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13-Halo Derivatives of *ent*-Kauranoic Acid. Synthesis and Structure

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Abstract—The *ent*-kauranoic acid 13-chloro-, bromo- and iodo-derivatives were synthesized in quantitative yield. Their molecular structure was established by the X-ray diffraction analysis.

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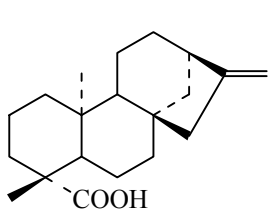
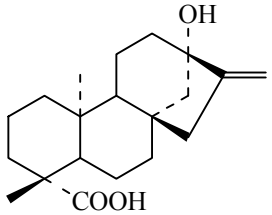
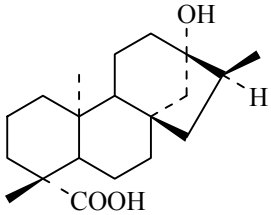
Kauranes are an important class of diterpenoids containing teteracyclic carbon frame. A wide range of biological actions of kaurane diterpenoids makes them an attractive platform for the preparation of new biologically active derivatives [1]. *ent*-Kaurenoic acid **I**, a key intermediate of the biosynthesis in many plants, as well as a metabolite of some fungi, is widely used for further chemical transformations [2].



I



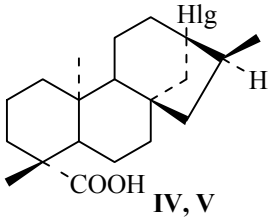
II



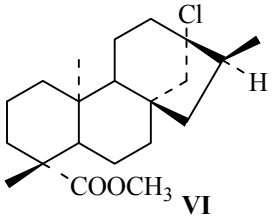
III

However, the content of *ent*-kaurenoic acid and its derivatives in natural sources is low. In this regard, the diterpenoid steviol (13-hydroxy-*ent*-kaurenoic acid) **II** , an aglycone of sweet glycosides of the plant *Stevia rebaudiana* Bertoni, which are commercially available on an industrial scale, is a promising precursor for synthesis of kaurane compounds with significant biological activity. The use of steviol **II** in medicinal chemistry is limited owing to high sensitivity of its hydroxyallyl system to acidic environments due to the Wagner–Meerwein rearrangement resulting in the product of *ent*-beierane structure.

We have recently shown [4] that the product of steviol hydrogenation 16(*S*)-dihydrosteviol (13-hydroxy-*ent*-kauranoic acid) **III** is stable in the acidic media, and the developed stereoselective synthesis method of its preparation from the available glycosides of the plant *S. rebaudiana* makes compound **III** an attractive starting compound for the synthesis of various kaurane derivatives in any media. In this study the 13-halo derivatives of *ent*-kauranoic acid were synthesized in quantitative yield, the molecular structure of them was established by X-ray diffraction analysis.



IV, V



VI

Hlg = I (**IV**), Br (**V**).

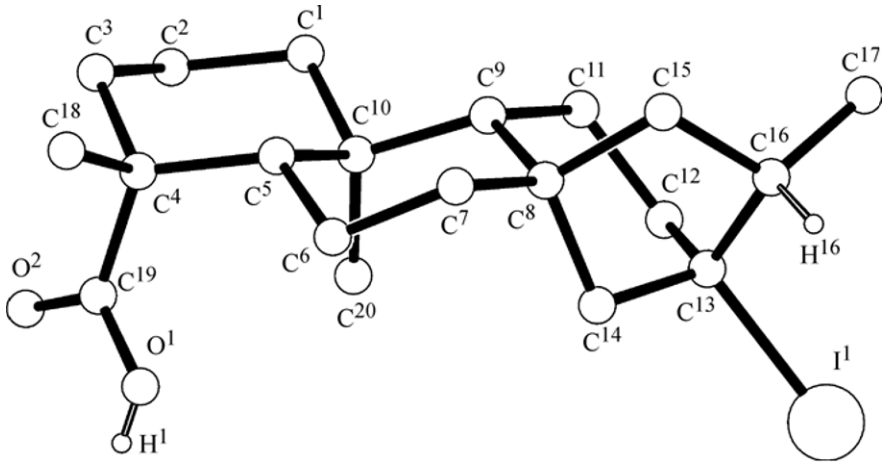


Fig. 1. Molecular structure of 13-iodo-*ent*-kauranoic acid **IV**. The hydrogen atoms are shown selectively.

