2nd International Electronic Conference on Synthetic Organic Chemistry (ECSOC-2), http://www.mdpi.org/ecsoc/, September 1-30, 1998

[a0014]

Synthetic and Kinetic Study of the Reaction of 3-Formylchromones with Aromatic Amino Acids

Henrieta Stankovicova[1*], Margita Lacova[2*], Anton Gaplovsky[1], Jarmila Chovancova[2], and Nada Pronayova[3]

1Institute of Chemistry and [2]Department of Organic Chemistry and , Faculty of Natural Sciences, Comenius University, Mlynská dolina CH-2, SK-842 15 Bratislava, Slovakia; Tel.: +421 7 60296338; Fax: +421 7 60296690

(stankovicova@fns.uniba.sk; lacova@ fns.uniba.sk)

3Central Laboratories, Faculty of Chemical Technology, Slovak University of Technology, Radlinského 9,

SK-812 37 Bratislava, Slovakia;

Abstract

Conditions of synthesis of 2-alkoxy- or 2-hydroxy-3-(arylaminomethylene)-4-chromanones and 3-(aryliminomethyl)-4-chromenones in the reaction of 3-formylchromones with arylaminoacids have been investigated. The alkylation of 2-alkoxy-3-(arylaminomethylene)-4-chromanones by alkylhalides was carried out.

Rate coefficients for the acid-catalyzed formation of chromanone-chromenone system were measured. Dependence of reaction rate upon the structure of starting compounds, the type of used reaction medium and the concentration of catalyst, respectively, have been studied.

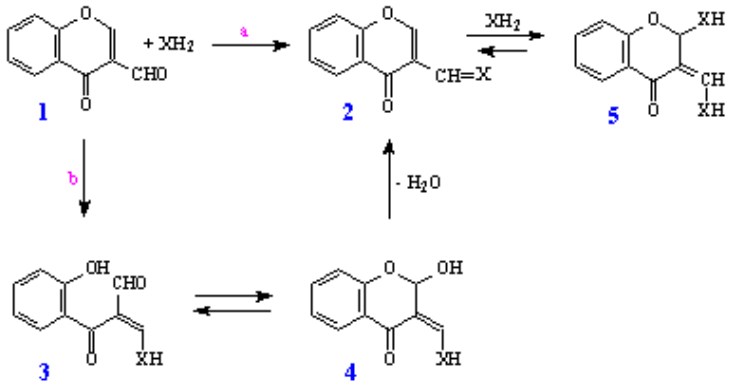
Key words: 4-oxochromene-3-carboxaldehydes; anils; enamines; reaction kinetics, rate constants

Introduction

Synthetic significance of 3-formylchromones **1** and their imine derivatives **2** results from their usefulness as reactive agents and valuable precursors for many different heterocycles. They contain three electron deficient sites (C-2, C-4, Cald) and rearrange easily under influence of nucleophiles.

Although the ambigous results of reaction of 3-formylchromones **1** with primary aromatic amines have been known for some years [1], the kinetics of these reactions have not been studied. The reactions are depending on reaction medium and nucleophility of amines. Imines **2** (X= NAr) were formed in aprotic solvents, enamines **5** in protic solvents (water, alcohols, thiols and amines). Sometimes mutual transformation of both types of products or very complicated structures consisting from two nucleophile components [2] were observed. Our conclusions on mechanism conclusions of these reactions were based on interpretation of isolated intermediates and products or upon theoretical calculations [3,4]. It is known, that from three electron deficient centres the carbon at position 4 of g -pyrone ring is having obviously the least electrophility compared to that at the other two centres. It is known that the reaction of **1** with any nucleophile XH_2 such as an amine gives initially the condensation product **2** that appears to arise by a straightforward 1,2-addition of the nucleophile to the aldehyde function (Scheme 1, path a). An alternative route involving 1,4-addition of the nucleophile with concomitant opening of the g -pyrone ring and subsequent recyclisation of the intermediate **3** *via* **4** (Scheme 1, path b) may also be used for the formation of **2**. Because of the "symmetry" after opening pyrone ring it is very difficult to find whether the nucleophile is undergoing 1,2- or 1,4-addition to 4-oxochromene-3-carboxaldehyde.

