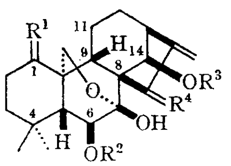
Oridonin, a New Diterpenoid from *Isodon* Species

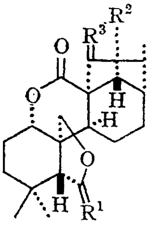
By EIICHI FUJITA, TETSURO FUJITA, HAJIME KATAYAMA, and MASAYUKI SHIBUYA
(Institute for Chemical Research, Kyoto University, Takatsuki, Osaka-fu, Japan)

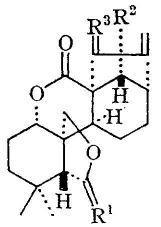
WE have reported the isolation of oridonin[1] [$C_{20}H_{28}O_6$, m.p. 248—250° (decomp.), $[\alpha]_D^{17}$ $-46°$], one of the minor diterpenoids, from the leaves of *Isodon japonicus* Hara (Japanese name: "Hikiokoshi", popular name: "Orido") and *I. trichocarpus* Kudo (Japanese name: "Kurobana-hikiokoshi"). Further investigation has led to a clarification of its structure and absolute configuration as shown in the formula (I) on the basis of the following spectral and chemical evidence.

The u.v. [λ_{max} 238 mμ(ϵ 10600)] and i.r. spectra [ν_{max}(KBr) 1705 and 1645 cm.$^{-1}$] indicated the presence of a conjugated ketone. The i.r. spectrum also indicated the presence of hydroxyl groups [ν_{max}(KBr) 3450 and 3200 cm.$^{-1}$]. The n.m.r. spectrum in deuteropyridine showed the presence of three secondary hydroxyl groups [δ 3·65 (1H, triplet, J = 8·0 c./sec.), 4·29 (1H, doublets of doublet, J = 10·0 and 7·0 c./sec.), and 5·35 p.p.m. (1H, singlet)], an exocyclic methylene group [δ 6·31 and 5·53 p.p.m. (each 1H, singlet)] which on hydrogenation gave a secondary methyl group, an ether-type methylene group [δ 4·61 p.p.m. (2H, AB type, J = 10·0 c./sec.), –CH_2–O–], and two tertiary methyl groups (δ 1·20 and 1·13 p.p.m.). Evidence for a tertiary alcohol was presented by oxidation of (I) with Jones' reagent followed by acetylation to give a keto-acetate (II), m.p. 213—215°, possessing a singlet signal ($\geqslant$C–OH) at δ 4·29 p.p.m. ($CDCl_3$) in n.m.r. spectrum. In addition, oridonin (I) on $NaBH_4$ reduction and subsequent acetylation afforded a triacetate (III) which was shown to have a tertiary alcohol on the basis of n.m.r. investigation [δ 4·41 p.p.m. ($CDCl_3$) (1H, singlet, $\geqslant$C–OH)].

The carbon skeleton and the functional groups were established by converting oridonin into dehydrotetrahydroisodocarpin (IV), m.p. 266—270°, by the following sequence. Periodate oxidation of oridonin gave a hemiacetal δ-lactone (V), m.p. >300° [λ_{max} 230 mμ (ϵ 5600), ν_{max}(KBr) 3500, 1745, 1707, and 1640 cm.$^{-1}$, δ 2·23 (1H, singlet, C-5–H), 4·43 (2H, AB type, J = 9·0 c./sec., –CH_2–O–), 4·84 (1H, triplet, J = 9·0 c./sec.,



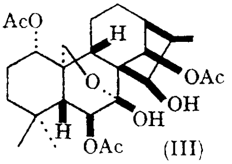




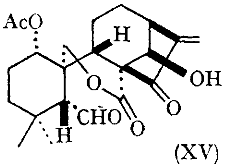
(I; $R^1 = \substack{\cdot\cdot OH \\ H}$, $R^2 = R^3 = H$, $R^4 = O$)
(II; $R^1 = O$, $R^2 = H$, $R^3 = Ac$, $R^4 = O$)
(XI; $R^1 = \substack{\cdot\cdot OH \\ H}$, $R^2 = H$, $R^3 = Ac$, $R^4 = O$)
(XII; $R^1 = \substack{\cdot\cdot OAc \\ H}$, $R^2 = H$, $R^3 = Ac$, $R^4 = O$)
(XIII; $R^1 = \substack{\cdot\cdot OAc \\ H}$, $R^2 = R^3 = H$, $R^4 = O$)

(IV; $R^1 = O$, $R^2 = H$, $R^3 = \substack{\cdot\cdot OH \\ H}$)
(VIII; $R^1 = O$, $R^2 = OH$, $R^3 = O$)
(IX; $R^1 = O$, $R^2 = OMs$, $R^3 = O$)
(X; $R^1 = O$, $R^2 = H$, $R^3 = O$)

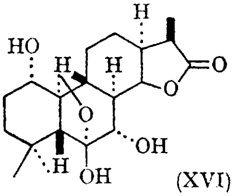
(V; $R^1 = \substack{OH \\ \cdot\cdot H}$, $R^2 = OH$, $R^3 = O$)
(VI; $R^1 = \substack{OAc \\ \cdot\cdot H}$, $R^2 = OH$, $R^3 = O$)
(VII; $R^1 = O$, $R^2 = OH$, $R^3 = O$)
(XIV; $R^1 = \substack{OH \\ \cdot\cdot H}$, $R^2 = OAc$, $R^3 = O$)



