CATALYTIC ACETYLATION OF FLAVONOIDS

V. A. Bandyukova and V. D. Ponomarev

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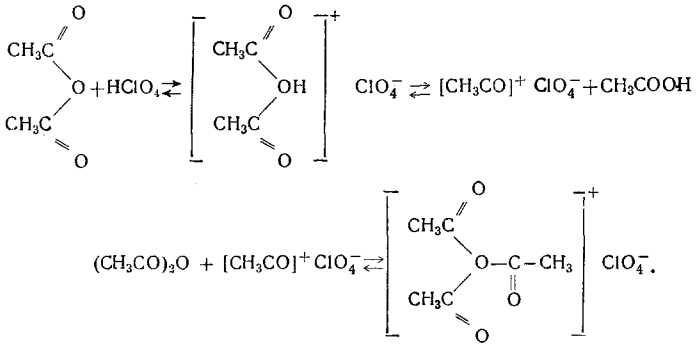
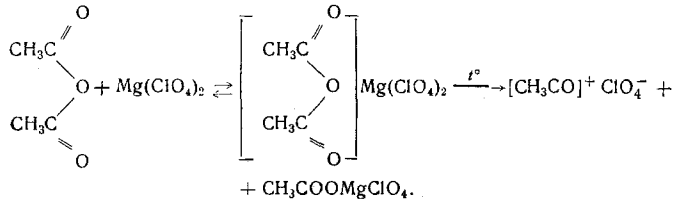
At present, acetylation of flavonoids is widely used to study the NMR and UV spectra of the derivatives, to determine their physical constants, and to determine the number of hydroxyl groups in the original molecule [1, 2]. The acetyl derivatives are generally obtained by the reaction of the flavonoid with acetic anhydride in pyridine or in the presence of sodium acetate, and extremely arbitrary ratios of the reactants and also various reaction conditions are used.

Zhdanov et al. [3, 4] have developed convenient preparative methods for the acetylation of a series of polyhydric alcohols, cyclitols, and some monosaccharides and O- and C-glycosides in the presence of perchloric acid or its salts. In this case, the perchloric acid forms with the acetic anhydride acetyl perchlorate, and with an excess of acetic anhydride gives the triacetyloxonium ion [4].



The resulting acetyl carbonium ion is an effective acetylating agent.

Dorofeenko et al. [5, 6] have shown that magnesium perchlorate (Anhydrone), benzyl perchlorate, and triphenylmethyl perchlorate can be good catalysts for acylation reactions with acid anhydrides. During acetylation, the formation of acetyl perchlorate takes place in the following manner:



We have developed a method for acetylating various flavonoids in the presence of Anhydrone using mathematical methods of planning the experiments in order to determine the optimum acetylation conditions. To obtain objective results and shorten the experiments, the method of randomized block planning, which permits the comparative evaluation of the degree of simultaneous influence of two factors (acetylating medium and catalyst) on the acetylation of quercetin [7] was selected. The plan and the results of the experiment are given below.

I				II				III			
$A\alpha$	$B\beta$	$C\gamma$	$D\delta$	10/30	20/40	30/50	40/60	0,5048	0,4128	0,3858	0,3818
$B\gamma$	$A\delta$	$D\alpha$	$C\beta$	20/50	10/60	40/30	30/40	0,4086	0,3890	0,3826	0,3950
$C\delta$	$D\gamma$	$A\beta$	$B\alpha$	30/60	40/50	10/40	20/30	0,3459	0,3592	0,4142	0,3406
$D\beta$	$C\alpha$	$B\delta$	$A\gamma$	40/40	30/30	20/60	10/50	0,2994	0,3247	0,3521	0,3979

A, B, C, D represent the amount of acetic anhydride;
I, plan: α, β, γ, δ represent amounts of catalyst;
II, conditions: numerator is the amount of acetic anhydride, g; denominator is the amount of anhydrone, mg per $1 \cdot 10^{-3}$ mol of quercetin.
III, results: yields of acetylated quercetin in each experiment, g.

