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THE STEREOCHEMISTRY OF GAILLARDIN

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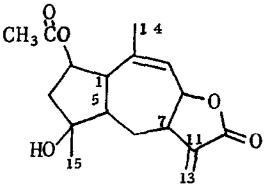
Gaillardin, a cytotoxic sesquiterpene lactone isolated[1] from Gaillardia pulchella Foug., has been assigned[2] structure 1. It is the purpose of this communication to describe chemical, spectral, and X-ray crystallographic evidence which confirms the structural assignment and establishes the absolute stereochemistry designated in 7 for gaillardin's six asymmetric centers.

Bromination of gaillardin in chloroform in the dark gave monobromogaillardin [2, 82% yield, mp 124-127° (dec, vac), $[\alpha]^{26}_{D}$ +155° (c 0.99, $CHCl_3$), λ^{MeOH}_{max} 211 mμ (ε 15,350), λ^{KBr}_{max} 5.71, 5.79, 6.01, 6.13 and 8.01 μ, nmr signals ($CDCl_3$) at τ 3.78 (1H, d, J = 3 cps, C-13), 4.45 (1H, d, J = 3 cps, C-13), 4.40 (1H, m, C-2), 5.12 (1H, J = 2 cps, C-9), 6.10 (1H, q, J = 2, 9 cps, C-8), 7.90 (3H, s, OAc), 8.12 (3H, m, C-14), and 8.80 (3H, s, C-15)]. The structure and absolute stereochemistry of 2 was determined by X-ray crystallographic analysis. The crystals are orthorhombic, of space group $P2_12_12_1$, with four molecules of $C_{17}H_{21}O_5Br$ in a unit cell of dimensions a = 11.01, b = 9.26, c = 17.03Å. Equi-inclination Weissenberg photographs were taken with CuK_α radiation, and the intensities of 1073 independent X-ray reflections obtained by visual estimation. The atoms, apart from hydrogen, were located in three-dimensional Patterson and electron-density distributions. The atomic co-ordinates and thermal parameters (anisotropic for the bromine atom, isotropic for the others) were subsequently adjusted by full-matrix least-squares calculations, and the average discrepancy between measured and calculated structure amplitudes fell smoothly to R = 10.7%. Anomalous-dispersion measurements established the absolute configuration of the molecule as that shown in 2.

The stereochemistry of the remaining asymmetric center (i.e., C-1) in gaillardin was indicated by spectral investigations of several gaillardin derivatives. Nmr spin decoupling experiments on gaillardin substantiated the chemical shift assignments previously made[2] and defined the magnitude of several coupling constants useful in precluding possible structural rearrangements during subsequent interconversions. Irradiation of both the C-14 vinyl



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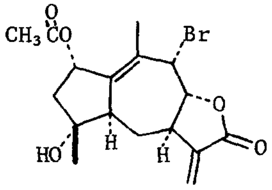

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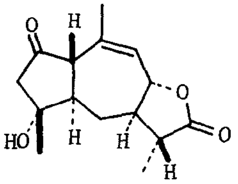

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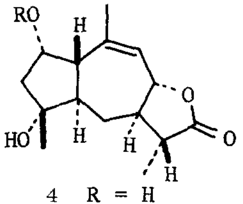
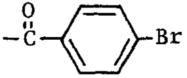
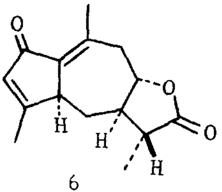


4 R = H

5 R =



$-\overset{O}{\overset{\|}{C}}-C_6H_4-Br$



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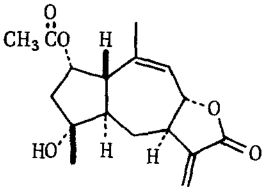

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methyl proton signal at τ 8.12 and the C-9 vinyl proton signal at τ 4.09 by triple resonance resulted in the collapse of the C-8 proton signal (τ 5.52) to a sharp doublet ($J_{7,8}$ = 9.5 cps), in accord with the view that the lactone ring was attached in a trans fusion. Likewise, irradiation of both the C-9 vinyl proton signal at τ 4.09 and the C-2 proton signal (τ 4.70) resulted in the collapse of the C-1 multiplet (τ 7.55) to a discernible doublet ($J_{1,5}$ = 12 cps) in accord with assignment of the trans A/B fusion.

The ord spectrum of β,γ-unsaturated ketone 3 supported the view that the configuration at C-1 was the same as in gaillardin (1), namely 1-β-H. Ketone 3 was obtained by Jones oxidation of dihydrodesacetylgaillardin (4),[2] known not to have epimerized at C-1 during hydrolysis because of its ready conversion to dihydrogaillardin upon acetylation. Jones oxidation of 4 in a deuterated medium[3] afforded 3, with an nmr signal for the C-1 proton identical to that of 3 synthesized in a protic medium, indicating that no epimerization had occurred during oxidation. The negative multiple Cotton effect curve observed for 3 [(c = 0.128, methanol); $[\alpha]^{25}_{600}$ -156^0, $[\alpha]_{327}$ -3600^0 (trough), $[\alpha]_{316}$ -3440^0, 305 mμ (sh), λ_0 301 mμ, 296 mμ (sh), $[\alpha]_{280}$ +2500^0 (peak); a = 61 x 10^2] was in accord with assignment of A/B-trans stereochemistry.[4,5] However, since 3 falls into a poorly precedented geometric arrangement of overlap of the C = C and C = O bonds, it was felt that a rigorous argument could be made only by comparison with the ord spectrum of the C-1 epimer. Attempted epimerization of **3** with diethylamine in methanol[6] and a variety of other alkaline reagents gave the previously-characterized[2] dienone **6** as the only isolable product.

X-Ray crystallographic analysis of desacetyldihydrogaillardin *p*-bromobenzoate [**5**, M^+ *m/e* 448, 450 (1:1), mp 191-193° $[\alpha]_D^{26}$ +3° (c 0.93, MeOH), λ_{max}^{MeOH} 244.5 mμ (ε 17,600), $\lambda_{max}^{CHCl_3}$ 2.78, 2.86, 5.65, 6.03 and 6.30 μ, nmr signals ($CDCl_3$) at τ 2.10 and 2.41 (4H, doublets, *J* = 8 cps, aromatic), 4.10 (1H, m, C-9), 4.43 (1H, m, C-2), 5.45 (1H, m, C-8), 8.20 (3H, m, C-14) 8.70 (3H, s, C-15) and 8.72 (3H, d, *J* = 6 cps, C-13)], confirmed the 1-β-H stereochemistry and independently conclusively established the structure and absolute stereochemistry of gaillardin as designated in **7**. The bromobenzoate **5** crystallizes in the orthorhombic space group $P2_12_12_1$ with four molecules of $C_{22}H_{25}O_5Br$ in a cell of dimensions *a* = 11.53, *b* = 16.30, *c* = 11.15Å. The X-ray intensity data were collected by means of a Hilger and Watts four-circle diffractometer controlled by a PDP-8 computer; Mo K_α radiation was employed and 1032 independent reflections were obtained with intensities significantly above background level. Preliminary co-ordinates for the bromine atom were derived from a Patterson synthesis, and the carbon and oxygen atoms were then located in three-dimensional electron-density distributions. The atomic co-ordinates and thermal parameter (anisotropic for the bromine atom, isotropic for the others) were refined by full-matrix least-squares calculations incorporating corrections for anomalous dispersion, and the discrepancy index R was reduced to 9.4%. The results define the absolute stereochemistry shown in **5**.

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