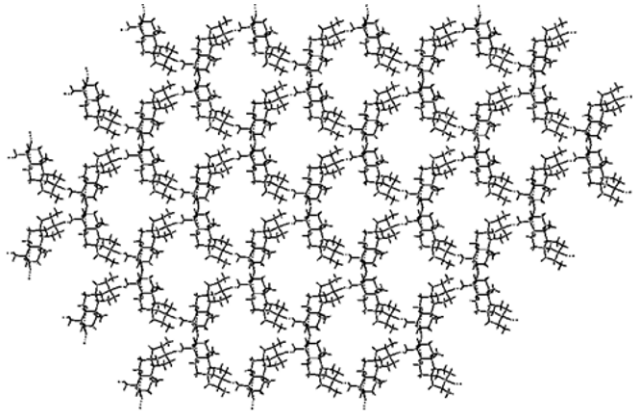


Fig. 2. Crystal structure of 13-iodo-*ent*-kauranoic acid **IV**.

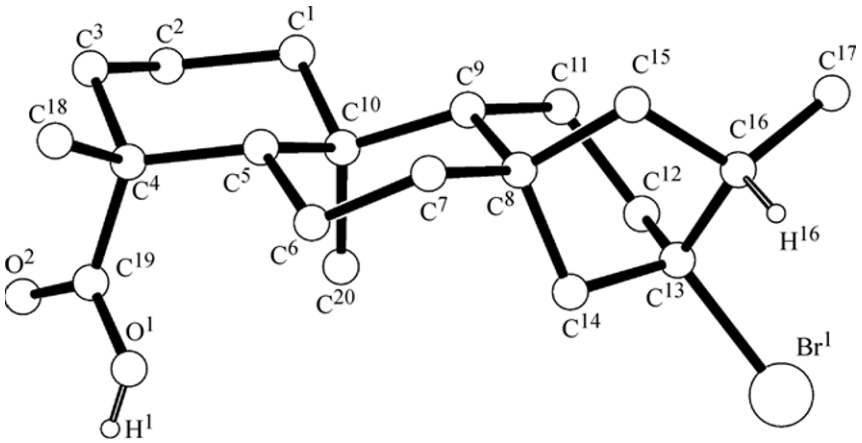


Fig. 3. Molecular structure of 13-bromo-*ent*-kauranoic acid **V.** The hydrogen atoms are shown selectively.

The iodo and bromo derivatives **IV–V** were obtained by heating of dihydrosteviol **III** with the corresponding hydrohalic acid. After the purification by column chromatography on silica gel and recrystallization, the yields of halides **IV** and **V** equal to 80–90%. It is interesting to note that the attempt to replace the tertiary hydroxy group in **III** with iodine by means of trimethyliodosilane by the Olah method [5] was not successful.

The chloro derivative **VI** was obtained by the recrystallization from methanol of 13-chloro-*ent*-kaura-

