REDUCTIVE ACETYLATION OF QUERCETIN

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The majority of methods of converting flavonols into anthocyanidins that have been described in the literature are unsuitable for the synthesis of the latter in view of the low yield of the products [1-6]. In this case, attention is merited by the reductive acetylation reaction, which enables the anthocyanidins to be obtained with a yield of 40-48% [7]. We have previously proposed a method for acetylating flavonoids with acetic anhydride in the presence of magnesium perchlorate (Anhydrone) [8]. The acetyl derivatives obtained were then subjected to reductive acetylation and the products of their reduction were studied.

In the present paper we give the results of the reductive acetylation of quercetin pentaacetate.

We first established that for reduction it is most effective to use zinc dust, while magnesium is less effective and tin and iron powders are ineffective.

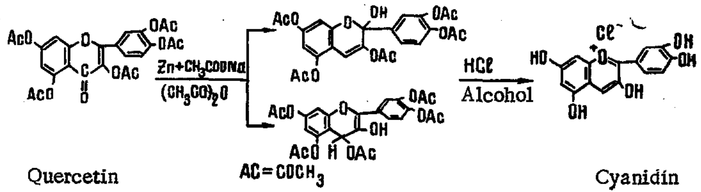
The product with the composition $C_{25}H_{22}O_{12}$ (C 60%, H 4.6%, CH_3CO 41.1%) obtained on reduction has the form of an orange-red powder with no sharp melting point. The compound is readily soluble in chloroform and in acetic acid and is insoluble in water; in an acid medium it acquires a bright red color, in an alkaline medium a greenish blue color.

In the UV spectrum there is only one absorption maximum, at 273 nm ($CHCl_3$), which is characteristic for the benzene part of the molecule. The IR spectrum of the substance (paraffin oil) shows the absence of a carbonyl group and the presence of a hydrogen bond (broad unsymmetrical band in the 2860-2980 cm^{-1} region), ester bonds of acetyl groups (1770 cm^{-1}), π-conjugation in both rings of the chromane (1620, 1470 cm^{-1}), and C_5 and C_7 substitution (1380 cm^{-1}) [9].

When the spectrum was recorded in chloroform, the presence of a hydroxy group (3030 cm^{-1}) and of C_3 and C_7 substitution (1470 cm^{-1}) was observed, and an absorption band also appeared at 1520 cm^{-1} $\left(>C=C<\right)$ [9].

In the NMR spectrum of the substance in chloroform, in addition to a multiplet in the 2.1-2.2-ppm region, which is characteristic of the signals of the protons of acetyl groups, and a number of signals corresponding to the protons of the benzene rings, there is a singlet at 8.28 ppm, characteristic for a flaven-3-ol [10] (in the anthocyans, a singlet in the 8.1-ppm region). This signal is absent from the NMR spectrum of the substance in carbon tetrachloride. The hydrolysis of the substance with alcoholic (ethanolic, propanolic, or isopropanolic) hydrogen chloride for 50-60 min formed cyanidin chloride, the identity of which was confirmed by UV and IR spectra and by a comparison with a reference sample.

The reaction product formed in the reduction of quercetin pentaacetate probably consists of a mixture of acetyl derivatives of flav-2-en-3-ol and flav-3-en-2-ol.



Quercetin pentaacetate

Cyanidin chloride

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In order to find the optimum conditions for performing the reduction reaction and to increase the yield of product we performed a multifactorial experiment of the 2^2 type and carried out a steepest ascent to the optimum region [11].

The following regression equation was obtained

$$Y = 31{,}7 + 8{,}4\ x_1 + 9{,}8\ x_2 + 0{,}2\, x_1 x_2. \qquad \text{(I)}$$

The theoretical values of the yield of product (percentage of cyanidin chloride) calculated from the equation agreed satisfactorily with the experimental figures, which shows the adequate nature of the equation of the process. Its adequacy was evaluated by Fisher's criterion [12].

The coefficients of the regression equation (I) obtained as the result of the experiment enabled us to move into the region of the optimum and to determine that the highest yield of product (52.2-52.4%) can be obtained when the reductive acetylation reaction is performed at 130-140° C for 126-138 min. A further rise in the temperature and increase in the time lowered the yield of cyanidin chloride.