The dispersion analysis (Table 1) was carried out according to the formulas given by Hicks [7]:

$$SS_{\text{tot}} = \sum\sum x_{ij}^2 - \frac{T^2}{N} = 2.3502 - \frac{37,09}{16} = 0.0321,$$

where

$\Sigma\Sigma x_{ij}^2$ is the sum of the squares of all the observations;

T is the sum of all the observations;

N is the number of experiments.

$$SS_{\text{factor}} = \sum \frac{T_j^2}{n} - \frac{T^2}{N},$$

where

ΣT_j^2 is the sum of the squares of the observations with respect to one of the factors;

n is the number of variants.

$$SS_{\text{error}} = SS_{\text{tot}} - SS_{\text{factor I}} - SS_{\text{factor II}} =$$
$$= 0,0321 - 0,0209 - 0,0013 = 0,0099.$$

$$S = \frac{SS_{\text{factor}}}{f},$$

where f is the number of degrees of freedom,

$$F = \frac{S_{\text{factor}}}{S_{\text{error}}}.$$

According to the dispersion analysis, only the amount of acetic anhydride has any noticeable influence on the yield of product (F-ratio $> F_{3.9}^{0.95}$) and the amount of anhydrone has almost no effect ($F_{\text{rat}} < F_{3.9}^{0.95}$). This may serve as proof that in the acetylation process the flavonoid does not react with the Anhydrone and the rôle of the latter is apparently limited to the formation of the reactive acetyl perchlorate. The highest yield was found when using the smallest amount of acetic anhydride ($1 \cdot 10^{-1}$ mole per $1 \cdot 10^{-3}$ mole of quercetin) and $3 \cdot 10^{-4}$ mole of Anhydrone. The synthesis of acetyl derivatives of other flavonoids was based on these results (Table 2).

The advantage of acetylation with acetic anhydride in the presence of Anhydrone consists in the rapidity of the experiment, the high yield, (85–98%), and the absence of by-products of the reaction. The melting points and UV and IR spectra of the acetates obtained agree with those given in the literature.

EXPERIMENTAL

The appropriate amounts of acetic anhydride ($1 \cdot 10^{-1}$ mole) and Anhydrone ($3 \cdot 10^{-4}$ mole) were heated in a water

Table 1. Results of a Dispersion Analysis

Factor	Number of degrees of freedom, f	Sum of the squares, SS	Mean square, S	F-ratio	$F^{0,95}_{3,9}$
Acetic anhydride (I)	3	0.0209	0.0069	6.3	1,63
Anhydrone (II)	3	0,0013	0,0004	0,36	1,63
Error	9	0,0099	0,0011	—	—
Sum	15	0,321	—	—	—

Table 2. Conditions for the Acetylation of Some Flavonoids in the Presence of Anhydrone

Substance acetylated	Reaction temperature, °C	Reaction time, min	Product	Mp of the product, °C
Apigenin	70—75	30—40	Triacetate	187
Luteolin	70—80	40—50	Tetraacetate	224
Luteolin 7-glucoside	60	30	Heptaacetate	240
Quercetin	60—75	35	Pentaacetate	175
Rutin	50—60	30—35	Peracetate	124,5
Kaempferol	65	35	Tetraacetate	181
Genistein	65—70	35—40	Triacetate	205
Sophoricoside	70	60	Hexaacetate	230

Note. The melting points are given for the unrecrystallized substances.

bath to 60° C and then, with constant stirring, $1 \cdot 10^{-3}$ mole of a flavonoid was added over 20–40 min. The reaction mixture was left for another 10–20 min (see Table 2) in the water bath, then cooled to room temperature and poured into a fivefold volume (with respect to the volume of anhydride used) of cold distilled water. An oily liquid first formed on the bottom of the flask and then a precipitate deposited. On the following day the precipitate was collected on a glass filter, dried over H_2SO_4 to constant weight, and weighed. The melting point, the presence of characteristic maxima in UV light, and absorption bands in the IR region were determined. In each case, paper chromatography showed the absence of by-products.

CONCLUSIONS

On catalytic acetylation in the presence of magnesium perchlorate, flavonoids do not react with the catalyst. The highest yield of product was found when using the smallest amount of acetic anhydride ($1 \cdot 10^{-1}$ mole per $1 \cdot 10^{-3}$ mole of quercetin) and $3 \cdot 10^{-4}$ mole of Anhydrone.

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Pyatigorsk Pharmaceutical Institute