

CHEMICAL MODIFICATION OF ARGOLIDE

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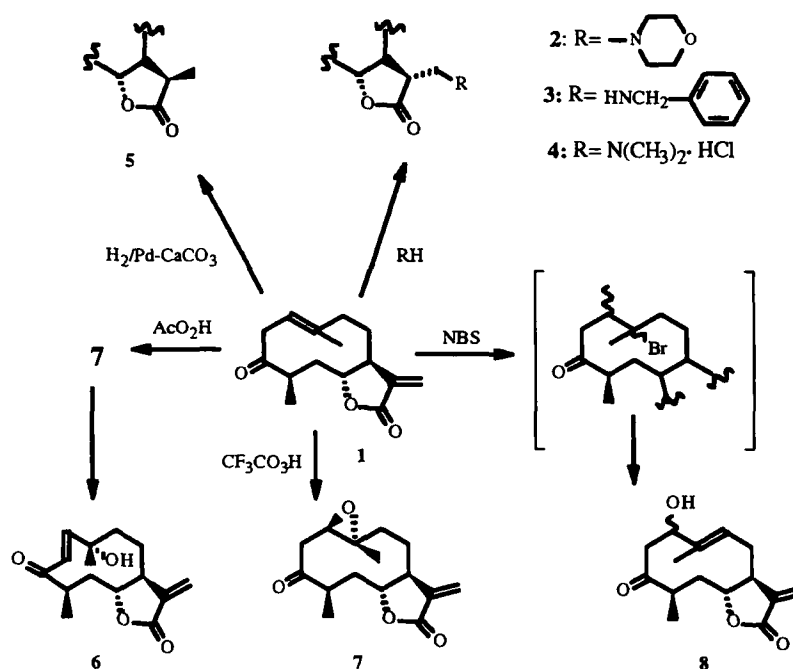
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Chemical transformations have been made of argolide, a sesquiterpene lactone of the germacrane type, as a result of which new epoxy, amino, and hydroxy derivatives of it have been obtained.

Argolide (1), a sesquiterpene lactone of the germacrane type, was first isolated from the epigeal part of *Artemisia glabella* Kar. et Kir. and described in 1989 [1]. The structure of its molecule has been established definitively by x-ray structural analysis [2]. Argolide (1) has also been isolated from *Ajania fruticulosa* [3] and *Stevia grisebachiana* [4].

Structural features of the argolide molecule are the presence of a keto group in the C-3 position, a trisubstituted double bond in the germacrane skeleton, and an exocyclic double bond at the lactone ring, these being the main reaction centers of the molecule.

In the present paper we give results of the chemical modification of argolide (1).



On the interaction of argolide with benzylamine, morpholine, and dimethylamine (scheme), regioselective Michael-type addition of the amines took place at the exocyclic methylene group of the γ -lactone, with the quantitative formation of the corresponding derivatives. The PMR spectra of the benzylamino, morpholino and dimethylamino derivatives of argolide lacked the signals of the protons of the α -exomethylene group of the γ -lactone (Table 1).

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TABLE 1. Chemical Shifts and Spin-spin Coupling Constants of Argolide and its Derivatives

