OLIVOMYCIN AND RELATED ANTIBIOTICS

XXII. Stereochemistry of Olivinic Acid*

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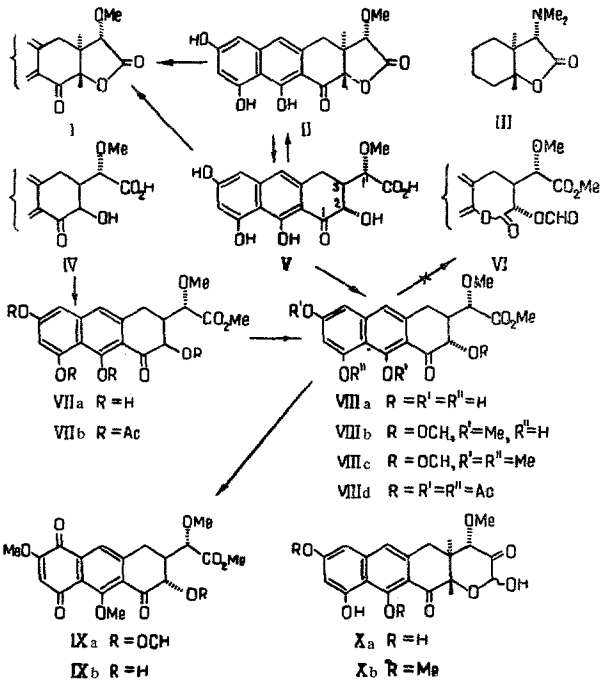
Khimiya Prirodnykh Soedinenii, Vol. 5, No. 6, pp. 580–589, 1969

UDC 615.779.931.+547.917

Olivinic acid (V), which is formed in the periodate oxidation of the aglycone of the olivomycins—olivin [2]—contains three of the five asymmetric centers of this compound, in consequence of which the elucidation of its stereochemistry is an important stage in the determination of the complete structure of the olivomycin antibiotics.

In order to establish the spatial arrangement of the substituents attached to the C_2 and $C_{1'}$ asymmetric atoms of olivinic acid, we first attempted the Baeyer-Villiger cleavage of the hydroaromatic ring in the tetramethyl ether of its 2-formyl derivative (VIIIc). The hydrolysis of the expected product of this reaction, VI, with subsequent O-methylation would lead to a structurally symmetrical α, α', β-trisubstituted glutaric ester the relative configuration of the C_α and $C_{\alpha'}$ asymmetric centers in which, corresponding to C_2 and $C_{1'}$ in olivinic acid, can be determined in a simple manner from its optical activity (presence or absence of intramolecular optical compensation). However, it was found that the action of CF_3CO_3H on the keto ester VIIIc led not to the Baeyer-Villiger reaction but to the oxidation of one of the aromatic rings with the formation of a 5,8-quinone (Xa), and the product of its desformylation IXb. The structures of these substances were confirmed on the basis of their interconversion (on hydrolysis and on acylation with formic-acetic anhydride) and by their spectral characteristics, especially the NMR spectrum of the main reaction product IXa. This lacks the signal of one O-methyl group found in the spectrum of the initial compound VIIIc, and instead of the peaks of three aromatic protons there are only two one-proton singlets, one of which (H_{10}) is displaced in the weak-field direction because of the deshielding effect of the carbonyl in the peri position, while the other (H_7), conversely, has undergone a diamagnetic shift because of the disturbance of the aromaticity of the system. A final proof of the structure of the quinone IXa was its formation from methyl dimethylformylolivinate (VIIIb) on oxidation with potassium nitrosodisulfonate (Fremy's salt).

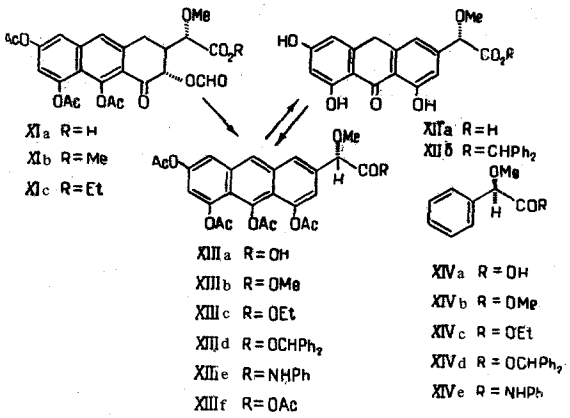


*For a preliminary communcation, see [1]; for part XXI, see [2].

