SUMMARY

Six new diterpene glycosides – doronicosides A, B, C, D, E, and F – have been detected in the roots of Doronicum macrophyllum Fisch. The qualitative and quantitative composition of the sugar chain of doronicoside D has been established. It has been shown that the negative aglycone of all the doronicosides is 15β-hydroxy-(–)-kaur-16-en-19-oic acid, which, in the process of hydrolysis, is converted into 15-oxo-(–)-kauran-19-oic acid.

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PRODUCTION OF PHENOLIC ALKALOIDS OF THE ISOCHONDODENDRINE SERIES

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We have previously reported the demethylation of cycleanine with hydrobromic acid [1]. Continuing work in this direction we have selected pyridine hydrochloride as a demethylating reagent; it has been used successfully by a number of workers in the production of phenol derivatives [2-5]. By keeping the optimum reaction temperature and time but varying the ratio of alkaloid and demethylating reagent we have demethylated one, two, or four methoxy groups. For monodemethylation about three molecules of pyridine hydrochloride per molecule of alkaloid must be used since two molecules of the reagent are consumed in forming the cycleanine salt. With a twofold excess of pyridine hydrochloride (ratio 4 : 1) norcycleanine and isochondodendrine are formed. A further increase in the excess of pyridine hydrochloride leads to the appearance in the reaction mixture of compounds with three and four hydroxy groups, while at a ratio of 7.2 : 1 the last-mentioned compound predominates (Table 1).

Analysis of the PMR spectra of the substance obtained showed that the formation of mono- and diphenolic reaction products is due to the splitting out of the methyl groups at C-7 and C-7'. Their PMR spectra lack the signals of the protons of, respectively, one and two methoxy groups in the strong field screened by the aromatic nucleus of the benzyl group. At the same time, no compounds isomeric with isochondodendrine and norcycleanine with hydroxy groups at C-6 and C-6' were detected. Tri-O-demethylcycleanine (IV) was not isolated in the pure form, but its presence in the minor components of the reaction products was detected mass spectrometrically.

Tetra-O-demethylcycleanine (V), like cycleanine (I) and isochondodendrine (III), has an axis of symmetry. Because of this all the fragments of its formula coincide on rotation through 180°, and the corresponding signals of the protons of the two benzylisoquinoline halves are superposed in the PMR spectra (solvent C_5D_5N, internal standard TMS). In norcycleanine (II) there are three methoxy groups and a hydroxy group, and these signals are not superposed. In the PMR spectrum of (V) the following signals are observed: a six-proton singlet at 2.47 ppm of two methylimino groups, a broadened doublet of the two protons at C-1 and C-1' (J = 10 Hz), a two-proton singlet at 6.92 ppm (C-5 and C-5'), and the signals of the protons of methoxy groups are absent. Since the macrocycle acquires the boat-shaped configuration, the protons at C-10 and C-11 (and at C-10' and C-11', respectively) undergo screening and because of this their signals are present in a stronger field than the signals of the protons at C-13 and C-14 (and C-13' and C-14', respectively): 6.53 ppm (q, J_1 = 8 Hz, J_2 = 2.5 Hz, 2 H, C-10 and C-10'), 6.33 ppm (q J_1 = 8 Hz, J_2 = 2.5 Hz, 2 H, C-11 and C-11'), and 6.75 ppm (q, J_1 = 8 Hz, J_2 = 2.5 Hz, 2 H, C-13 and C-13'). The signal of the protons at C-14 and C-14' is masked by the corresponding signal of the pyridine protons and is therefore not observed in the spectrum.

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TABLE 1. Influence of Ratio of the Reactants on the Yield of Demethylation Products

Ratio of reactants, mole, (I) : Py • HCl	Reaction conditions			Compounds isolated and their yields, %
	time, min	temp. °C	solvent	
1:2,8	40	210	Ethylene glycol	II—13,4; I—24,15
1:3	40	210	Ethylene glycol	II—5,36; III—4,34 I—65, 68
1:21,5	32	225	None	V—65; I—0,46
1:15,8	25	225	None	V—57,4; I—0,17
1:10,7	15	210	Ethylene glycol	V—65
1:10,7	7	207	Ethylene glycol	V—69,1; I—0,95

The mass spectrum of this compound has the peaks of the M^+ 566 ion and of an ion with m/e 284 (100%).

Thus, a distinct sequence in the demethylation reaction is observed: cycleanine (I)→norcycleanine (II) →isochondodendrine (III)→[tri-O-demethylcycleanine (IV)]→tetra-O-demethylcycleanine (V). The increase in the rate of the reaction in the later stages of demethylation is due to the activation of the carboxy groups at C-6 and C-6' by the neighboring hydroxyls. In contrast to the reaction with hydrobromic acid, stepwise demethylation by pyridine hydrochloride is readily controlled. Since the methyl ether of isochondodendrine (cycleanine) has been obtained by complete synthesis [6-10], its conversion into phenolic alkaloids by stepwise demethylation is the completing stage of their complete synthesis.