Compound	CDCl ₃ , δ, ppm, multiplicity, SSCC (Hz, in parentheses)						
	Me-10	Me-4	H-2	H-6	H-13a	H-13a	other protons
Argolide (1)	1.67 br.s	1.03 d (3H, 6.5)	3.04 br.d (2H, 8.5)	3.63 dd (1H, 11.5, 2.5)	5.63 d (1H, 1.0)	6.21 d (1H, 1.0)	H-1: 5.55 t (1H, 8.5) H-7: 2.66 br.d. (1H, 11.0) H-4: 2.82 m (1H)
Morpholinoargolide (2)	1.58 br.s	1.04 d (3H, 6.5)	3.04 br.d (2H, 8.0)	3.65 d (1H, 10.0)			H-1: 5.55 t (1H, 8.0)
Benzylaminoargolide (3)	1.59 br.s	1.05 d (3H, 6.5)	3.04 br.d (2H, 8.0)	3.54 dd (1H, 12.0, 3.0)			H-1: 5.48 t (1H, 8.0) CH ₂ Ar: 3.87 br.d.(2H, AB, 13.0) Protons of the aromatic nucleus: 7.35 m(5H)
13-Dimethylaminoargolide hydrochloride (4)	1.55 br.s	1.06 d (3H, 7.0)		3.58 br.d (1H, 12.0)			N-Me ₂ : 2.88 br.s (6H) H-1: 5.56 br.t (1H, 9.0)
Dihydroargolide (5)	1.59 br.s	1.05 d (3H, 7.0)	3.03 br.d (2H, 8.6)	3.54 dd (1H, 12.0, 2.5)			Me-11: 1.15 d (3H) H-1: 5.47 t (1H, 8.5)
10-Hydroxy-Δ ¹⁽²⁾ -argolide (6)	1.47 s	1.10 d (3H, 6.5)	6.00 d (1H, 17.0)	4.22 dd (10.5, 4.5, 1.5)	5.69 d (1H, 1.5)	6.24 d (1H, 1.5)	H-1: 6.90 d (1H, 17.0)
1β,10α-Epoxyargolide (7)	1.25 s	1.10 d (3H, 7.0)	3.21 dd (1H, 14.5; 5.5) 2.16 dd (1H, 14.5, 10.0)	4.02 dd (1H, 11.5, 3.0)	6.21 d (1H, 1.0)	5.66 d (1H, 1.3)	H-1: 3.28 dd (1H, 10.0, 5.5)
1-Hydroxy-Δ ⁹⁽¹⁰⁾ -argolide (8)	1.69 s	1.07 d (3H, 7.0)	2.97 dd (1H, 14.5; 11.0) 3.43 dd (1H, 14.5, 7.5)	3.74 ddd (1H, 11.0, 5.0, 2.2)	5.62 d (1H, 2.7)	6.31 d (1H, 3.2)	H-1: 4.99 dd (1H, 11.0, 7.5); H-9: 5.55 dd (1H, 4.0, 1.0)

Hydrogenation over Pd/CaCO₃ led to the formation of the 11,13-dihydro derivative (5), identical according to physicochemical and spectral characteristics with ketopelenolide B.

On the interaction of argolide with peracetic acid in chloroform, instead of the expected 1,10-epoxide we obtained its isomerization product — hydroxyisoargolide (6). Apparently, under the reaction conditions the 1,10-epoxyargolide (7) first formed underwent an acid-catalyzed rearrangement with the opening of the epoxy ring and the formation of a *trans*-substituted double bond in the C₂—C₃ position [2]. The occurrence of such a rearrangement, shown in the scheme, must be favored by the keto group, since the double bond formed enters into conjugation with it. It is interesting to note that the 1α,10β-epoxide (7) is produced in the interaction of argolide with trifluoroperacetic acid [5], which is probably connected with the high reactivity of the reagents, permitting a considerable shortening of the reaction time. The stereospecificity of the reaction is due to the *trans*-orientation of the C₁—C₁₀ bond.

The interaction of argolide with N-bromosuccinimide took place at the C₁—C₁₀ double bond, but the addition of the halogen atom to C₁₀ and the OH group to C₁ proceeded with subsequent dehydrobromination and the formation of a multiple bond at C₉—C₁₀ (see scheme), which was confirmed by the presence in the PMR spectrum of derivative (8) of a doublet of doublets at 5.5 ppm, corresponding to an olefinic H-9 proton.

Thus, in the main, the chemical transformations of the germacranolide argolide took place at the exomethylene group of the γ-lactone and at the trisubstituted C₁—C₁₀ double bond, and, as a result, new amino, epoxy, and hydroxy derivatives of this germacranolide were obtained.