Consequently, to elucidate the relative configuration we subjected olivinic acid (V) to dehydration with carbodiimides. This gave a high yield of the corresponding γ-lactone, olivinolide (II), isolated previously as a byproduct in the oxidation of olivin with periodate [2]. The lactone II is hydrolyzed by alkali to the initial acid (V), and under the action of pyridine or on heating it is converted into an isomeric lactone, epiolivinolide (I), the hydrolysis of which leads to epiolivinic acid (IV).

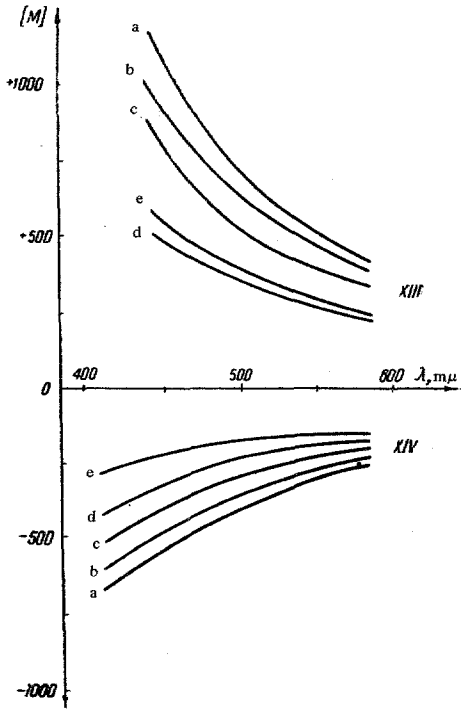
The chemical properties of epiolivinic acid (IV) and its derivatives, on the one hand, and of olivinic acid (V) and its derivatives, on the other hand, show the cis and trans positions, respectively, of the hydroxyl groups with respect to the side chain. Thus, the hydroxy acid IV lactonizes spontaneously on storage, while the acid V is converted into the lactone only under the action of dehydrating agents, which is completely analogous to the behavior of cis- and trans-2-hydroxy-cyclohexylacetic acids [3]. The lactone of the cis acid I is more stable than the trans isomer (II), and is formed from it on thermal treatment (compare the trans → cis isomerization of the lactone of 2-hydroxy-2-methoxycarbonylcyclohexylacetic acid [4]), and is also obtained from the trans acid V when it is heated and, partially, on lactonization under the action of dicyclohexylcarbodiimide or p-toluenesulfonic acid. The ester of the cis acid VIIa, in contrast to its lactone (I), is the less stable isomer and is converted into the trans ester (VIIa) under the action of pyridine or under the conditions of acid methanolysis, while the ester VIIIa remains unchanged under the same conditions. The acetates of the two esters VIIb and VIIId give the same anhydro derivative (XIIIb) on being heated with acetic anhydride.

In the NMR spectra of the lactones and the O_2-acylated esters of olivinic and epiolivinic acids (I, II, VIIIb–VIIId, XIb), the H_2 proton is represented by an isolated doublet in the 5.1–5.8 ppm region. In the compounds of the epi series, this doublet has $J_{2,3}$ 6–7 Hz, while in the derivatives of olivinic acid $J_{2,3}$ is 12.5 Hz, which definitely confirms the conclusion drawn above concerning the 2,3-cis and 2,3-trans configurations of these substances. In the spectra of the lactones I and II, the $H_{1'}$ signal is located at 4–4.5 ppm and forms a doublet with a $J_{1',3}$ value of about 10 Hz. This value is close to that found for the model compound III ($H_{1'}$: doublet at 3.15, J 12) the configuration of which we have demonstrated previously [5]. It follows from this that in both lactones $H_{1'}$ is in the trans position with respect to H_3, i.e., olivinic acid and its derivatives have the trans-threo-2,3,1' and epiolivinic acid and its derivatives the cis-threo-2,3,1' configuration. The correctness of this conclusion was further confirmed by a study of the NMR spectra of olivinal (Xa) and dimethylolivinal (Xb), which are intermediates in the oxidation of olivin and dimethylolivin to olivinic acid derivatives [2]. In the first of these compounds, the H_2 and $H_{1'}$ protons are represented, respectively, by doublets at 5.2 and 4.4 ppm with $J_{2,3}$ 12 and $J_{1,3}$ 10 Hz, and in the second compound by doublets at 5.02 and 4.46 ppm with $J_{2,3}$ 12.5 and $J_{1,3}$ 10 Hz, which confirms the trans arrangement of the H atoms at C_2, C_3, and $C_{1'}$.



