ANDELIN—A NEW DIHYDROPYRANOCOUMARIN FROM THE ROOTS OF ANGELICA DECURSIVA

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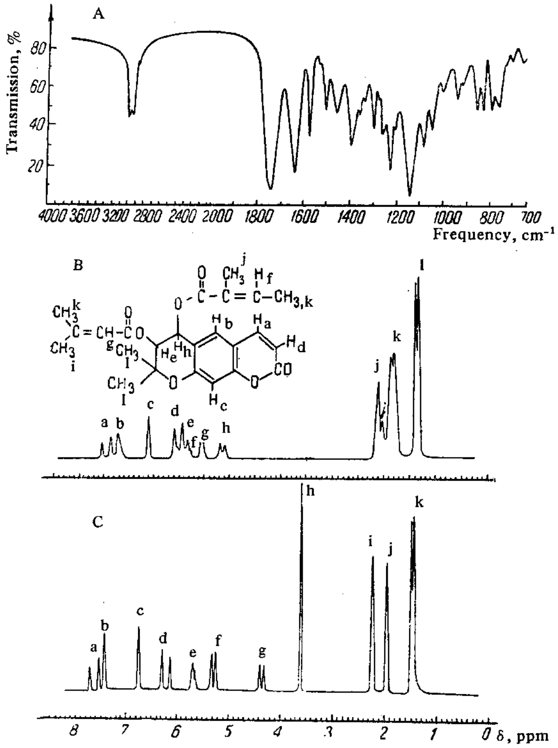
Khimiya Prirodnykh Soedinenii, Vol. 6, No. 2, pp. 190–194, 1970

UDC 577.15/17.582.89

The roots of Angelica decursiva (Miq.) Franch. et Savat. have previously yielded nodakenin [1] and the aglycone of this glycoside, nodakenetin, umbelliferone, decursin, decursidin, and the diester of 3',4'-dihydroxy-3',4'-dihydroxanthyletin with angelic and isovaleric acids [2].

In a study of the roots of a white-flowered form of Angelica decursiva (Miq.) Franch et Savat., we have isolated a new coumarin with the composition $C_{24}H_{26}O_7$, which we have called "andelin."

In the UV spectrum of andelin, maxima at 222 and 322 mμ (log ε 4.56 and 4.22) and also a small peak in the neighborhood of 255 mμ (log ε 3.62) show that the substance is a dihydrofuro- or dihydropyranocoumarin [3]. The IR spectrum of the lactone (figure, A) shows absorption bands at, cm^{-1}: 1760–1735 (CO of an α-pyrone ring and of an ester) and 1640 and 1570 (aromatic nucleus). In the NMR spectrum (figure, B) doublets a and d (δ 7.57 and 6.05, J = = 10 Hz) and singlets b (δ 7.25) and c (δ6.65) are due to the protons in positions 4, 3, 5, and 8 of a coumarin nucleus respectively, and show that andelin is a 6,7-disubstituted coumarin.



IR spectrum of andelin (A); NMR spectrum of andelin (in CCl_4) (B); NMR spectrum of methyl isokhellactone (in $CDCl_3$) (C).

The signals e, h, and l show the presence in the andelin nucleus of a dihydropyran ring [4]. The singlets l (δ 1.43 and 1.40, 6H) are due to two non-equivalent methyl groups on a quaternary carbon atom. The doublets e and h (δ 5.95 and 5.20, J = 5.2 Hz) are due to two interacting methine protons in positions 4' and 3' of a disubstituted dihydropyran ring.