EXPERIMENTAL

Melting points were determined on a Kofler stage. IR spectra were taken on a UR-20 spectrophotometer (in KBr). NMR spectra were recorded on Bruker WP 200 SY, Bruker TWP 400 SY, and Bruker DRX-500 spectrometers (working frequencies — for ^1H : 200, 400, and 500 MHz, respectively; and for ^{13}C : 125 MHz) in CDCl_3 with TMS as internal standard, δ scale. Mass spectra (EI, 70 eV) were obtained on a Finnigan MAT 8200 instrument (direct injection, 70, 90, and 120°C). Optical rotations were determined on a Polamat A polarimeter (at 580 and 589 nm). The course of the reactions was monitored and the purity of the compounds obtained was checked by TLC on Silufol plates in the following systems: 1) diethyl ether; 2) ether—acetone; 3) petroleum ether—ethyl acetate, the spots being revealed with 1% aqueous KMnO_4 . For flash chromatography we used Chemapol 100/250 silica gel. The results of elementary analyses agreed with the calculated figures.

Argolide (1). This was isolated, and extracted preparatively, from the epigeal part of *A. glabella* as described previously [1]. Colorless crystalline substance with mp 133—135°C, $[\alpha]_{\text{D}}^{23} +203.8^\circ$ (*c*) 0.52; CHCl_3).

IR spectrum (KBr, ν , cm^{-1}): 1755, 1705, 1660.

Mass spectrum (*m/z*, *I* (%)): 248 $[\text{M}^+]$ (9.28), 204(10), 192(5.71), 175(5.71), 161(2.85), 149(100), 131(9.28), 121(34.28), 107(11.42), 99(22.85), 93(62.85), 79(37.14), 71(14.28), 67(25.71), 53(40).

General Amination Procedure. The reaction was conducted at room temperature by adding a primary or secondary amine to a methanolic solution of the substance and then maintaining the same temperature for a day. The course of the reaction was monitored by TLC in the diethyl ether system. This showed the formation of an amino derivative with a R_f value of from 0.15 to 0.3. The reaction mixture was extracted with chloroform (1:8), and the chloroform layer, containing the desired substance, was separated off, dried over MgSO_4 , and filtered, and the solvent was distilled off under vacuum.

Hydrochlorides were obtained by passing gaseous HCl through methanolic solutions of the substances at room temperature for 2—5 min. After evaporation of the methanol, the mixture was diluted with diethyl ether and was then washed successively with 3% NaHCO_3 solution and with water, dried over MgSO_4 and filtered, and the solvent was distilled off under vacuum.

13-Morpholinoargolide (2). Colorless crystalline substance with mp 84—85°C (ether—ethanol), $[\alpha]_{\text{D}}^{20} +41.2^\circ$ (*c*) 0.56; CHCl_3). Yield 94%.

IR spectrum (KBr, ν , cm^{-1}): 1770, 1710, 1635.

13-Benzylaminoargolide (3). Colorless crystalline substance with mp 148—149°C (CH_2Cl_2 —ether). $[\alpha]_{\text{D}}^{20} +208^\circ$ (*c*) 0.64; CHCl_3). Yield 91%.

IR spectrum (KBr, ν , cm^{-1}): 1760, 1710, 1660.

Mass spectrum (*m/z*, *I* (%)): 355(5.14), 327(0.57), 310(0.28), 264(4.86), 217(0.85), 177(2.14), 158(0.85), 149(2.57), 133(1), 122(44.28), 106(100), 91(75.71), 79(2.58), 65(2.85), 55(2.85)

13-Dimethylaminoargolide Hydrochloride (4). Colorless crystalline substance with mp 205—207°C. Yield 83%.

IR spectrum (KBr, ν , cm^{-1}): 3450 (br.), 1765, 1700, 1650, 1465, 1365, 1190, 1160, 1000, 970.

Dihydroargolide (Ketopelenolide B) (5). When 0.1 g of argolide (1), dissolved in 10 ml of ethyl acetate, was hydrogenated over 5% Pd/ CaCO_3 , a reaction mixture was obtained that gave two spots on TLC: R_f 0.5, and R_f 0.45 (ether). The mixture was filtered, the solvent was distilled off under vacuum, and the residue was chromatographed on a column of silica gel. Elution with petroleum ether—diethyl ether (1:1) led to the isolation of colorless crystals of (5) with mp 170—172°C, $[\alpha]_{\text{D}}^{20} +45.0^\circ$ (*c*) 0.43; CHCl_3). Yield 85%.