To determine the absolute configuration of olivinic acid, it appeared desirable to aromatize its saturated ring in order to retain in the molecule only one of the three asymmetric centers. We have performed such aromatization previously by heating tetraacetylolivinic ester with acetic anhydride [6]. It was found that on being heated with Ac_2O the triacetylformylolivinates XIb and XIc give, similarly, the tetraacetylanhydroolivinic esters XIIIb and XIIIc, but the free acid XIa reacts differently with the formation of substances of unknown structure. In view of this, to obtain the desired tetraacetylanhydroolivinic acid (XIIIa) we selected a roundabout route. Olivinic acid (V) was converted via the esters VIIId and XIIIb into the previously-described anhydroolivinic acid (XIIa) [6]. The acetylation of this acid led to the optically inactive anhydride XIII; therefore, to exclude racemization, the acid was first esterified with diphenyldiazomethane, after which the anthrone system was aromatized by acetylation and the protective benzhydryl group was eliminated by hydrogenolysis: XIIa → XIIb → XIIId → XIIIa.

The tetraacetylanhydroolivinic acid (XIIIa) obtained by this route was converted by the usual method into the derivatives XIIIc–XIIIe. Simultaneously, D-methoxyphenylacetic acid (XIVa) and its derivatives XIVb–XIVe were synthesized from D-mandelic acid. A comparison of the optical rotatory dispersion curves of compounds XIII and XIV showed (figure) that they belong to different steric series, i.e., the $C_{1'}$ asymmetric center in anhydroolivinic and olivinic acids possess the S configuration.



Optical rotatory dispersion of compounds of the tetraacetylanhydroolivinic acid (XIII) series and of the D-α-methoxyphenylacetic acid (XIV) series: a) acid; b) methyl ester; c) ethyl ester; d) benzhydryl ester; e) anilide.

Thus, olivinic acid has the spatial structure 2S,3R,1'S (V), and the formulas given in the present paper reflect not only the relative but also the absolute configurations of the compounds studied.

EXPERIMENTAL

General information on the experimental work has been given previously [2]. The chromatographic systems were as follows: 1) benzene–acetone (1 : 1), 2) benzene–acetone (3 : 1), 3) benzene–acetone (5 : 1), and 4) benzene–acetone (10 : 1).

The NMR spectra were measured by G. Yu. Pek, the IR spectra were recorded by V. A. Krasnova, and the mass-spectrometric determinations of the molecular weights were performed by V. G. Zaikin and B. V. Rozynov.