(III)



(XV)



(XVI)

C-1-H), 5·22 (1H, singlet, C-14-H), 5·72 (1H, singlet, C-6-H), 5·40, and 6·12 p.p.m. (C_5D_5N) (each 1H, singlet, $\rangle C{=}CH_2$)] which on treatment with acetic acid gave a hemiacetal acetate (VI), m.p. 206—208°, [δ 1·95 ($COCH_3$) and 6·13 p.p.m. ($CDCl_3$) (1H, singlet, C-6-H)] just as in the case of enmein.[2] The hemiacetal δ-lactone (V) on oxidation with small excess of Jones' reagent yielded $\gamma\delta$-dilactone (VII), m.p. 254—257°, [ν_{max}(KBr) 1780, 1750, 1710, and 1640 cm.$^{-1}$] catalytic hydrogenation of which gave a dihydrodilactone (VIII), m.p. 230—235°. Treatment of the latter with methanesulphonyl chloride in pyridine gave a mesylate (IX), m.p. 153—157°, which was reduced with Raney nickel to give a dilactone alcohol which proved to be identical with dehydrotetrahydroisodocarpin (IV), m.p. 266—270°, [ν_{max}(KBr) 3400, 1775, and 1712 cm.$^{-1}$] prepared by $NaBH_4$ reduction of dehydrodihydroisodocarpin (X).[1] Thus, it was clarified that oridonin can be represented as formula (I), although stereochemistry of C-6 and the location of hydroxyl group at C-14 remain unresolved.

Acetylation of oridonin with acetic anhydride in pyridine at room temperature for one hour afforded a monoacetate (XI), m.p. 243—245°, [ν_{max}($CHCl_3$) 3550, 3300, 1710, and 1631 cm.$^{-1}$, δ 2·06 ($COCH_3$) and 5·83 p.p.m. ($CDCl_3$) (1H, singlet, C-14-H)] and diacetate (XII) [ν_{max}($CHCl_3$) 3550, 3370, 1740, 1721, and 1645 cm.$^{-1}$, δ 2·02, 2·08 (each 3H, singlet, $COCH_3$), 4·63 (1H, broad, C-1-H), and 5·85 p.p.m. ($CDCl_3$) (1H, singlet, C-14-H)]. Partial hydrolysis of the latter by the treatment with oxalic acid in water resulted in the formation of the isomeric monoacetate (XIII), m.p. 220—222°, [ν_{max}(KBr) 3350, 1725, and 1640 cm.$^{-1}$, δ 1·98 ($COCH_3$), 4·60 (1H, broad, C-1-H), and 4·88 p.p.m. ($CDCl_3$) (1H, singlet, C-14-H)]. On treatment with $NaIO_4$, monoacetate (XI) gave hemiacetal lactone monoacetate (XIV), m.p. 246—249°, [λ_{max} 231 mμ, ν_{max}($CHCl_3$) 1750, 1720, and 1645 cm.$^{-1}$], while the isomeric monoacetate (XIII) yielded aldehyde lactone monoacetate (XV) [ν_{max}($CHCl_3$) 1738, 1712, and 1645 cm.$^{-1}$, δ 2·28 (1H, doublet, J = 4·0 c./sec., C-5-H) and 9·72 p.p.m. ($CDCl_3$) (1H, doublet, J = 4·0 c./sec., C-6-H]. Thus, the abnormal u.v. and i.r. spectral data for five-membered ring ketone of (I), (XI), and (XIII) proved to be due to hydrogen bonding with the hydroxyl group at C-6, because their periodate oxidation products (V), (XIV), and (XV) showed the normal values for the five-membered ring ketone which conjugated with exocyclic methylene group. Hence, β-configuration was assigned to the hydroxyl group at C-6.

Assignment of β-configuration at C-14 to the remaining secondary hydroxyl group was based on the following facts: (i) The proton signal of the hydrogen attached to the carbon atom on which the hydroxyl group stands appeared always as a singlet in the n.m.r. spectra of the foregoing compounds; (ii) Dihydro-oridonin on treatment with 3% KOH afforded a γ-lactone (XVI) [ν_{max}($CHCl_3$) 1763 cm.$^{-1}$, δ 3·77 (2H, AB type, J = 9·0 c./sec.) and 4·88 p.p.m. ($CDCl_3$) (1H, quartet, J = 4·0 and 2·0 c./sec., C-14–*H*)] which was formed by base cleavage of the β-diketone group and by rearrangement of α-ketol.

(*Received, February 3rd*, 1967, *Com.* 101.)

---

[1] E. Fujita, T. Fujita, and M. Shibuya, *Tetrahedron Letters*, **1966**, 3153.

[2] T. Kubota, T. Matsuura, T. Tsutsui, S. Uyeo, H. Irie, A. Numata, T. Fujita, and T. Suzuki, *Tetrahedron*, 1966, **22**, 1659.