The correctness of the conclusion concerning the andelin nucleus was confirmed by the results of a chemical study. Alkaline hydrolysis in aqueous dioxane yielded a hydroxylactone with the composition $C_{14}H_{14}O_5$. The compound was identified by a comparison of its IR spectrum with that of an authentic sample and by the results of elementary analysis, as isokhellactone. Alkaline methanolysis yielded a substance $C_{15}H_{16}O_5$, identical in respect of its IR spectrum and elementary analysis with methylisokhellactone; under conditions of severe acid hydrolysis a compound $C_{14}H_{12}O_4$ was obtained giving a reaction with 2,4-dinitro-phenylhydrazine. The physicochemical constants and the IR spectrum of this compound identified this substance as 3'-oxo-3',4'-dihydroxanthyletin [5]. The products obtained show that the structure of andelin is based on a 3',4'-dihydropyrano-5',6' : 6, 7-coumarin nucleus.

Peaks i, j, and k in the NMR spectrum of andelin (see figure, B) are due to the presence of two acid residues in the molecule. The broadened peak k (δ 1.90 and 1.86) is formed as a result of the superposition of signals from methyl groups of angelic and β,β-dimethylacrylic (senecioic) acids. Peak j (δ 2.07) is due to the methyl group of angelic acid. Peak i (δ 2.18) corresponds to one of the methyl groups of β,β-dimethylacrylic acid. Signals f (δ 5.85) and g (δ5.61) are due to the vinyl protons of angelic [6] and senecioic [7] acids, respectively.

The presence of these acids was confirmed by their isolation in the free state on alkaline hydrolysis. They were identified by means of their p-phenyl-phenacyl esters.

It follows from what has been said above that andelin is a diester of isokhellactone with senecioic and angelic acids.

The positions of the acid residues in the molecule of the coumarin were shown by a study of the hydrolysis products. Acid hydrolysis in methanol gave a monoester $C_{19}H_{20}O_6$. The nature of the acid residue was shown by the NMR spectrum (figure, C), in which the signals at 2.27 and 1.19 ppm (6H) due to the protons of methyl groups and at δ 5.62 (1H) of the vinyl proton of senecoic acid had been retained. The peak at δ 3.66 (1H) corresponds to the proton of the hydroxyl group formed by the splitting off of angelic acid. From theoretical considerations, the latter should be present in position 4', which is the most labile position [8, 9]. The alkaline methanolysis of andelin gave an analogous product with composition $C_{20}H_{22}O_6$ in which, because of etherification after hydrolysis, position 4' was occupied by a methoxyl group giving in the NMR spectrum of the product (see figure, B) the singlet h at δ 3.57 (3H).

Thus, on the basis of a study of the products of the chemical reactions and the features of its UV, IR, and NMR spectra, andelin is 4'-angeloyloxy-3'-senecioyloxy-3',4'-dihydropyrano-5',6' : 6,7-coumarin.

EXPERIMENTAL

The IR spectra of the substances were recorded on a UR-10 spectrophotograph (mulls in paraffin oil), the UV spectrum on an SF-4 spectrophotometer (solution of the substance in ethanol), and the NMR spectra on a JNM-4H-100 instrument (in CCl_4 and $CDCl_3$). The positions of the signals were determined relative to tetramethylsilane as internal standard, taken as 0.

Chromatography was carried out on Leningrad type "B" paper impregnated with a 10% solution of formamide in methanol, using the solvent system n-hexane–benzene–methanol (5 : 4 : 1).

Samples of isokhellactone and methylisokhellactone were kindly given to us by A. I. Sokolova. The microanalyses were performed by E. A. Nikonova and E. A. Plokhova.

Isolation of andelin. One kilogram of comminuted angelica roots was extracted three times with methanol (6, 6, and 4 liter). The extracts were concentrated in vacuum to 500 ml, diluted with 1 liter of water, and extracted with ether (3×300 ml). The ethereal extract was treated with 0.25% caustic potash solution, washed with water, and dried with anhydrous sodium sulfate and the solvent was distilled off. The residue (62.45 g) was chromatrographed on a column (24×8 cm) of acid alumina (Brockmann activity grade II). The column was eluted with a mixture of petroleum and diethyl ethers (10 : 1). Fractions 1-20 of the eluate (250 ml each) were concentrated and rechromatographed on a column of alumina (25 × 4 cm), being eluted with petroleum ether. The concentration of fractions 1-27 gave 10.5 g of a substance with a glasslike consistency, $[\alpha]^{22}_{D}$ −28.0 (c 0.89; ethanol), R_f 0.9, readily soluble in methanol, chloroform, and ether, and sparingly soluble in petroleum ether.

