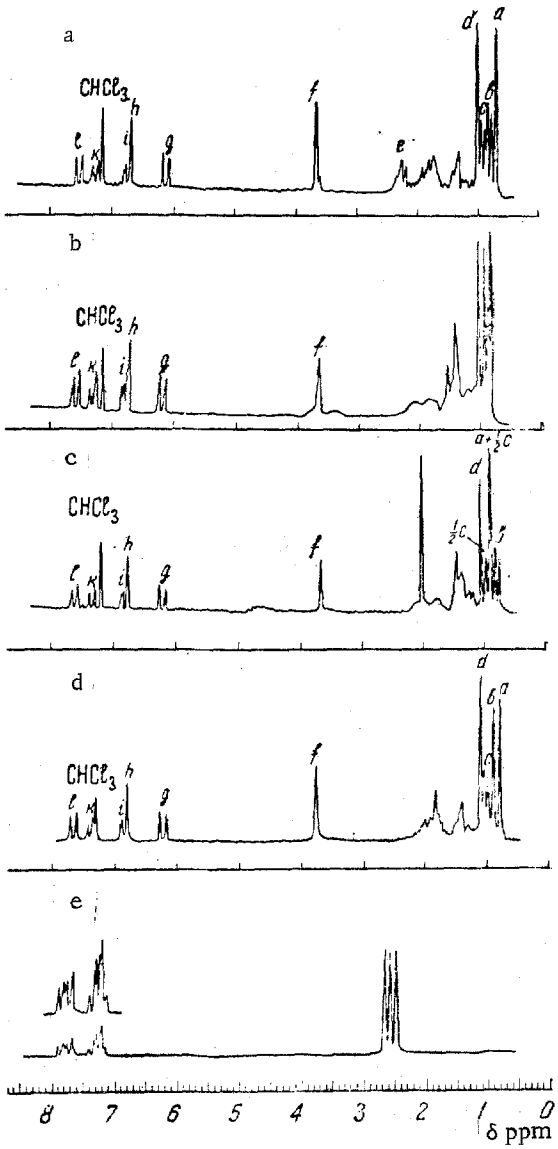
UDC 547—314

STRUCTURE OF KAMOLONE AND KAMOLOL—NEW COUMARINS FROM FERULA PENNINERVIS

N. E. Ermatov, A. I. Ban'kovskii, M. E. Perel'son, G. P. Syrova, and Yu. N. Sheinker

Khimiya Prirodnykh Soedinenii, Vol. 5, No. 2, pp. 79-84, 1969

We have previously [1] reported the isolation from Ferula penninervis Rgl. et Schalh. of two new umbelliferone derivatives, kamolone (I) and kamolol (II). The molecule of the first contains a keto group and that of the second



NMR spectra of kamolone (a), kamolol (b), kamolol acetate (c), deuterated kamolone (d), and 1,2,5-trimethylnaphthalene (d). (The signal from tetramethylsilane is taken as zero. Spectra recorded in $CDCl_3$ and CCL_4).

hydroxy group. This paper gives the results of a further study of the structures of these compounds.

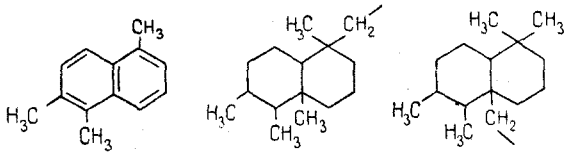
Oxidation of II with Beckmann's mixture in acetone at room temperature gave a product which was identical in physicochemical properties with I.