1. Methyl 6,9-dimethyl-5,8-dioxo-5,8-dihydroolivinate (IXb) and its 2-formate (IXa). A) At −30° C, 1.8 ml of a 0.1 M dichloromethane solution of CF_3CO_3H prepared from 6.3 g of $(CF_3CO)_2O$ and 1 g of 95% H_2O_2 was added in 0.3-ml portions every 20–30 min to a solution of 50 mg of methyl 2-formyl-6,8,9-trimethylolivinate (VIIIc) [2] in 2.5 ml of CH_2Cl_2. The reaction mixture was extracted with chloroform, the extract was washed with $NaHCO_3$ and NaCl solutions, dried, and evaporated, and the residue was chromatographed in system 4. The zone with R_f 0.50–0.60 yielded 27 mg (54%) of the 2-formyloxy-5,8-quinone (IXa) with mp 166–167° C (from ethanol); $[\alpha]_D^{22}$ +12° (c 1; chloroform); λ_{max}, mμ 222, 258, 356 (log ε 4.48,4.35,3.64); ν_{max}, cm^{-1}: 1587, 1630, 1660, 1687, 1712, 1736, 1745; δ 2.80–3.40 (3H,m,H + + $2H_4$), 3.47 (3H,s,alip. OMe), 3.86 (3H,s,OMe), 3.90 (3H,s,OMe), 3.95 (3H,s,CO_2Me), 4.13 (1H,d,J 2.5,$H_{1'}$), 5.67 (1H,d,J 12.5,H_2), 6.15 (1H,s,H_7), 7.82 (1H,s,H_{10}), 8.40 (1H,s,OCHO).

Found, %: C 58.2; H 4.9; m/e 434 (M + 2; cf. [7]). Found for $C_{21}H_{20}O_{10}$, %: C 58.3; H 4.7; mol. wt. 432.

The zone with R_f 0.4–0.5 yielded 5 mg (10%) of the 2-hydroxy-5,8-quinone (IXb), with mp 187–190° C (decomp., from ethanol); $[\alpha]_D^{22}$ +93° (c 1; chloroform); λ_{max}, mμ: 220, 258, 358 (log ε 4.46,4.36,3.65); ν_{max}, cm^{-1}: 1585, 1618, 1647, 1687, 1704, 1749.

Found, %: C 59.4; H 5.3; m/e (M + 2; cf. [7]). Calculated for $C_{20}H_{20}O_9$, %: C 59.4; H 5.0; mol. wt. 404.

The formate IXa underwent hydrolysis to the alcohol IXb under the action of 0.1 N KOH (20° C, 5 min) and was formed from IXb on acylation with a mixture of 100% HCO_2H and Ac_2O in pyridine (0° C, 15 min).

B) To a solution of 50 ml of methyl 2-formyl-6,9-dimethylolivinate (VIIIb) [2] in 2 ml of ethyl actate was added a solution of 250 mg of $ON(SO_3K)_2$ [8] in 10 ml of water and then ethanol until a homogeneous mixture had been formed (about 3 ml). The reaction solution was kept at 20° C for 10 hr and was then extracted with ethyl acetate, and the extract was washed with NaCl solution, dried, and evaporated. The residue was chromatographed in system 4 the zone with R_f 0.5–0.6 being isolated. This gave 24 mg (46%) of the 2-formyloxy-5,8-quinone (IXa) described in the preceding experiment.

2. 2-Epiolivinolide (I), olivinolide (II), and their 6,9-dimethyl ethers. A) Olivinic acid (V) [2], distributed in a thin layer on the bottom of a flask, was heated in 10-mg portions in a current of argon at 215° C until the substance had melted completely, and then it was dissolved in tetrahydrofuran and chromatographed in system 3. After 10 repetitions of the experiment, the product consisted of 10 mg (10%) of the initial acid V, R_f 0.18; 9 mg (10%) of olivinolide (II) [2], R_f 0.53; and 60 mg (65%) of 2-epiolivinolide (I), R_f 0.65, which crystallized from ethanol in two forms, with mp 215–218° C (plates) and mp 242–247° C (needles); $[\alpha]_D^{20}$ −274° (c 0.3; methylcellosolve); λ_{max}, mμ::226, 282, 326, 420 (log ε 4.24,4.64,3.74,4.22); ν_{max}, cm^{-1}: 1585, 1645, 1782, 3300; $\delta^{(CD_3)_2SO}$ 2.80–3.40 (3H,m,H_3 + 2H_4), 3.50 (3H,s,slip. OMe), 4.07 (1H,d,J 10,H_1'), 5.26 (1H,d,J 7.5,H_2), 6.39 (1H,d,J 2,$H_{[7(5)]}$), 6.56 (1H,d,J 2,$H_{[5(7)]}$), 6.90 (1H,s,H_{10}).