It is known that chromones are usually cleaved by nucleophiles [5] . However, not every interaction of position C-2 with nucleophiles leads to g -pyrone ring-opening. The presence of certain substituents (*e.g.* aryliminomethyl group) at position 3, especially those which are in conjugation with C2-C3 double bond, changes the reactivity of the chromenone system. This substituent not only stabilises the pyrone ring of **2** towards usual ring cleavage, but also facilitates the addition of other external nucleophiles which could not otherwise react with the pyrone ring as evident Michael addition of second molecule of XH_2 to form compound **5** [6].



Scheme 1. *Reaction of 3-formylchromone 1 with nucleophile XH2*

Reaction of amines with 3-aryliminomethyl-4-oxochromenes is reversible [5]. Primary aromatic amines have sufficiently nucleophilic properties to add to the C-2 position of benzopyrone ring [6, 7], but they are not sufficiently basic for deprotonise compounds **5** to form **2** [6, 8]. 3-Aryliminomethyl-4-oxochromenes **2** (X = N-Ar) were prepared using aldehydes **1** with the primary aromatic or the heterocyclic, respectively, amine in presence of 4-toluenesulfonic acid as catalyst in dry benzene at reflux [9, 10] or from 1,4-adducts **5** (XH = NH-Ar) by elimination of molecule XH_2 by heating of compound **5** to its melting point under vacuum [6].

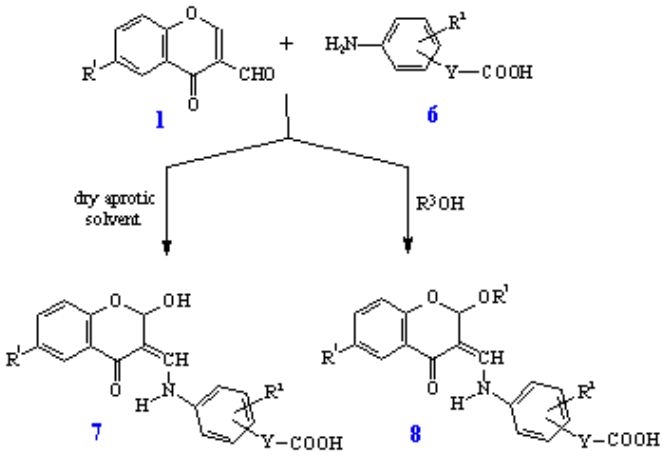
We now report a synthetic and kinetic investigation of reaction of 6-substituted 4-oxochromene-3-carboxaldehyde with aromatic amino acids. The aim of this study was a contribution to clarification of production of imines **2**, enamines **5** and their mutual transformation in the reaction of weak nucleophiles with aldehydes **1**. We assumed non-splitting mechanism. The sample of five amino acids (4-aminobenzoic acid, 4-aminohippuric acid, 3-, 4-, 5-aminosalicylic acids) was singled out for investigation. Some of the prepared compounds have been active against mycobacterial strains [11], in phytotoxicity [12] and have hereditary bleaching effect on plastid system of Euglena gracilis [13].

We investigated the reaction of 6- substituted 4-oxochromene-3-carboxaldehyde **1** (R = H, CH_3, Cl, Br, NO_2) with aromatic amino acids **6** in the presence of 4-toluenesulfonic acid as catalyst in the protic or the dry aprotic, respectively, reaction medium. As the protic solvents we used methanole, ethanole, 1-propanole, 2-propanole, 1-butanole and as the aprotic ones benzene and toluene.

Results and discussion

Synthetic study

Reactions in dry aprotic solvents. We found that 6-substituted 4-oxochromene-3-carboxaldehydes **1** with all aromatic amino acids **6** yielded only 3-arylaminomethylene-2-hydroxy-4-oxochromane **7** at room temperature or reflux, respectively (Scheme 2). According to the knowledges from earlier papers [1, 6] we assumed the formation of the compound structuraly related to **2** if the reaction were carried out at reflux. We have never isolated the mixture of imine **2** (X= N-Ar-COOH) and 1,4-adduct **5** (X = N-Ar-COOH) by treatment of all components of reaction mixture (1:1 molar ratio) in dry aprotic solvents as in the case of more basic aniline derivatives [6, 14]. In case of anilines having a nucleophilic functionality at its *ortho* position fused seven-membered heterocycles were prepared [15]. Formation of this type of compounds were not proved in case of 3-aminosalicylic acid.