The NMR spectra of I, II, and the acetate of II (figure, a,b,c) confirm the conclusion drawn on the basis of chemical data that the compounds studied are umbelliferone derivatives [2]. Thus, in the spectrum of I the doublets g(δ = = 6.16; J = 10 Hz) and *l* (δ = 7.57; J = 10 Hz) are due to the protons at C_3 and C_4, the doublet k (δ = 7.30; J = 8.5 Hz) relates to H_5, the quartet i (δ = 6.78; J_1 = 8.5 Hz; J_2 = 2 Hz) relates to the proton in position 6, interacting with H_5 and H_8, and, finally, the rather broad peak h appears as the result of the superposition of a doublet from H_8 (δ = 6.74; J = 2 Hz) and one of the doublets of the quartet i from H_6. The position of the singlet *f* (δ = 3.74) with an intensity of two proton units is characteristic for the signal from a methylene group attached through an oxygen atom to an aromatic ring [3]. The lack of splitting of the signal *f* shows that the methylene group is attached to a quaternary carbon atom. The singlets *a* (δ = 0.75) and d (δ = 1.05), each having an intensity of three proton units, show the presence in the molecule of kamolone of two methyl groups on saturated quaternary carbon atoms. In addition, the molecule of kamolone contains two methyl groups attached to saturated tertiary carbon atoms, as is shown by the presence in the spectrum of the doublets b (δ = 0.86; J = 7.5 Hz) and c (δ = 0.98; J = 7.5 Hz), each with an intensity of three proton units. An analysis of the NMR spectrum of kamolone taken at 60 MHz confirms the conclusions relating to the nature of the splitting of the signals.

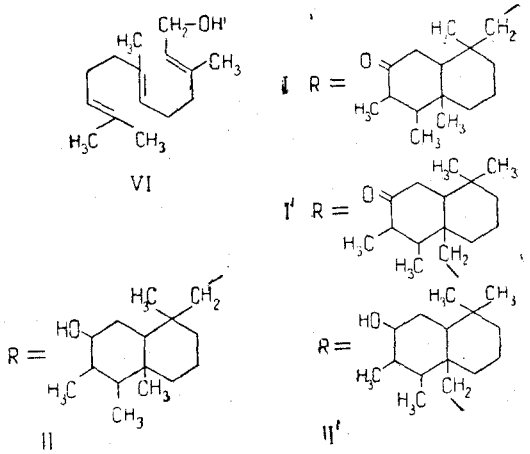
The NMR spectra of kamolol and its acetate also confirm the conclusions on the elementary structures of these compounds drawn on the basis of a consideration of the spectrum of kamolone. Some difference between the patterns of the signals of the methyl groups in the spectrum of II and those of I and of the acetate of II is probably connected with a small difference in the chemical shift of one of the methyl groups in this compound with the corresponding methine proton. In the case of I and the acetate of II, this difference is greater, which is due to the electron-accepting influence of the keto and ester groups. The NMR spectra of I, II, and the acetate of II show that the sesquiterpene residue does not contain double bonds. In agreement with this, the hydrogenation of II over platinum gave only 3,4-dihydrokamolol, in the IR spectrum of which the band of the stretching vibrations of the C=O group of the α-pyrone ring is displaced to 1763 cm^{-1}. Thus, the sesquiterpene residue in I and II is bicyclic and is attached to the coumarin nucleus through a $-CH_2-O-$grouping.

The selenium dehydrogenation of I and II gave a hydrocarbon (III) with n_D 1.5960 forming a picrate with mp 138–140° C, a styphnate with mp 131° C, and a 1,3,5-trinitrobenzene derivative with mp 158–159° C. The NMR spectrum of III (figure, e) has signals of three methyl groups attached to an aromatic ring and a number of peaks with a total intensity of five proton units in the region of aromatic protons. A comparison of the results obtained permitted III to be identified as 1,2,5-trimethylnaphthalene [4].

The formation of III enables the position of three methyl groups out of the four to be established. Taking into consideration the nature of the methyl groups in I and II, the presence of a $-C-CH_2-O-$grouping, the result of dehydrogenation, and the isoprene rule, one can arrive at only two most likely variants—IV and V—of the carbon skeleton of the sesquiterpene substituent in I and II.



Structures given are in complete agreement with modern ideas on the biogenesis of sesquiterpene compounds, the precursor of which is farnesol (VI) [5,6].