Found, %: C 60.0; H 4.4; mol. wt. 330. Calculated for $C_{17}H_{14}O_7 \cdot 0.5H_2O$, %: C 60.0; H 4.41; mol. wt. (anhydrous) 330.

Epiolivinolide (I) is also formed by heating olivinic acid (V) with a 0.4 N solution of TsOH in benzene–acetic acid (1 : 1) (80° C, 4 hr). Yield 35% (calculated on the acid that had reacted).

B) A solution of 100 mg of olivinic acid (V) in 1 ml of tetrahydrofuran was mixed at −10° C with solution of 60 mg of N-cyclohexyl-N'-(γ-dimethylamino-propyl)carbodiimide [9] in 0.2 ml of tetrahydrofuran, and after 5 min the mixture was chromatographed in system 2. The zone with R_f 0.23–0.33 yielded 19 mg (19%) of the initial acid (V), the zone with R_f 0.72–0.82 yielded 29 mg (31%) of epiolivinolide (I), and the zone with R_f 0.50–0.69 yielded 40 mg (43%) of olivinolide (II) with mp 228–235° C (decomp., from dioxane); $[\alpha]_D^{20}$ −180° (c 0.3; methylcellosolve); $\delta^{(CD_3)_2SO}$ 2.90–3.50 (3H,m,H_3 + 2H_4), 3.57 (3H,s,alip. OMe), 4.55 (1H,d,J 11,H_1'), 5.15 (1H,d,J 11,H_2), 6.41 (1H,d,J 2,$H_{[7(5)]}$), 6.54 (1H, d,J 2,$H_{[5(7)]}$), 6.96 (1H,s,H_{10}); for the UV and IR spectra, see [2].

On hydrolysis with 0.1 N NaOH (20° C, 15 min), olivinolide (II) gave olivinic acid (V) (yield quantitative), and under the action of pyridine (20° C, 1 hr) or on heating (215° C, 5 min) it was converted into epiolivinolide (I) (yield 70–90%).

C) A solution of 100 mg of 6,9-dimethylolivinic acid [2] in 0.5 ml of tetrahydrofuran was mixed at 20° C with a solution of 55 mg of N-cyclohexyl-N'-(γ-dimethylaminopropyl)carbodiimide in 1 ml of the same solvent, and after 5 min the mixture was chromatographed in system 3. This gave 20 mg (20%) of the initial acid with R_f 0.35, 21 mg (23%) of 6,9-dimethyl-2-epiolivinolide with R_f 0.70, and 50 mg (54%) of 6,9-dimethylolivinolide with R_f 0.63, mp 169–175° C (from ethanol); $[\alpha]_D^{20}$ −146° (c 0.2; chloroform); δ 2.80–3.40 (3H,m,H_3 + 2H_4), 3.62 (3H,s,alip. OMe), 3.85 (3H,s,ar. OMe), 3.97 (3H,s,ar. OMe), 4.20 (1H,d,J 11,H_1'), 4.60, (1H,d,J 12,H_2), 6.45 (2H,s,H_5 + H_7); for the UV and IR spectra, see [2].

3. 2-Epiolivinic acid (IV) and its derivatives (VIIa and VIIb). A) A solution of 30 mg epiolivinolide (I) in 5 ml of 0.1 N KOH was left at 20° C for 35 min and was then acidified with dil H_2SO_4 to pH3 and was extracted with ethyl acetate. After chromatography in system 2, 30 mg (95%) of 2-epiolivinic acid (IV) was obtained with R_f 0.59 [benzene–acetone–acetic acid (14 : 5 : 1) system], [mp 156–159° C (from acetonitrile); $[\alpha]_D^{20}$ −37° (c 1; ethanol); γ_{max}, mμ 228, 278, 325, 405 (log ε 4.30,4.56,3.68,3.97) ν_{max}, cm^{-1}: 1462, 1515, 1640, 1727, 3400.

Under the action of a carbodiimide, as in Experiment 2B, or on standing at room temperature, the hydroxy acid IV was converted into the lactone I.

