THE STRUCTURE OF METHOXYLATED FLAVONOIDS

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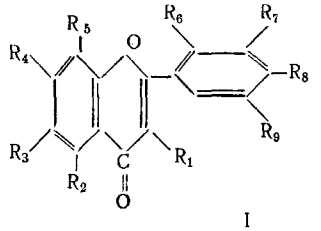
UDC 547.972

In generalizing literature information on the structure and distribution of flavonoids in higher plants, we directed our attention to the diverse structures of methylated and methoxylated derivatives of flavones, flavonols, flavanones, and isoflavonoids [1-5] and also came to the conclusion that in plants O-methylated compounds are more widely distributed than C-methylated compounds.

C-Methylation is characteristic of a small number of families (Acanthaceae, Asteraceae, Fabaceae, Lamiaceae, Pinaceae, Zingiberaceae), the number of methyl groups is not more than two, and they are generally in position 6 or 8 of the A nucleus of the flavonoid.

The structures of the O-methylated flavones and flavonols are more diverse. In these compounds the methoxy groups may be present in positions 3, 5, 6, 7, 8, 2', 3', 4', and 5' of the flavone nucleus; the maximum number of methoxy groups amounts to seven [4]. In view of the fact that the molecule generally contains hydroxy groups as well as methoxy groups, a large number of different combinations may be considered probable. At the present time about 130 methoxylated flavones and flavonols are known. The number of methoxylated flavanones and flavanonols is considerably smaller (about 30), and there are about 50 methoxylated isoflavonoids (we have not taken into account the number of methoxylated furano- and pyranoflavonoids). In the flavanones, the maximum number of methoxy groups is four, and they may be present in positions 5, 6, 7, 8, 2', 3', and 4', while in the flavanonols they are present in positions 7 and 4'. The isoflavones have from one to three methoxy groups located among positions 5, 6, 7, 8, 2', 3', and 4', and the isoflavanones one or two methoxy groups among positions 7, 4, and 4'.

In the last three years, the structures of a number of new compounds have been established. We give some of these structures below (forms I-III).

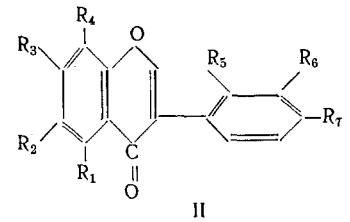


I

$R_1=R_3=R_5=R_6=R_7=R_9=H$ $R_2=R_4=OH$, $R_8=OCH_3$ [6];
$R_1=R_5=R_6=R_7=R_9=H$, $R_2=OH$ $R_3=R_4=R_8=OCH_3$— salvigenin [7];
$R_1=R_5=R_6=R_7=R_9=H$, $R_2=R_3=R_4=R_8=OCH_3$— tetramethylscutellarein [8];
$R_1=R_3=R_6=R_7=R_9=H$, $R_2=R_4=R_5=R_8=OCH_3$=isoscutellarein tetramethyl ether [9];
$R_1=R_3=R_5=R_6=R_9=H$, $R_2=R_4=OH$, $R_7=R_8=OCH_3$— linoside [10];
$R_1=R_5=R_6=R_9=H$, $R_2=R_4=R_3=R_8=OH$, $R_7=OCH_3$— batatifolin [11];
$R_3=R_9=H$, $R_2=OH$, $R_4=R_5=R_6=R_7=R_8=OCH_3$— serpyllin [12];
$R_1=R_4=R_9=OH$, $R_1=R_6=H$, $R_3=R_5=R_7=R_8=OCH_3$— scaposin [13,14];
$R_3=R_5=R_6=R_7=R_9=H$, $R_2=R_8=OH$, $R_1=R_4=OCH_3$— jaranol [15];
$R_3=R_6=R_9=H$, $R_1=R_2=R_4=R_7=R_8=OH$, $R_5=OCH_3$— corniculatusin [16];
$R_5=R_6=R_9=H$, $R_2=R_4=R_8=OH$, $R_1=R_3=R_7=OCH_3$— jacein [17];
$R_5=R_6=R_9=H$, $R_2=R_4=R_7=OH$, $R_1=R_3=R_8=OCH_3$— centaurein [17];

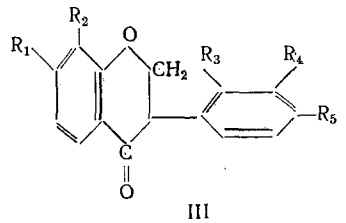
Pyatigorsk Pharmaceutical Institute. Translated from Khimiya Prirodnykh Soedinenii, No. 3, pp. 259-263, May-June, 1971. Original article submitted February 11, 1971.