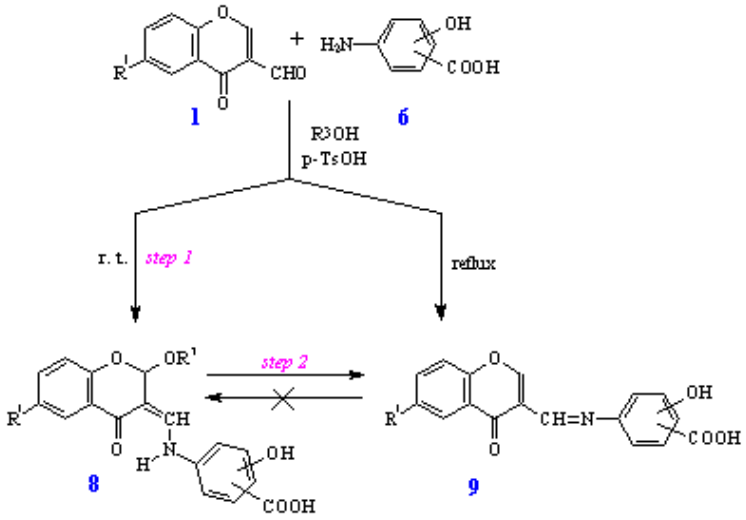


Scheme 2. *Reaction of 1 with aromatic amino acids in aprotic and protic reaction media*

Reactions in protic solvents. Use of the protic solvents gave different reaction products than that of dry aprotic ones. 2-Alkoxy-3-arylaminomethylene-4-oxochromane derivatives **8** have been treated by 4-oxochromene-3-carboxaldehydes **1** with arylaminoacids in the presence of 4-toluenesulfonic acid as catalyst in alcoholic reaction medium at room temperature (Scheme 2).

4-Aminobenzoic and 4-aminohippuric acids yielded the 2-alkoxyderivatives **8a-e** at both reaction conditions - room temperature or reflux, respectively. Aminosalicylic acids reacted differently. 2-Alkoxyderivatives **8f-8t** were formed by reaction at room temperature. 3-Aryliminomethylderivatives **9a-b** were formed after prolonged heating of 2-alkoxyderivatives **8** in alcoholic reaction media at reflux for 14 - 16 hrs (Scheme 3). The prepared 3-aryliminomethyl-4-oxochromenes **9** did not give 2-alkoxy-3-arylaminomethylene-4-oxochromanes **8** either after 3 days at standing at room temperature or after 6 hrs reflux in alcohol.

These synthetic results were controversial to the conclusion about anils **2** [6, 8-10] and were supported by kinetic study of aminosalicylic acids - 4-oxochromene-3-carboxaldehyde reaction in another part of this study.