B) A solution of 160 mg of the acid IV in 5 ml of tetrahydrofuran was mixed at −5° C with 14 ml of a 0.037 M ethereal solution of CH_2N_2, and after 1 min the mixture was evaporated and chromatographed in system 3. This gave 120 mg (73%) of methyl 2-epiolivinate (VIIa), R_f 0.50; mp 130–134° C (from chloroform); $[\alpha]_D^{26}$ −11.5° (c 1; ethanol); λ_{max}, mμ: 230, 276, 324, 405 (log ε 4.24, 4.56, 3.63, 4.02); ν_{max}, cm^{-1}: 1520, 1615, 1647, 1737, 3300, 3400, 3450, 3500.

Found, mol wt. 362; calculated for $C_{18}H_{18}O_8$: mol. wt. 362.

The action on this substance of pyridine (20° C, 1 hr) or a 3% methanolic solution of TsOH (65° C, 6 hr) formed a mixture of the 2-epimeric esters VIIa and VIIIa (the ester VIIIa undergoes no change under the same conditions).

C) The ester VIIa (100 mg) was acetylated with 1 ml of acetic anhydride–pyridine mixture (20° C, 24 hr), and the substance isolated in the usual way was chromatographed in system 3. This gave 93 mg (62%) of methyl tetraacetyl-2-epiolivinate (VIIb), R_f 0.61; $[\alpha]_D^{24}$ −45° (c 1; chloroform); λ_{max}, mμ: 258, 302, 358 (log ε 4.74, 3.86, 3.49); ν_{max}, cm^{-1}: 1575, 1633, 1710, 1750, 1770; δ 2.20 (3H, s, OAc), 2.25 (3H, s, OAc), 2.30 (3H, s, OAc), 2.40 (3H, s, OAc), 2.80–3.40 (3H, m, H_3 + $2H_4$), 3.05 (3H, s, OMe), 3.75 (3H, s, CO_2Me), 4.00 (1H, d, J 3, $H_{1'}$), 5.57 (1H, d, J 6, H_2), 6.87 (1H, d, J 2, $H_{[7(5)]}$), 7.32 (1H, d, J 2, $H_{[5(7)]}$), 7.40 (1H, s, H_{10}).

Found: mol. wt. 530. Calculated for $C_{26}H_{26}O_{12}$: mol. wt. 530.

4. Benzhydryl anhydroolivinate (XIIb). A solution of 30 mg of Ph_2CN_2 in 3 ml of ether was added at −15° C to a solution of 34 mg of anhydroolivinic acid (XIIa) [6] in 1 ml of tetrahydrofuran. After 5 min, the solvent was distilled off and the residue was chromatographed in system 2. This gave 49 mg (96%) of the ester XIIb, R_f 0.64, mp 103–107° C (from benzene–acetone); $[\alpha]_D^{23}$ −58° (c 1; ethanol); λ_{max}, mμ: 257, 272, 314, 370 (log ε 4.05, 3.98, 4.08, 3.98); ν_{max} cm^{-1}: 1585, 1610, 1635, 1720, 3320.

Found, %: C 69.9; H 5.2. Calculated for $C_{30}H_{24}O_7 \cdot H_2O$, %: C 70.2; H 5.1.

5. Tetraacetylanhydroolivinic acid (XIIIa) and its derivatives (XIIIb-f). A) The benzhydryl ester (XIIId). The anhydroolivinic ester XII (43 mg) was acetylated with 1 ml of acetic anhydride–pyridine mixture (0° C, 12 hr), the mixture was evaporated, and the residue was crystallized from benzene–hexane. This gave 34 mg (60%) of the ester XIIId, R_f 0.72 (system 2); mp 108–112° C; $[\alpha]_D^{25}$ +38.6° (c 0.2; chloroform); λ_{max}, mμ: 264, 340, 358, 376, 396 (log ε 5.15, 3.58, 3.68, 3.67, 3.63); ν_{max}, cm^{-1}: 1470, 1775.

Found: mol. wt. 664. Calculated for $C_{38}H_{32}O_{11}$: mol. wt. 664.