EXPERIMENTAL

The IR spectra were taken on a UR-10 instrument, the mass spectra on a CH-8 mass spectrometer at 230°C with an energy of the ionizing electrons of 70 eV, and the NMR spectra on a Varian HA-100D spectrometer. The melting points were determined in sealed capillaries at a pressure of 0.1 mm. The specific rotations of the substances were measured on a Polamat A polarimeter at 20°C. Chromatographic investigation was performed in a thin layer of LS 5/40 silica gel treated with a 0.1 N solution of sodium hydroxide in the methanol–chloroform (1 : 5) system with iodine as the revealing agent.

Norcycleanine. A mixture of 2.77 g of cycleanine, 1.39 g of pyridine hydrochloride, and 7 ml of anhydrous ethylene glycol was heated at 207-210°C under reflux for 40 min. The reaction mixture obtained was extracted with chloroform, and the chloroform extract was washed with distilled water. The aqueous layer was made alkaline with ammonium hydroxide solution and was treated repeatedly with benzene, and then the solvent was evaporated off and the residue was dissolved in citrate–phosphate buffer solution at pH 5.2, and from this solution benzene extracted 1.99 g of cycleanine. After the treatment of the buffer solution with ammonium hydroxide solution and extraction with benzene, 0.097 g of norcycleanine was obtained with mp 263-264°C (from ethanol), mp 270°C (from methanol), $[\alpha]_D^{20} - 10.7°$ (c 0.33; methanol).

Isochondodendrine. A mixture of 3.00 g of cycleanine and 2.36 g of pyridine hydrochloride was heated in ethylene glycol solution at 210°C for 40 min. The reaction mixture was treated in the same way as in the preceding experiment to eliminate cycleanine and norcycleanine. The alkaline solution after extraction with benzene was reextracted with chloroform, and evaporation of the chloroform yielded 0.019 g of isochondodendrine, mp 306°C (from ethanol), $[\alpha]_D^{20} + 64°$ (c 0.3; pyridine).

Tetra-O-demethylcycleanine. A mixture of 3.00 g of cycleanine and 6.00 g of pyridine hydrochloride was heated in anhydrous ethylene glycol solution at 210°C under reflux for 15 min. The solidified light yellow reaction mixture was dissolved in the minimum amount of distilled water at 60°C. When the solution so obtained was cooled, it deposited the snow-white hydrochloride of tetra-O-dimethylcycleanine, $C_{34}H_{34}N_2O_6 \cdot 2HCl$, mp 329-330°C (from water) $[\alpha]_D^{20} + 15.75°$ (c 0.3; water). Yield 2.75 g (65%). Base, mp 261-262°C (from ethanol). IR spectrum: 3000-3600 cm^{-1} (phenolic hydroxy groups).

SUMMARY

Cycleanine has been demethylated with pyridine hydrochloride. It has been shown that the reaction takes place in stepwise fashion with the successive formation of 7-norcycleanine, isochondodendrine, and tetra-O-dimethylcycleanine.

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MASS-SPECTROMETRIC DISTINCTION OF LINEAR AND ANGULAR 2,2'-DIMETHYL-3'-OXO-DIHYDROPYRANOCOUMARINS

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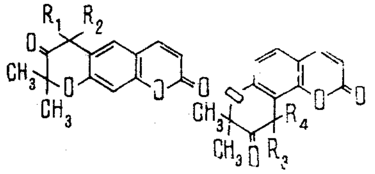
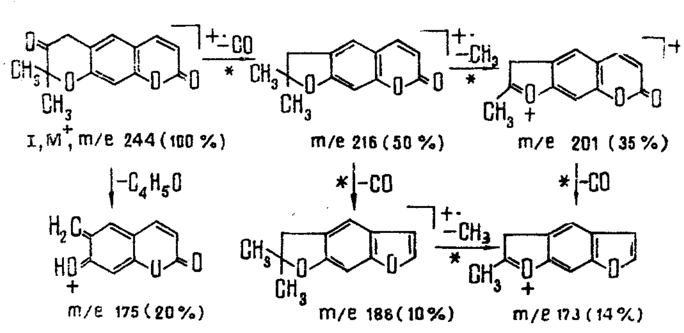
The dissociative ionization of the angular 2',2'-dimethyl-3'-oxo-dihydrocoumarin (II) hasbeen studied previously [1]. We have established a mass-spectrometric difference between this compound and its linear isomer (I). With this aim, we have investigated the mass spectra of substances (I) and (II) and their deuterium analogs (III) and (IV) under identical conditions and energies of the ionizing electrons of 50 and 15 eV.

Compounds (I) and (II) were obtained from natural 3',4'-diacyloxydihydropyramocoumarins [2, 3], which possess a pronounced spasmolytic effect [4] and their presence in plant raw material and in the form of products of the metabolism of the 3',4'-dihydropyranocoumarins when they are used as drugs is not excluded. Because of this, the reliable identification of compounds (I) and (II) by a mass-spectrometric method is required.



I. $R_1=R_2=-H$, II. $R_3=R_4=-H$,
III. $R_1=R_2=-D$, IV. $R_3=R_4=-D$.

The mass spectra of (I) and (II) (Figure 1) contain the peaks of ions with the same m/e values, but the intensities of some ions differ considerably. Since in the case of the fragmentation of the deuterium analogs (III) and (IV) (see Fig. 1) the corresponding ions are displaced by the same number of atomic mass units, at 50 and 15 V compounds (I) and (II) exhibit monotypical fragmentation under the action of electron impact which can be represented for the most characteristic ions in the form of Scheme 1



Scheme 1

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