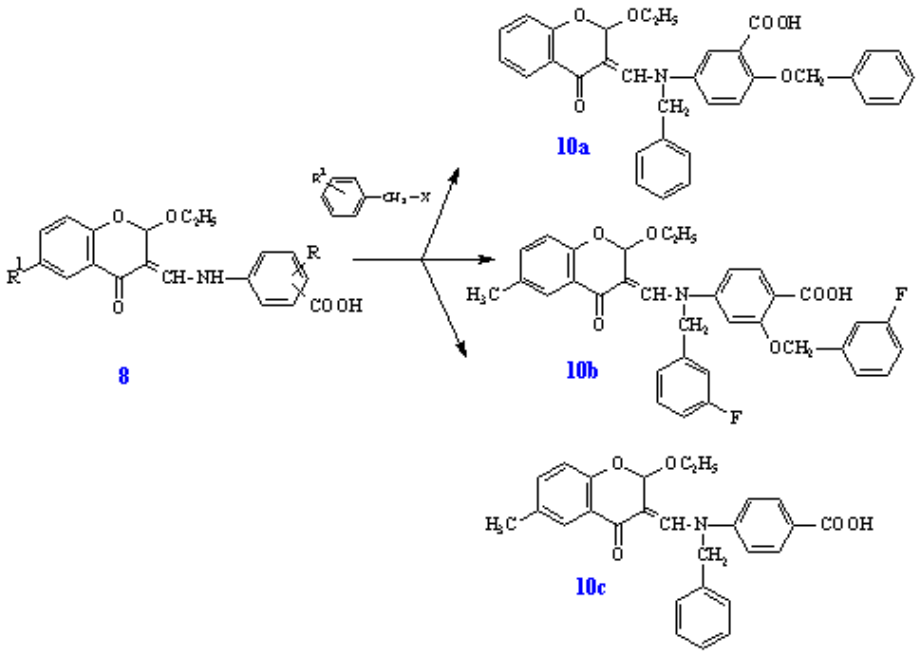
Scheme 3. *Reaction of 1 with aminosalicylic acids in alcoholic reaction media*

The structures of all prepared compounds (Table 1) were proved by ^{1}H NMR and IR spectra. The ^{1}H NMR spectra of compounds **7**, **8** showed singlets of H-2 of pyranone ring at 5.958± 0.037 - 6.555± 0.389, dublets of methylene group at 8.132± 0.104 and dublets of NH group at 11.168 - 12.075. IR spectra revealed a presence of a strong band of a stretching frequency of pyrone carbonyl at 1653 - 1650 cm^{-1} and strong band of stretching frequency of COOH groups at 1673 - 1669 cm^{-1}.

1H NMR spectra of 3-aryliminomethyl-4-oxochromenes **9** showed singlet signals of H-2 of pyrone at 8.799 - 9.104 and singlets of iminomethyl group at 8.1 - 8.213. IR spectra indicated the presence of strong band of stretching frequency of C=N group.

No products were obtained as a result of the rearrangement of benzopyrone ring and no evidence was found for the occurrence of any reaction between the aldehyde **1** and the 2 moles of aromatic amino acid **6**, which gives rise to an analogy with the compound **5** in both types of reaction media (protic and dry aprotic solvents). This differences can be explained by lower nucleophility of arylamino acids in comparison with aniline derivatives.

Enamine compounds **7**, **8** reacted with alkylating agents at amino group in dry acetonitrile and yielded derivatives **10** in very good yields (Scheme 4).



Scheme 4. *Reactions of enamines 8 with alkylating agents*

Kinetics

Kinetic study elucidated how the reaction of 6-substituted 4-oxochromene-3-carboxaldehydes **1** with arylamino acids **6** proceeds. The conversion of reactants into products **8**, **9** led through steps which may be competitive, parallel or consecutive. We have studied the dependence of reaction rate upon (i) structure of starting compounds - 3- and 4-aminosalicylic acids and 4-oxo-6-R-chromene-3-carboxaldehydes, (ii) type of used reaction medium - alcohol and (iii) concentration of catalyst - 4-toluenesulfonic acid. The mechanistic pathway of studied reaction is depicted in Scheme 3. The UV-VIS absorption spectra were used for monitoring of the kinetics of above process. The absorbances of all components of reaction mixture differ in the position of absorption band as well as in their intensities (Figure 1). Both products **8**, **9** have the absorption maximum bathochromicaly shifted in comparison with starting compounds and catalyst. The intensity of absorption band of **8** is aproximately 10 times larger than that of **9**.