B) The acid XIIIa. The benzhydryl ester XIIId (34 mg) in 1 ml of tetrahydrofuran was hydrogenated at 22° C in the presence of 30 mg of Pb black until 1 mole of H_2 had been absorbed. After crystallization from ethanol, the yield of the acid XIIIa was 22 mg (86%), R_f 0.25 (system 2); mp 222–227° C; $[\alpha]_D^{27}$ +90° (c 0.2; chloroform); λ_{max}, mμ: 228, 262, 322, 356, 374, 394 (log ε 4.39, 5.20, 3.51, 3.83, 3.81, 3.79); ν_{max}, cm^{-1}: 1640, 1720, 1742, 1765, 3180.

Found, %: C 59.7; H 4.7. Calculated for $C_{25}H_{22}O_{11}$, %: C 60.2; H 4.4.

C) The methyl ester (XIIIb). 1) A solution of 50 mg of methyl triacetylformylolivinate (XIb) [2] in 5 ml of acetic anhydride was boiled for 18 hr, after which it was evaporated and the residue was crystallized from ethanol. This gave 34 mg (69%) of the ester XIIIb, with mp 210–215° C, $[\alpha]_D^{20}$ +84° (c 1; chloroform) (cf. [6]).

2) A solution of 30 mg of methyl tetraacetylepiolivinate (VIIb) in 0.5 ml of acetic anhydride was heated in a sealed tube at 200° C for 3 hr, and then it was evaporated and the residue was dissolved in chloroform, the solution was filtered through a layer of silica gel, and the solvent was distilled off. After crystallization from ethanol, the yield of the anhydroester XIIIb was 12 mg (42%), mp 212–217° C. $[\alpha]_D^{20}$ +84° (c 1; chloroform).

D) The ethyl ester XIIIc. 1) A solution of 20 mg of the acid XIIIa in 2 ml of tetrahydrofuran was treated at 0° C with an excess of a 0.1 M ethereal solution of diazoethane, the solvent was distilled off, and the residue was chromatographed in system 3. The yield of the ester XIIIc was 19 mg (90%); R_f 0.50; mp 197–201° C (from ethanol);

$[\alpha]_D^{23}$ +69° (c 0.2; chloroform); λ_{max}, mμ: 227, 263, 322, 340, 356, 376, 396 (log ε 4.26,5.20,3.50,3.60,3.72,3.70, 3.67); ν_{max}, cm^{-1}: 1465, 1645, 1747, 1765.

Found: mol. wt. 526. Calculated for $C_{27}H_{26}O_{11}$: mol. wt. 526.

2) A solution of 40 mg of triacetylformylolivinic acid (XIa) [2] in 1.5 ml of tetrahydrofuran was treated with 1 ml of 0.1 M ethereal diazoethane, the mixture was evaporated, and the residue was chromatographed in system 3. This gave 39 mg (95%) of the ester XIc; R_f 0.66: $[\alpha]_D^{23}$ −68° (c 1; chloroform); λmax, mμ: 259, 304, 358 (log ε 4.76,3.72, 3.50); ν_{max}, cm^{-1}: 1465, 1630, 1700, 1748, 1773.

Found: mol. wt. 530. Calculated for $C_{26}H_{26}O_{12}$: mol. wt. 530.

When this substance was heated with a 20-fold amount of Ac_2O in a sealed tube (200° C, 5 hr), the ester of tetraacetylanhydroolivinic acid (XIIIc) was formed. After crystallization from ethanol, the yield was 80%, mp 197–201° C; $[\alpha]_D^{20}$ + 68° (c 1; chloroform).

E) The anilide XIIIe. At 20° C, 9 mg of dicyclohexylcarbodiimide in 0.1 ml of tetrahydrofuran was added to 20 mg of the acid XIIIa and 4 mg of aniline in 2 ml of the same solvent. After 5 min the solution was filtered and evaporated, and the residue was chromatographed in system 3. This gave 17 mg (74%) of the anilide XIIIe; R_f 0.45; $[\alpha]_D^{25}$ +47° (c 0.2; chloroform); λ_{max}, mμ: 264, 320, 340, 356, 374, 396 (log ε 5.20,3.36,3.59,3.71,3.70,3.69); ν_{max}, cm^{-1}: 1463, 1528, 1600, 1642, 1668, 1765, 3310.