IR spectrum, cm^{-1}: 1760, 1735, 1640, 1580, 1510, 1450, 1400, 1360, 1340, 1300, 1260, 1230, 1150, 1080, 1045, 1000, 940, 855, 830. UV spectrum, λ_{max}: 222, 255, 322 mμ (log ε 4.56, 3.62, 4.22).

Found, %: C 67.80, 67.46; H 6.48, 6.40. Mol. wt. 424.3 (Rast). Calculated for $C_{24}H_{26}O_7$, %: C 67.59; H 6.15.

Isokhellactone. A solution of 0.5 g of the substance in 10 ml of dioxane was treated with 10 ml of 5% aqueous caustic soda and the mixture was left for a day [7]. Then it was acidified with 20% H_2SO_4 and treated with ether. The extracts were washed with saturated sodium carbonate solution and then with water, and the solvent was distilled off. This gave colorless crystals, $C_{14}H_{14}O_5$, mp 151–152° C (from water), $[\alpha]_D^{20.1}$ +92.1° (c 0.89; ethanol), R_f 0.00. IR spectrum, cm^{-1}: 3450, 1700, 1630, 1565, 1470, 1380, 1295, 1190, 1140, 1080, 1030.

Methylisokhellactone. A solution of 1 g of the substance in 15 ml of methanol was treated with 15 ml of a 1 N methanolic solution of caustic soda, and the mixture was heated in the water bath for 1.5 hr [8]. The cooled mixture was diluted with water (100 ml) and treated with ether (3 × 25 ml). The extracts were washed with 5% sodium carbonate solution and then with water, and the solvent was driven off. Colorless acicular crystals deposited; $C_{15}H_{16}O_5$, mp 99–101° C (from water), $[\alpha]_D^{20.9}$ +102.3 (c 0.97; ethanol), R_f 0.07. IR spectrum: 3450, 1730, 1635, 1570, 1500, 1470, 1380, 1295, 1200, 1160.

3'-Oxo-3', 4'-dihydroxanthyletin. A mixture of 0.4 g of the substance and 50 ml of 50% aqueous H_2SO_4 was heated for 1 hr. The reaction mixture was diluted with water and cooled, to give 0.2 g of yellowish acicular crystals, $C_{14}H_{12}O_4$, mp 164–166° C (from ethanol). Literature data, mp 164–165.5° C [5]. IR spectrum, cm^{-1}: 1730, 1635, 1575, 1500, 1470, 1385, 1345, 1315, 1260, 1150, 1115, 960, 930, 870, 820.

4'-Hydroxy-3'-senecioyl-3', 4'-dihydropyrano-5', 6' : 6, 7-coumarin. A solution of 0.5 g of the substance in 10 ml of 2.5% H_2SO_4 in methanol was heated for 15 min. The reaction products were extracted with ether and the extract was washed with saturated sodium carbonate solution and then with water. The residue from the evaporation of the solvent was chromatographed on a column of alumina (activity grade II) and was eluted with ether. The eluate deposited colorless crystals, $C_{19}H_{20}O_6$, mp 197–199° C, R_f 0.46. IR spectrum, cm^{-1}: 3450 (OH group), 1760–1730 (C=O of an α-pyrone ring and an ester grouping), 1640, 1575 (aromatic nucleus).