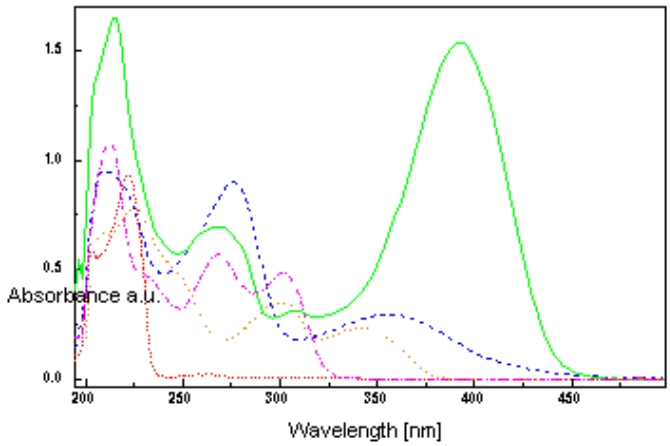


Fig. 1. *UV - VIS spectra of reactants and products in ethanol (c= 5x10^{-3} mol.dm^{-3})*

3-formylchromone **1**; 4-aminosalicylic acid; p-TsOH ; imine **9**; enamine **8**

It was corroborated that enamines **8** are formed by reaction of 6-substituted 4-oxochromene-3-carboxaldehydes **1** with aminosalicylic acids in alcoholic reaction medium (Scheme 3, step 1) and consecutively are transformed into chromenes **9** (Scheme 3, step 2) under the same conditions (at 40.5 ° C). The reaction rate was monitored in u. v. absorption band at 380 nm due to the 6-substituted 2-alkoxy-3-arylaminomethylene-4-oxo-chromenas **8**. At first, the absorbance of **8** increases, reaches a maximum and then decreases again. With decreasing the values of **8** the absorbance of **9** increases (Figure 2).

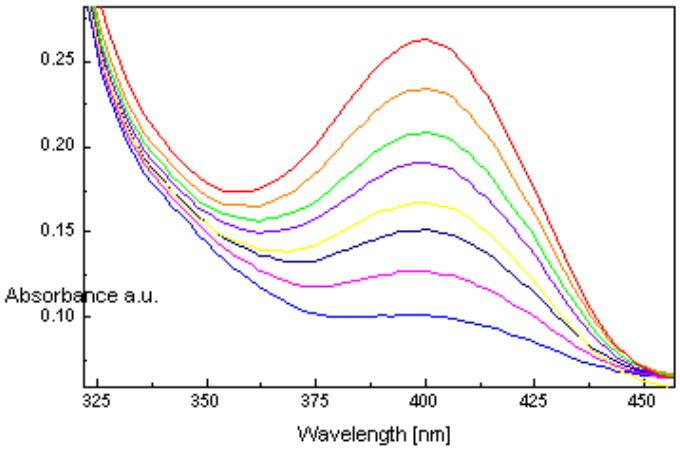


Fig. 2a. *Increase of absorbance of enamine 8r in dependence on reaction time t = 30, 65, 100, 135, 170, 205, 275, 520 s*

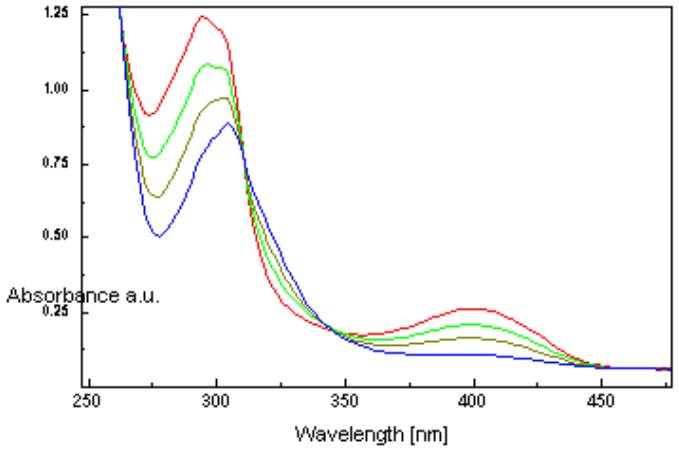


Fig. 2b. *Decrease of absorbance of enamine 8r in dependence on reaction time t = 520, 1780, 3530, 7700 s*

The presence of 2-alkoxy-3-arylaminomethylene-4-oxochromanes **8** and 3-aryliminomethyl-4-oxochromenes **9** in the reaction mixture was confirmed spectrometrically from their UV-VIS and ^{1}H NMR spectra.