Assuming that the hydrolysis of the reduced quercetin acetate is a first-order reaction and is described by the equation

$$-\frac{dx}{d\tau} = kx, \qquad \text{(II)}$$

where x is the amount of substance; k is the hydrolysis rate constant; and τ is the time, we determined the rate constant of hydrolysis at different reaction times, using one of the solutions of Eq. (II).

$$k = \frac{-2\ 303 \lg \dfrac{c}{c_0}}{\tau},$$

where c is the amount of starting material at time τ and c_0 is the initial amount of starting material, g.

The study of the hydrolysis process showed that its highest rate was in propanol.

After ~50% of the substance had been converted into cyanidin chloride, the formation of by-products (dimers and oxidation products) was observed, and therefore it does not appear possible to increase the yield by lengthening the time of hydrolysis.

EXPERIMENTAL

Reductive Acetylation. A solution of 0.25 g of quercetin pentaacetate ($8 \cdot 10^{-4}$ mole), obtained as described previously [8] in 15 ml of acetic anhydride was treated with 0.2 g of freshly fused sodium acetate and 1.0 g of the corresponding metal powder (Mg, Zn, Sn, Fe), taking a Latin square as the experimental plan.

	A_1	A_2	A_3	A_4
B_1	C_1	C_2	C_3	C_4
B_2	C_4	C_1	C_2	C_3
B_3	C_3	C_4	C_1	C_2
B_4	C_2	C_3	C_4	C_1

Plan of the experiment:

Reducing agent:

A_1 – Zn; A_2 – Mg; A_3 – Sn; A_4 – Fe

reaction time:

B_1 – 40', B_2 – 60'; B_3 – 90'; B_4 – 120'

temperature:

C_1 – 75°; C_2 – 95°; C_3 – 115°; C_4 – 135° C

The best results were obtained on using zinc dust as reducing agent with a reaction time of 90-120 min at 115-135° C.

TABLE 1. Hydrolysis Rate Constants for Different Reaction Times

Time, min	$\frac{c}{c_0}$	$\lg \frac{c}{c_0}$	Reciprocal of $\log c/c_0$	K
In boiling propanol				
20	0,550	1,740	–0,260	0,0299
30	0,425	1,628	–0,372	0,0286
40	0,390	1,590	–0,410	0,0266
50	0,360	1,556	–0,444	0,0204
Mean				0,0263
In isopropanol–3 N hydrochloric acid (1:1) (boiling water bath)				
10	0,835	1,920	–0,080	0,0184
30	0,605	1,782	–0,218	0,0169
40	0,477	1,678	–0,322	0,0185
50	0,430	1,634	–0,366	0,0168
Mean				0,0176

In the optimization of the process of obtaining reduced quercetin acetate with zinc dust, the experiments were performed at 100-160° C for a time of 90-162 min (at 140-160° C the mixture was heated in sealed tubes). The results and the regression equation have been given above. In all cases, after the end of the reaction the mixture was freed from metal powder and poured into a tenfold volume of water. After a day, the precipitate was separated off, washed with water, and dried in a vacuum desiccator over phosphorus pentoxide to constant weight.

Hydrolysis of the Reduced Quercetin Acetate. The reduced quercetin acetate (0.1 g) was hydrolyzed with a mixture of isopropanol (or propanol) and 3 N hydrochloric acid (1 : 1) in the boiling water bath or an air bath for 40 min. The resulting bright red solution (where zinc or magnesium was used), after cooling, was transferred to a 100-ml measuring flask and the volume was brought up to the mark with the same mixture of solvents. A definite volume of the solution was again diluted with the mixture to obtain the optimum values of the optical density, and the amount of cyanidin chloride was determined in a SF-4A spectrophotometer at 540 nm. Chemically pure cyanidin chloride was used to construct the calibration curve.

The yield of cyanidin chloride with different times of hydrolysis was as follows:

time, min	5	10	15	20	25	30	40	50	55*
yield, %	1.1	8.2	16.2	23.0	28.0	40.5	44.4	54.4	57.0

The calculation of the hydrolysis rate constants is given in Table 1.

SUMMARY

The reductive acetylation of quercetin under the action of various reducing agents and of different times and temperatures, and also the conversion of the flavonols obtained into cyanidin chloride have been studied by the methods of the mathematical planning of experimentation.

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*When heating was performed for more than 55-60 min, another two reaction products appeared.