The position of the carbonyl group in I was established by a study of the NMR spectrum of the product of its deuteration. When ketones are deuterated in an alkaline medium, the hydrogen atoms in the α-position to the C=O group

are replaced. In the NMR spectrum of the deuteration products of I (figure, d), the splitting of one of the methyl groups has disappeared, which shows the replacement of hydrogen by deuterium in a $CH-CH_3$ grouping. Signal b from this methyl group is somewhat broadened because of the interaction of the protons with deuterium. In addition, the multiplet e with an intensity of two proton units has disappeared, which is due to the replacement of hydrogen by deuterium in a methyl group adjacent to the carbonyl group. Thus, in one of the α-positions with respect to the carbonyl group there is a $CH-CH_3$ grouping and in the other a methylene group. Only one position in structures IV and V satisfies these conditions. This position of the carbonyl group in I (and, consequently, of the hydroxy group in II) is also in agreement with the results of dehydrogenation. If the OH group were adjacent to the gem-dimethyl grouping, tetramethylnaphthalene would be obtained as the result of a retropinacolone rearrangement [7].

What has been said above permits the assumption of two possible variants of the structure of the sesquiterpene residue in the compounds studied: I or I' for kamolone and II or II' for kamolol.

It does not appear possible to make a choice between formulas I and I' and between II and II' on the basis of the available data, although structures I and II are the most likely since so far no compound with an ether linkage at an angular methylene group has been found among the sesquiterpenes.

Experimental

The IR spectra were recorded on a UR-10 spectrophotometer and the NMR spectra on a JNM-4H-100 instrument (operating frequency 100 MHz).

Oxidation of kamolol. At room temperature, 0.15 g of kamolol in 20 ml of acetone was treated with 2 ml of 8 N Beckmann's mixture for 7 min. After dilution with water, the crystalline precipitate that had deposited was filtered off with suction, carefully washed with water, and recrystallized from ethanol. This gave 0.12 g of colorless elongated needles with mp 191–192° C. For analysis, the substance was dried in vacuum at 110° C for 7 hr. IR spectrum: ν, cm^{-1}: 1733, 1715, 1618, 1562, 1512.

Found, %: C 75.38, 75.16; H 7.91, 8.24. Calculated for $C_{24}H_{30}O_4$, %: C 75.37; H 7.94. According to its IR spectrum, the product of the oxidation of kamolol was identical with kamolone. A mixture of the substance with an authentic sample of kamolone gave no depression of the melting point.

A similar result was obtained when kamolol was oxidized with chromic anhydride in glacial acetic acid at room temperature.

Hydrogenation of kamolol. A solution of 2.095 g of kamolol in 145 ml of glacial acetic acid was hydrogenated in the presence of 0.194 g of an Adams platinum catalyst.

After 5 hr, 255 ml of hydrogen had been absorbed. The catalyst was filtered off, and the solution was diluted with water and extracted with chloroform (6 × 50 ml). The organic phase was washed three times with 5% sodium carbonate solution and once with water, at 25 ml each time, and was then dried with anhydrous sodium sulfate and distilled to give 2.0 g of a substance with mp 119–121° C (from aqueous ethanol). IR spectrum, ν, cm^{-1}: 3230, 1763, 1618, 1576, 1503.

Found, %: C 74.49, 74.72; H 8.78, 8.90. Calculated for $C_{24}H_{34}O_4$, %: C 74.57; H 8.90.

Dehydrogenation of kamolone. A fine powder consisting of a mixture of 1.44 g of kamolone and 1.2 g of selenium was heated at 330–340° C for a day. The reaction mixture was treated with hot petroleum ether (bp 40–60° C; 10 × × 25 ml). The resulting solution was extracted with 5% caustic soda solution (4 × 20 ml), washed with water, dried with anhydrous sodium sulfate, and distilled to give 150 mg (23% of the theoretical yield) of a yellowish mobile oil.

The alkaline solution was acidified with 20% sulfuric acid and extracted with chloroform (4 × 50 ml). The extract was washed with water and dried with anhydrous sodium sulfate, and the solvent was distilled off to give 70 mg of a residue which did not react with a solution of ferric chloride (absence of phenols or naphthols). The acid fraction was not investigated further. The neutral hydrocarbon fraction was purified by chromatography on a column of alumina (10 g, activity grade I, 1 × 10 cm), being eluted with hexane. Evaporation of the solvent yielded 106 mg of a colorless oil with n_D^{20} 1.5960. IR spectrum (liquid film), ν, cm^{-1}: 2740, 2370, 1915, 1850, 1605, 1520, 818, 800, 750, 725 cm^{-1}.