Influence of structure of reactants. We found that reaction rate of the reaction of 4-oxochromene-3-carboxaldehyde **1** with 4-aminosalicylic acid **6c** is aproximately 14.6 times lower than that of reaction of 3-aminosalicylic acid **6d** (Table 2). Lower basicity of 4-aminoderivative nitrogen is the reason for the decrease in the reaction rate. Similarly, the substituent at position C-6 of benzopyrane ring affects the reaction rate. The reaction rate decreases in the following order H > NO2 > Cl (Figure 3). The substituent at position C-6 leads to a change of fragment charge on aldehydic carbon and modifies the reactivity, and the reaction rate, respectively.

Table 2. *Dependence of reaction rate on structure of reactants in ethanole ($c_{p\text{-}TsOH}$ =1x10^{-4} mol.dm^{-3})*

R1	**k [dm3.mol-1.s-1]** 4-aminosalicylic acid	**k [dm3.mol-1.s-1]** 3-aminosalicylic acid
Cl	2.86 x 10-5 ± 1 x 10-6	4.30 x 10-4 ± 1 x 10-5
NO2	7.99 x 10-5 ± 6 x 10-6	1.16 x 10-3 ± 2 x 10-5
H	8,15 x 10-5 ± 5 x 10-7	2.10 x 10-3 ± 2 x 10-5

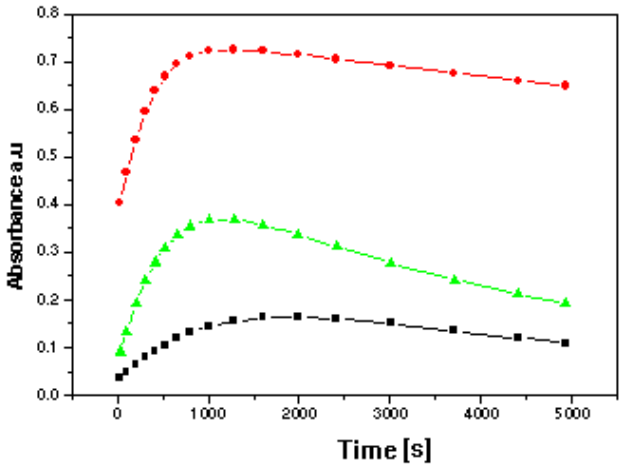


Fig. 3. *Absorbance change at* l *=388nm during transition enamime 8® imine9 in ethanol*

● -nitroderivative; ● - unsubstituted derivative; ● - chloroderivative

Influence of solvent used. Another part of our study deals with the influence of alcoholic reaction medium on reaction rate of reaction of 4-oxochromene-3-carboxaldehyde with aminosalicylic acids.

We found that ethanole and 1-butanole are optimal solvents for preparation of enamine derivatives **8**. It follows from the reaction rate measurements that the rate of formation of imine derivative **9** is lower than that for formation of enamine (Table 3). Consequently, it is possible to isolate 2-alkoxy-3-(2-hydroxy-3-carboxyphenylaminomethylene)-4-oxochromane from reaction mixture in high yields.

Table 3. *Effect of solvent on reaction rate of reaction of unsubstituted aldehyde 1, formation of enamines 8 ($c_{p\text{-}TsOH}$ = 1x10^{-4} mol.dm^{-3})*

Solvent	**k [dm3.mol-1.s-1]** 3-aminosalicylic acid	**k [dm3.mol-1.s-1]** 4-aminosalicylic acid
methanol	1.90 x 10-4 ± 5 x 10-6	4,16 x 10-6 ± 1 x 10-7
ethanol	2.10 x 10-3 ± 1 x 10-4	8,15 x 10-5 ± 5 x 10-7
2-propanole	5.63 x 10-4 ± 8 x 10-6	-
1-propanole	5.44 x 10-4 ± 3 x 10-5	7,41 x 10-5 ± 3 x 10-6
1-buthanole	8.92 x 10-4 ± 5 x 10-6	6,40 x 10-5 ± 2 x 10-6
Terc.buthanole	3.28 x 10-3 ± 3 x 10-5	-

However, the findings for 4-aminosalicylic acid are different. The rate of formation of enamine **8** is comparable to the rate of formation of imine **9**. Therefore, the abundance of 2-alkoxy-3-(3-hydroxy-4-carboxyphenylaminomethylene)-4-oxochromanes **8** in reaction mixture is substantially lower than that in case of 3-aminosalicylic acid.