Found, %: N 2.93; mol. wt. 573. Calculated for $C_{31}H_{27}NO_{10}$, %: N 2.44; mol. wt. 573.

F) The mixed anhydride XIIIf. The acid XIIa (40 mg) was acetylated with 2 ml of Ac_2O–Py mixture (20° C, 48 hr). After the standard treatment and chromatography in system 3, 36 mg (56%) of the anhydride XIIIf was isolated; R_f 0.74; mp 210–215° C (from benzene–acetone); $[\alpha]_D^{20}$ 0° (c 1; chloroform); λ_{max}, mμ: 266, 320, 338, 354, 385, 405 (log ε 5.16,3.64,3.81,3.77,3.71,3.74); ν_{max}, cm^{-1}: 1663, 1777, 1827.

6. D-α-Methoxyphenylacetic acid (XIVa) and its derivatives (XIVb-e). A) The acid XIVa. A mixture of 500 mg of D-mandelic acid, 5 ml of dimethylformamide, 3 ml of CH_3I, and freshly-prepared Ag_2O (from 6.24 g of $AgNO_3$) was stirred at 20° C for 24 hr and was then diluted with benzene, filtered, washed free from $HCONMe_2$ with water, worked up in the usual way, and distilled in vacuum. The resulting ester (XIVb) (525 mg, n_D^{23} 1.504; cf. [10]) was saponified with 16 ml of 0.4 N KOH in 50% methanol (20° C, 1.5 hr), and the acid liberated (XIVa) was crystallized by trituration with petroleum ether. Yield 245 mg (50%); R_f 0.31 (in system 4); mp 63–65° (from heptane); $[\alpha]_D^{23}$ −164° (c 1; chloroform); $[\alpha]_D^{23}$ − 146° (c 1; ethanol) (cf. [11]).

B) The methyl ester XIVb was obtained by methylating 20 mg of the acid XIVa with an excess of diazomethane and was purified in ethereal solution by filtration through a layer of Al_2O_3. Yield 14.5 mg (66%); R_f 0.67 in system 4; $[\alpha]_D^{23}$ −132° (c 1; chloroform) (cf. [11]).

C) The ethyl ester XIVc was obtained by heating 35 mg of the acid XIVa with 2 ml of 2.5 N ethanolic HCl (6 hr at the boil); the crude product was purified by filtration through a layer of Al_2O_3 in benzene solution. Yield 25 mg (62%); R_f 0.67 (in system 4); $[\alpha]_D^{23}$ −103° (c 1; chloroform).

Found: mol. wt. 194. Calculated for $C_{11}H_{14}H_3$: mol. wt. 194.

D) The benzhydryl ester XIVd. The acid XIVa (20 mg in 0.5 ml of ether) was esterified with diphenyldiazomethane under the conditions of Experiment 4 and the substance obtained was washed free from oily impurities with petroleum ether. The yield of the benzhydryl ester XIVd was 28 mg (70%); mp 93–94° C (from ether–petroleum ether); $[\alpha]_D^{29}$ −51° (c 1; chloroform).

Found, %: C 80.0; H 6.4. Calculated for $C_{22}H_{20}O_3$, %: C 79.5; H 6.0.

E) The anilide XIVe. At 20° C, 60 mg of dicyclohexylcarbodiimide in 0.5 ml of acetonitrile was added to 40 mg of the acid XIVa and 24 ml of aniline in 0.2 ml of acetonitrile and after 1 hr the mixture was worked up as in Experiment 5E. After chromatography in system 4, the yield of the anilide XIVe was 40 mg (70%); R_f 0.68; $[\alpha]_D^{24}$ −63° (c 1; chloroform).

Found, %: C 74.8; H 6.3; N 6.0; mol. wt. 241. Calculated for $C_{15}H_{15}NO_2$, %: C 74.7; H 6.2; N 5.8; mol. wt. 241.

CONCLUSIONS

It has been established that olivinic acid possesses the 2S, 3R, 1'S configuration (V).

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24 September 1968

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