Found, %: C 91.56, 91.46; H 8.93, 8.89. Calculated for $C_{13}H_{14}$, %: C 91.76; H 8.34.

Preparation of the picrate of III. A 1% ethanolic solution of picric acid (3 ml) was added to the liquid hydrocarbon (100 mg). The red-brown crystals that deposited were filtered off with suction and washed with the minimum amount of ether. For analysis, the substance was dried in a vacuum desiccator over phosphorus pentoxide for 4 days; mp 138–140° C.

Found, %: C 57.35, 57.30; H 4.29, 4.79; N 10.35, 10.77; $C-CH_3$ 11.00. Calculated for $C_{19}H_{17}N_3O_7$, %: C 57.16; H 4.29; N 10.52; $C-CH_3$ 11.27.

Preparation of the trinitrobenzene derivative of III. The picrate of III was decomposed by passing its solution in chloroform through a column of alumina (activity grade I, 1 × 10 cm). The solvent was evaporated, leaving the aromatic hydrocarbon, to which a hot saturated ethanolic solution of trinitrobenzene was added. Bright yellow plate-like crystals with mp 158–159° C (from ethanol) deposited. For analysis, the substance was dried at 60° C in vacuum for 12 hr.

Found, C 59.80; H 4.87. Calculated for $C_{19}H_{17}N_3O_6$, %: C 59.52; H 4.47.

Styphnate of III. This was obtained in a similar manner to the trinitrobenzene derivative—by the addition of a solution of styphnic acid to the hydrocarbon, mp 131° C (from ethanol).

Dehydrogenation of kamolol. The process was carried out under conditions analogous to those described for kamolone at 290–300° C. The following derivatives of the resulting hydrocarbon were prepared: picrate with mp 138–140° C; 1,3,5-trinitrobenzene derivative with mp 158–159° C; and styphnate with mp 131° C. Mixtures with the corresponding derivatives obtained by the dehydrogenation of kamolone gave no depression of the melting points.

Deuteration of kamolone [8]. 0.2 g of sodium was dissolved in a mixture of 2 ml of heavy water and 6 ml of completely deuterated methanol, 0.1 g of kamolone was added, and the mixture was heated for 30 min. The solvent was driven off in vacuum in a current of nitrogen. The residue was treated with 2 ml of heavy water and 6 ml of deuteromethanol, after which the mixture was heated for 20 min. The methanol was distilled off in an atmosphere of nitrogen and the heavy-water solution was acidified with deuterated sulfuric acid. The crystalline precipitate that deposited was filtered off, washed several times with heavy water, and dried in a vacuum desiccator over phosphorus pentoxide. Mp 186–188° C.

Conclusions

On the basis of chemical reactions and spectral data, the structures of the umbelliferone ethers of 3-oxo-1,2,5,9-tetramethyldecal-5-ylmethanol and of 3-hydroxy-1,2,5,9-tetramethyldecal-5-ylmethanol have been proposed for kamolone and kamolol, respectively.

REFERENCES

1. N. E. Ermatov, A. I. Ban'kovskii, and M. E. Perel'son, KhPS [Chemistry of Natural Compounds], 2, 158, 1966.
2. Yu. N. Sheinker, G. Yu. Pek, and M. E. Perel'son, DAN SSSR, **158**, 1382, 1964.
3. K. Nukada, O. Iamamoto, T. Suzuki, M. Takeuchi, and M. Ohnishi, Anal. Chem., **35**, 1892, 1963.
4. L. Ruzicka and J. R. Hosking, Helv. Chim. Acta, **13**, 1402, 1930.
5. L. Ruzicka, in the book: Perspectives in Organic Chemistry, ed. A. Todd [Russian translation], Moscow, p. 187, 1959.
6. P. De Mayo, The Higher Terpenoids [Russian translation], Moscow, p. 413, 1963.
7. L. Cagliotti, H. Naef, D. Arigoni, and O. Jeger, Helv. Chim. Acta, **41**, 2278, 1958.
8. D. H. William, J. M. Wilson, and C. Djerassi, J. Am. Chem. Soc., **85**, 2091, 1963.

25 December 1967

All-Union Scientific-Research Institute for Medicinal Plants

All-Union Chemical and Pharmaceutical Scientific-Research Institute