When the reaction of 4-aminosalicylic acid was carried out in 2-propanole or methanole, respectively, the rate of formation of imine **9a** (for 2-propanole k = 0.00019) is higher than that of enamine (Table 3). The enamine being formed reacts immediately to yield an imine (Figure 4).

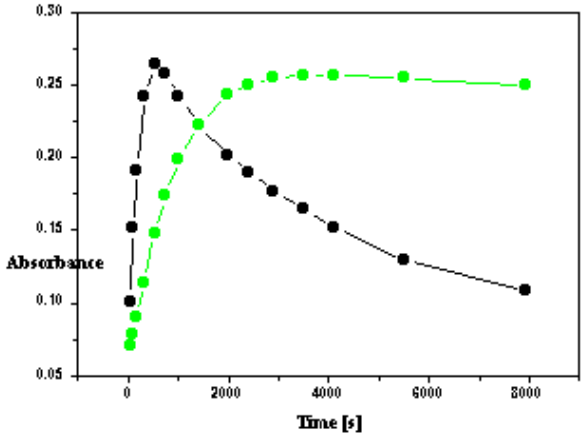


Fig. 4. *Time - absorbance relationship (formation of imine 9 at λ =388 nm) for reaction of 3-aminosalicylic acid with aldehyde 1 in 2-propanole ● or in methanole ● , respectively, ($c_{p\text{-}TsOH}$=1x10^{-4} mol.dm^{-3})*

Influence of concentration of catalyst. Concentration of 4-toluenesulfonic acid influences the reaction rate and the ratio of enamine **8** and imine **9** in reaction mixture. This effect of concentration of catalyst on the course of reaction depends on structure of reactants. Rate of formation of enamines derived from 3-aminosalicylic acid decreases with increasing catalyst concentration. The reverse is true for 4-aminosalicylic acid derivatives (Figure 5).

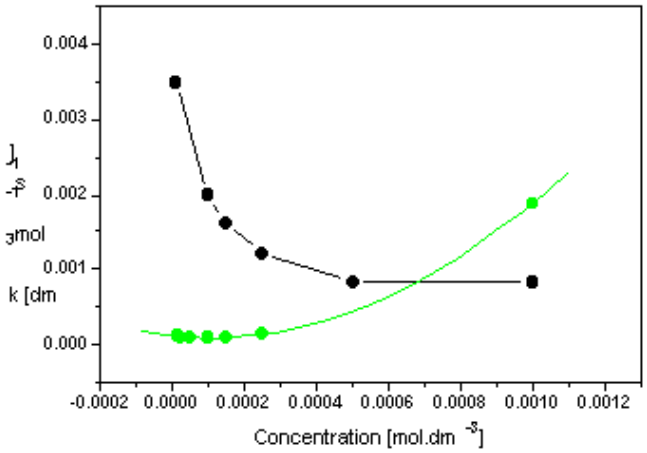


Fig. 5. *Dependence of rate constant of rection of 1 with aminosalicylic acids on concentration of p-TsOH*

● - 3-aminosalicylic acid; ● - 4 -aminosalicylic acid

The rate constant of transformation of enamine to imine (**8** ® **9**) depends upon the concentration of catalyst, the rate of 3-aryliminomethyl-4-oxochromene **8** formation is proportional to the concentration of 4-toluenesulfonic acid (Table 4, 5; Figure 6).