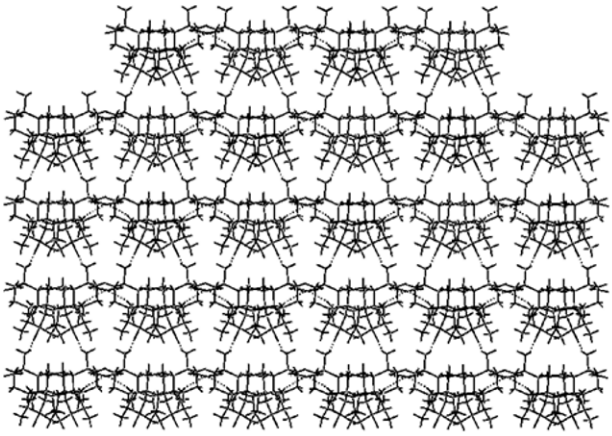


Fig. 4. Crystal structure 13-bromo-*ent*-kauranoic acid **V.**

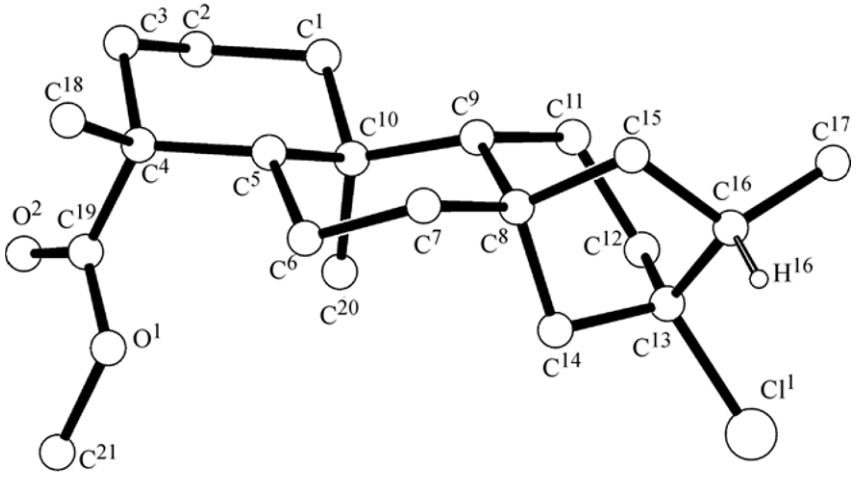


Fig. 5. Molecular structure of methyl 13-chloro-*ent*-kauranate **VI**. The hydrogen atoms are shown selectively.

noyl chloride synthesized by the reaction of dihydrosteviol **III** with an excess of thionyl chloride.

Compared with the original dihydrosteviol **III**, in the IR spectra of compounds **IV–VI** there is no absorption band of OH groups at 3400 cm^{-1}, and in the ^1H NMR spectra the doublet of $C^{17}H_3$ group is shifted downfield. The shift value significantly depends on the halogen nature. Thus, the maximal shift (0.18 ppm) is observed in the case of iodide **IV**, in bromide **V** it is smaller (0.14 ppm), and it is the least in chloride **VI** (0.10 ppm). The replacement of the hydroxy group of dihydrosteviol **III** with halogen leads to the downfield strong shift of the proton signals at the C^{16} atom: 2.42 (**IV**), 2.55 (**V**) and 2.26 ppm (**VI**).

The crystals of **IV** (Fig. 1) crystallize in a space group $P2_12_12$. Parameters of its molecular structure (Fig. 3) are similar to the parameters of chloride **VI**, but the intermolecular structure is different. The classical hydrogen bonds of O–H···O type cause the formation of centrosymmetric dimers, which are typical of carboxylic acids, and the C–H···I interactions lead to the formation of two-dimensional network along the *x*0*z* plane (Fig. 2).

The molecular structure of bromide **V** is shown in Fig. 3. Its crystalline structure is a little changed compared with the structure of compound **IV**: The decrease in the halogen atom size leads to the appearance of one more hydrogen bond of C–H···O type. The two-dimensional nets formed by the classical hydrogen bonds O–H···O and intermolecular C–H···Br interactions are more complicated (Fig. 4).

Chloride **VI** crystallizes in a chiral space group $P2_12_12$. Its molecular structure is shown in Fig. 5. Due to the intermolecular interactions of C–H···O type

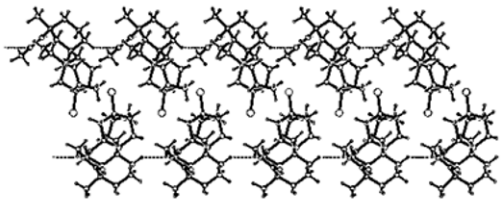


Fig. 6. Crystal structure of methyl 13-chloro-*ent*-kauranate **VI**.

