{CHCl_3}$ 3·3–3·7 (broad), 5·87, 5·91, 6·12, and 6·25 μ; NMR ($CDCl_3$), τ 4·00 and 4·10 (C-3 H and C-6 H, broad), 7·64 and 7·89 (C-4 Me and C-10 Me), 8·80 (C-11 Me, d, J = 11 Hz).

Treatment of 0·5 g of achillin with a 0·5 M soln of NaOMe in CH_2Cl_2—MeOH (5 ml, 4:1) for 23 hr, gave the same acid, IVa, which was purified by silica gel chromatography. Fractions eluted with pet ether–ether, 9:1 to 3:1, gave the acid (0·15 g) as a transparent glass, which was distilled at 140° under high vacuum. (Found: C, 72·31; H, 7·52. $C_{15}H_{18}O_3$ requires: C, 73·14; H, 7·37%).

The methyl ester (diazomethane) had $\lambda_{max}^{CCl_4}$ 5·76, 5·92, 6·11 and 6·25 μ, and was homogeneous on TLC and VPC (4% SE-30 on Chromosorb W, ¼″ × 3′, 173°). It could also be formed in good yield when achillin was allowed to stand 12 hr in MeOH to which dry HCl or H_2SO_4 was added.

Trienone acid IVb *from desacetoxymatricarin* (Ib). Desacetoxymatricarin (11·4 mg) was treated with NaOH in MeOH in a polarimeter cell as described for achillin. The rotation stopped changing after 90 min at $[\alpha]_D^{24}$ +188°. The acid obtained (IVb) crystallized readily from ether, m.p. 215–219°; λ_{max}^{EtOH} 237, 245, 254, 320 mμ (log ε, 4·39, 4·45, 4·47, 3·88). (Found: C, 73·02; H, 7·43. $C_{15}H_{18}O_3$ requires: C, 73·14; H, 7·37%). The oily methyl ester was not distinguishable by VPC from the one derived from achillin, but the IR spectra of the two were slightly different.

Synthesis of achillin Ia. A soln of 60 mg of VII, 3 ml of 1·0N t-butyl chromate soln, 1 ml of HOAc, and 1 ml of Ac_2O in 10 ml CCl_4 was refluxed 9 hr under N_2. The soln was cooled, stirred 0·5 hr with 0·1 g of oxalic acid in 5 ml H_2O, then the CCl_4 soln was separated, washed with H_2O, and dried. Removal of solvent gave 10 mg of oil which showed one major component by TLC and VPC identical to authentic achillin. Purification by preparative TLC gave 3 mg (5%) of Ia, which after two crystallizations from ether gave material of m.p. 142–143°, (hot stage) undepressed upon admixture with authentic achillin of m.p. 144–145·5°; the detailed IR spectra (KBr) were also identical.

Similar oxidation of 60 mg of the isomeric hydroxy olefin Vb, gave 3 mg (5%) of desacetoxymatricarin of m.p. 199–201°.[3, 5]

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