$R_5=R_9=H$, $R_6=R_7=OH$, $R_1=R_2=R_3=R_4=R_8$ – apulein [18];
$R_5=R_6=R_7=R_9=H$, $R_1=R_2=OH$, $R_3=R_4=R_8=OCH_3$—mikanin [19];
$R_2=R_6=R_9=H$, $R_4=R_5=R_7=R_8=OH$, $R_1=OCH_3$— transilitin [20];
$R_1=R_6=R_9=H$, $R_2=R_4=OH$, $R_8=R_5=R_8=OCH_3$—nevadensin [13];
$R_2=R_5=R_6=R_7=R_8=OCH_3$— isosinensetin [9];
$R_2=R_3=R_5=R_6=R_9=H$, $R_1=R_4=R_7=R_8=OCH_3$ – tetra-O-methylfisetin [21];
$R_5=R_6=R_9=H$, $R_1=R_2=R_7=OH$, $R_3=R_4=R_8=OCH_3$–eupatin [22];
$R_5=R_6=R_9=H$, $R_1=R_7=OH$, $R_2=R_3=R_4=R_8=OCH_3$– eupatoretin [22];
$R_3=R_6=R_7=R_8=R_9=H$, $R_1=R_2=OH$, $R_4=R_5=OCH_3$– graphalin [28];
$R_1=R_5=R_6=R_9=H$, $R_2=R_4=R_8=OH$, $R_3=R_7=OCH_3$— 4',5,7-trihydroxy-3',6- dimethoxyflavone [29].



II

$R_1=R_4=R_5=R_6=H$, $R_2=R_3=OH$, $R_7=OCH_3$— texasin [23];
$R_1=R_2=R_4=R_5=H$, $R_3=R_6=OH$, $R_7=OCH_3$—calycosin [21];
$R_1=R_2=R_4=R_5=H$, $R_3=OH$, $R_6=R_7=OCH_3$—cladrin [27];
$R_1=R_4=R_5=H$, $R_3=OH$, $R_2=R_6=R_7=OCH_3$— cladastrin [27];
$R_2=R_3=R_5=OCH_3$ R_6 and R_7– methylenedioxy milldurone [25].



III

$R_1=R_4=OH$, $R_2=R_3=R_5=OCH_3$– duratin [26];
$R_1=R_4=OH$, $R_2=H$, $R_3=R_5=OCH_3$– mucronulatol [26];
$R_2=R_4=H$, $R_1=R_3=OH$, $R_5=OCH_3$— vestitol [26].

We decided, by using the methods of combinatorial analysis [30-32], to determine the number of theoretically possible combinations of methoxylated derivatives for various types of flavonoids.

Let us consider a system N (the nucleus of flavone or some other flavonoid) consisting of n points (vertices), each of which can exist in any of K "states" (levels). The state of this system of n points is given by the vector

$$x = \left(x_{i_1},\ x_{i_2},\ \ldots\ldots x_{i_n}\right),$$

where x_{i_j} is the level of the j-th point ($i_j = 1, 2, \ldots, k$).

In view of the independence of the levels at each individual point of the system N, the total number of possible states of the system or, which is the same thing, the power of the set of vectors x is

$$S_n^{(k)} = K^n. \qquad \text{(IV)}$$

We now require that in each state of a system N at least one of its points exist at some fixed, previously selected, level x_{i_j}.

Let us call the limitation introduced condition A and pose the problem: to calculate the number S of possible states of the system N satisfying the condition A.

For this we form the difference $S_n^{(k)} - S_n^{(k-1)}$.

Interpreting it in the terms of the system studied, N, we shall establish directly that this difference denotes the maximum number of possible states of the system N with the necessary presence of one of the levels at an arbitrary point of each of the states of the system N, i.e.,

$$S = S_n^{(k)} - S_n^{(k-1)} = k^n \left(k-1\right)^n = \sum_{j=1}^{n} \left(-1\right)^{j-1} C_n^j k^{n-j}. \quad (V)$$

We may then show the possibility of applying the calculating formula (V) obtained to concrete examples.

As we have shown above, in the natural flavonols described in the literature the methoxy groups may be present in positions 3, 5, 6, 7, 8, 2', 3', 4', and 5'.

In other words, the system N consists of nine points at each of which a carbon atom may be linked with hydrogen or with a hydroxyl group or with a methoxy group, while there must be a methoxy group at at least one of these points (K=3), and the role of the fixed level x_{i_j} is played here and below by a methoxy group.

Calculation by means of formula (V) gives S=19,171.

Since, in the cases reported in the literature, of the five positions in the chromone nucleus only four can be occupied simultaneously by methoxy groups and of the four permissible positions in the lateral phenyl radical only three can be occupied by methoxy groups (for example, digicitrin, 3',5-dihydroxy-3,4', 5',6,7,8-hexamethoxyflavone; gardenin, 5-hydroxy-3,3',4',5',6,8-hexamethoxyflavone, etc.), the number of theoretically possible compounds must be decreased by $5 \times 3^4 = 1397$.* A further decrease may apparently be brought about because of the presence of glycosidated monomethoxylated compounds in positions 3 and 7, but even then a considerable number of compounds remained that may still be found in nature.

For the flavones, with n=8, K=3, we must have 6305 compounds containing $-OCH_3$ groups. In the lateral phenyl radical of the four permissible positions not more than three are usually occupied, and therefore the number of 6305 found can be decreased by the number $4 \times 3^4 = 324$.

For the flavanones and isoflavonoids (isoflavones, isoflavanones, and isoflavans) a pattern similar to that found in the study of the flavones is obtained.

SUMMARY

Using combinatorial analysis, the maximum theoretically possible number of methoxylated flavones, flavonols, flavanones, and isoflavonoids that may be found in nature has been determined, which opens up prospects for the development of chemistry in this field.

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