IR spectrum (KBr, ν , cm^{-1}): 1765, 1710, 1675.

Mass spectrum (*m/z*, *I* (%)): 250 $[\text{M}^+]$ (28.76), 235(10), 208(12.85), 193(55.71), 177(155.71), 149(14.28), 123(47.14), 119(28.57), 108(100), 99(82.85), 95(62.85), 81(58.57), 71(35.71).

10-Hydroxy- $\Delta^{1(2)}$ -argolide (6). With stirring, 5 g of sodium carbonate and then a solution of peracetic acid in chloroform (35 mg in 1 ml of chloroform) were added to a solution of 1.45 g of argolide in 50 ml of chloroform. After 1.5 h, another 30 ml of the peracetic acid solution was added, and the mixture was left at room temperature for three days. TLC showed the presence not only of the initial substance but also of a compound giving a spot with R_f 0.63 (ether—acetone). The reaction mixture was treated with an aqueous solution of sodium carbonate, and the chloroform layer was dried over MgSO_4 and evaporated under vacuum. The residue (1.35 g) was subjected to chromatographic separation on a column of type L 40—100 silica gel. Elution of the column with petroleum ether—diethyl ether yielded 0.92 g of a colorless crystalline substance with mp 171—173°C. $[\alpha]_{\text{D}}^{21} -298^\circ$ (*c*) 2.15; CHCl_3). Yield 60%.

IR spectrum (KBr, ν , cm^{-1}): 3600 (OH), 1765, 1720, 1670.

Mass spectrum (m/z , I (%)): 264[M^+] (1.62), 246(13.75), 203(16.25), 193(8.75), 175(23.12), 151(56.25), 121(20.62), 109(27.5), 95(42.5), 81(23.75), 69(33.75), 55(45.62), 43(100)

Argolide Epoxide (7). With cooling (0°C) and stirring, a freshly prepared solution of trifluoroacetic acid was added dropwise to a solution of 252 mg (1 mmole) of argolide (1) in 20 ml of CH_2Cl_2 containing a threefold excess of Na_2CO_3 until the initial substance had disappeared (monitoring by TLC). The reaction mixture was treated with dilute NaHCO_3 solution, washed with water and with saturated NaCl solution, dried over Na_2SO_4 , and evaporated under vacuum. The product obtained was crystallized from ethyl acetate. Yield 87%. Colorless crystalline substance with mp $203\text{--}205^\circ\text{C}$ (ethyl acetate) $[\alpha]_{580}^{23} +40.3^\circ$ (c 1.19; CHCl_3) [5].

IR spectrum (KBr, ν , cm^{-1}): 1760, 1710, 1450, 1280, 1200, 1150, 1120, 1100.

Mass spectrum (m/z , I (%)): 264[M^+] (0.5), 246(5.0), 175(12.9), 167(15.4), 166(97.4), 147(23.4), 124(47.9), 109(26.9), 99(38.7), 97(85.3), 81(27.0), 79(25.0), 71(42.9), 43(100), 41(64.4)

1-Hydroxy- $\Delta^{9(10)}$ -argolide (8). With stirring, an aqueous acetic solution of *N*-bromosuccinimide (0.1 g in 3 ml) was added to a solution of 0.2 g of argolide (1) in 10 ml of acetone, and the mixture was left for a day. TLC revealed a spot differing from that of the initial substance, with R_f 0.40 (ether). The reaction mixture was treated with a 5% solution of HCl (30 ml) and ether (50 ml). The ethereal extract was dried over MgSO_4 , and the solvent was evaporated under vacuum. The residue (0.16 g) was chromatographed on a column of silica gel. Elution with petroleum ether—diethyl ether (1:1) permitted the isolation of a crystalline mass the recrystallization of which from ether gave 0.07 g of a colorless crystalline substance with mp $125\text{--}126^\circ\text{C}$. $[\alpha]_{\text{D}}^{22} +36.36^\circ$ (c 0.43; CHCl_3). Yield 33%.

IR spectrum (KBr, ν , cm^{-1}): 3415 (OH), 1760, 1720, 1680.

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