(parameters of the hydrogen bond C^1–$H^{1b}\cdots O^{1'}[1 + x, y, z]$ are as follows: C^1–H^{1b} 0.97 Å, $H^{1b}\cdots O^{1'}$ 2.70 Å, $C^1\cdots O^{1'}$ 3.499 Å, $C^1H^{1b}O^{1'}$ 140°) in a crystal of this compound there are infinite chains along the 0*x* axis, formed by a simple translation (Fig. 6).

EXPERIMENTAL

The X-ray analysis of compounds **IV–VI** was performed in the Department of X-ray diffraction spectral-analytical Center of Collective Use of the Russian Foundation for Basic Research on a SMART Apex diffractometer at 20°C (MoK_α-scanning). The structures were solved by the direct method using SIR program [6] and refined first in isotropic and then in anisotropic approximation. The hydrogen atoms of hydroxy groups were detected from the difference series of electron density. The hydrogen atoms at carbon atoms were placed in the calculated position and refined later in the *rider* model. The structures of compounds **IV–VI** were refined using the program SHELXL97 [7], WinGX [8]. Parameters of the crystals and conditions of X-ray experiments are given in Table 1. Complete data on the structures of **IV–VI** are deposited in the Cambridge Structural Database.

13-Iodo-*ent*-kauran-19-ic acid (IV). To a solution of 0.5 g of dihydrosteviol **III** in 50 ml of benzene was added 10 ml of concentrated HI. The reaction mixture was stirred under reflux for 24 h, cooled, and poured into ice water. The product was extracted with diethyl ether. The organic layer was washed with $Na_2S_2O_3$ and Na_2SO_4 aqueous solutions, dried over $MgSO_4$ and concentrated. The residue was chromatographed on a silica gel eluting with a petroleum ether–ethyl acetate mixture (7:1). The product was recrystallized from acetone. Yield 0.45 g (83%), mp 252–253°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.75–2.38 m (30H, kaurane), 0.98 s (3H, $C^{20}H_3$), 1.15 d (3H, $C^{17}H_3$, *J* 7), 1.24 s (3H, $C^{18}H_3$), 2.55 m (1H, $C^{16}H$). Found, %: C 55.81; H 7.23; I 29.95. $C_{20}H_{31}IO_2$. Calculated, %: C 55.82; H 7.26; I 29.49.

13-Bromo-*ent*-kauran-19-ic acid (V). A mixture of 0.1 g of dihydrosteviol **III**, 20 ml of 48% HBr, and 10 ml of concentrated H_2SO_4 was refluxed for 24 h, cooled and poured into ice water. The product was extracted with diethyl ether. The organic layer was washed with $Na_2S_2O_3$ and Na_2SO_4 aqueous solutions, dried over $MgSO_4$, and concentrated. The residue was chromatographed on a silica gel eluting with a petroleum ether–ethyl acetate mixture (7:1). The product was recrystallized from a petroleum ether–ethyl acetate mixture. Yield 0.11 g (85%), mp 196–200°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.75–2.38 m (30H, kaurane), 0.97 s (3H, $C^{20}H_3$), 1.11 d (3H, $C^{17}H_3$, *J* 7), 1.24 s (3H, $C^{18}H_3$), 2.42 m (1H, $C^{16}H$). Found, %: C 62.87; H 8.74; Br 20.41. $C_{20}H_{31}BrO_2$. Calculated, %: C 62.66; H 8.15; Br 20.84.

Methyl 13-chloro-*ent*-kauran-19-ate (VI). A mixture of 0.12 of dihydrosteviol **III** and 1 ml of $SOCl_2$ was kept at 45ºC for 1 h. Then thionyl chloride excess was removed at the reduced pressure. The residue was recrystalled from methanol. Yield 0.10 g (80%), mp 96–98°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.75–2.38 m (30H, kaurane), 0.83 s (3H, $C^{20}H_3$), 1.07 d (3H, $C^{17}H_3$, *J* 7), 1.15 s (3H, $C^{18}H_3$), 2.26 m (1H, $C^{16}H$), 3.64 s (3H, OCH_3). Found, %: C 71.58; H 9.45; Cl 9.84. $C_{21}H_{33}ClO_2$. Calculated, %: C 71.46; H 9.42; Cl 10.04.

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