Methylisokhellactone senecioate. 10 ml of a 2 N methanolic solution of caustic potash was added to 4 g of the substance. After a minute, the solution was diluted with water (100 ml). The unsaponified part of the starting material was extracted with ether (3 × 25 ml). The aqueous solution was acidified with 20% H_2SO_4 and treated with ether (2 × 25 ml). The extracts were washed with 20% sodium carbonate solution (solution A) and then with water.

The concentration of the ethereal extract and the recrystallization of the residue obtained gave colorless crystals crystals in the form of nodules with mp 145–147° C, $[\alpha]_D^{20.8}$ +94.1 (c 0.94; ethanol), R_f 0.8. IR spectrum, cm^{-1}: 1750, 1730 (C=O of an α-pyrone ring and an ester grouping), 1635, 1570 (aromatic nucleus).

Found, %: C 66.99, 66.94; H 6.12, 6.27. Calculated for $C_{20}H_{22}O_6$, %: C 67.02; H 6.19.

p-Phenylphenacyl angelicate. The sodium carbonate solution A after the separation of the monoester was acidified with 20% H_2SO_4 and extracted with ether (4 × 20 ml). The ethereal fraction was washed with water, the solvent was driven off, and the residue was sublimed. This gave colorless acicular crystals with mp 46–47° C. The sublimate was neutralized with sodium bicarbonate and the solution was treated with p-phenylphenacyl bromide (0.3 g) in ethanol (5 ml) and the mixture was heated for 1 hr. Crystals of p-phenylphenacyl angelicate with mp 84–86° C (ethanol) deposited. Literature data: mp 86–87° C [10].

p-Phenylphenacyl β,β-dimethylacrylate. One gram of methylisokhellactone senecioate was saponified with a solution of 5% H_2SO_4 in dioxane with heating for 1 hr.

The sodium carbonate solution obtained in the usual way was acidified and distilled with steam. The distillate was saturated with sodium chloride and extracted with ether. Then the solvent was driven off to give β,β-dimethylacrylic acid with mp 69–70° C [11].

The p-phenylphenacyl ester of senecioic acid was obtained by the method described above, mp 137–140° C (ethanol).

CONCLUSIONS

A new coumarin, $C_{24}H_{26}O_7$, which has been called "andelin," has been isolated from the roots of the white-flowered form of Angelica decursiva (Miq.) Franch. et Savat.

On the basis of its IR, UV, and NMR spectra and the characteristics of a number of derivatives, the structure of 4'-angeloyloxy-3'-senecioyloxy-3',4'-dihydropyrano-5',6' : 6,7-coumarin has been proposed for andelin.

REFERENCES

1. J. Arima, J. Chem. Soc. Japan, 48, 457, 1927; 49, 530, 1928.
2. K. Hata and K. Sano, Tetrah. Let., 14, 1461–1465, 1966; Yakugaku Zasshi, 89, 4, 549–557, 1969.
3. G. A. Kuznetsova, Natural Coumarins and Furocoumarins [in Russian], Leningrad, 30, 1967.
4. A. I. Sokolova, G. K. Nikonov, and M. E. Perel'son, KhPS [Chemistry of Natural Compounds], 4, 280–283, 1968.
5. J. Lemmich, E. Lemmich, and B. E. Nilson, Acta Chem. Scand., 20, 2497, 1966.
6. R. R. Fraser, Can. J. Chem., 38, 549, 1960.
7. P. J. Collin and S. Sternhell, Austr. J. Chem., 19, 317, 1967.
8. R. E. Willette and T. O. Soine, J. Pharm. Sci., 51, no. 2, 149–156, 1962.
9. H. D. Shroeder, W. Bencze, and H. Schmid, Ber., 92, 2338, 1959.
10. K. Hata, M. Kozawa, J. Ikeshiro, and Yakugaku Zasshi, 87, no. 9, 1118–1124, 1967.
11. G. A. Kuznetsova and L. M. Belenovskaya, KhPS [Chemistry of Natural Compounds], 2, 235, 1966.

1 December 1969

All-Union Scientific-Research Institute of Medicinal Plants