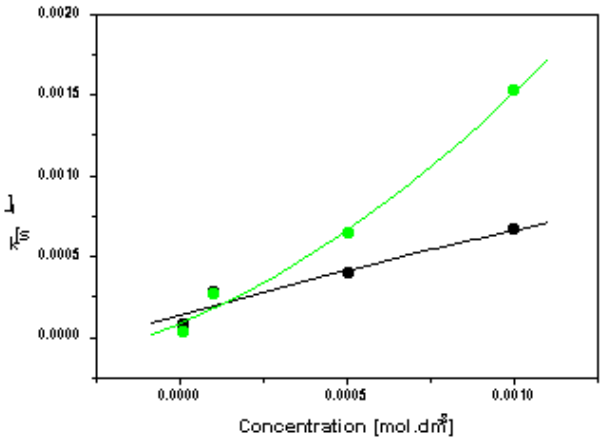


Fig. 6a. *Rate constant of transformation 8 ® 9- concentration of p-TsOH relationship in ethanol*

● - 3-aminosalicylic acid; ● - 4-aminosalicylic acid

Table 4. *Dependence of reaction rate of reaction of unsubstituted aldehyde with aminosalicylic acids on concentration of p-TsOH in ethanol*

Concentration of catalyst [mol·dm^{-3}]	**3-aminosalicylic acid** k [dm^{3}mol^{-1}s^{-1}]	**4-aminosalicylic acid** k [dm^{3}mol^{-1}s^{-1}]
0.00001	**3.55 x 10-3 ± 2 x 10-4**	**-**
0.000025	**-**	**9,28 x 10-5 ± 5 x 10-6**
0.00005	**3.99 x 10-3 ± 7 x 10-5**	**9,40 x 10-5 ± 3 x 10-7**
0.0001	**2.10 x 10-3 ± 1 x 10-4**	**8,15 x 10-5 ± 5 x 10-7**
0.00015	**1.60 x 10-3 ± 3 x 10-5**	**8,56 x 10-5 ± 1 x 10-6**
0.00025	**1.21 x 10-3 ± 7 x 10-4**	**1.07 x 10-5 ± 5 x 10-6**
0.0005	**8.26 x 10-4± 5 x 10-5**	**-**
0.001	**8.25 x 10-4 ± 7 x 10-5**	**1.89 x 10-3± 2 x 10-5**
0.01	**3.38 x 10-4 ± 2 x 10-5**	**-**

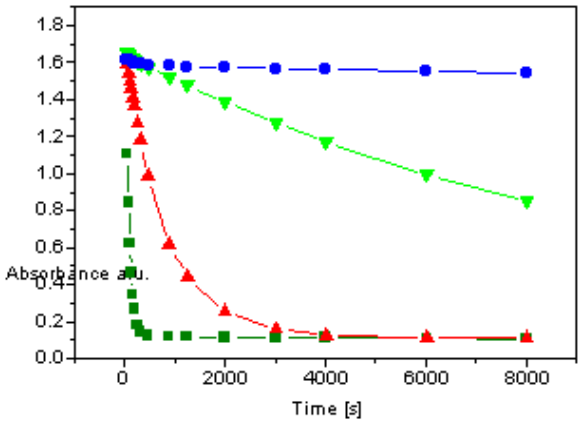


Fig. 6b. *Time - concentration of catalyst relationship for enamine 8 ® imine 9 transformation in ethanol*

● 10^{-2} mol. dm^{-3} ● 10^{-3} mol. dm^{-3} ● 10^{-4} mol. dm^{-3} ● 10^{-5} mol. dm^{-3}

Table 5. *Dependence of reaction rate of reaction of unsubstituted aldehyde with aminosalicylic acids on concentration of p-TsOH in 2-propanole*

Concentration of catalyst [mol.dm-3]	k [s-1] 3-aminosalicylic acid	k [s-1] 4-aminosalicylic acid
0.00001	8.58 x 10-4 ± 5 x 10-6	2.00 x 10-4 ± 3 x 10-5
0.0001	5.78 x 10-4 ± 5 x 10-5	3.16 x 10-4 ± 1 x 10-5
0.001	very fast *	1.53 x 10-3 ± 3 x 10-5
0.01	very fast *	8.63 x 10-3 ± 6 x 10-4

* it is impossible to prepare enamines 8 at concentration of catalyst > $1x10^{-4}$ $mol.dm^{-3}$

because the reaction is very fast, imine 9 is formed immediately

Ratio of derivatives 8 and 9 in reaction mixture can be controlled by change of catalyst concentration. In case of 3-aminosalicylic acid reaction the enamine 8 accumulates in the reaction mixture, because the transition rate 8 ® 9 is slow (Figure 7).

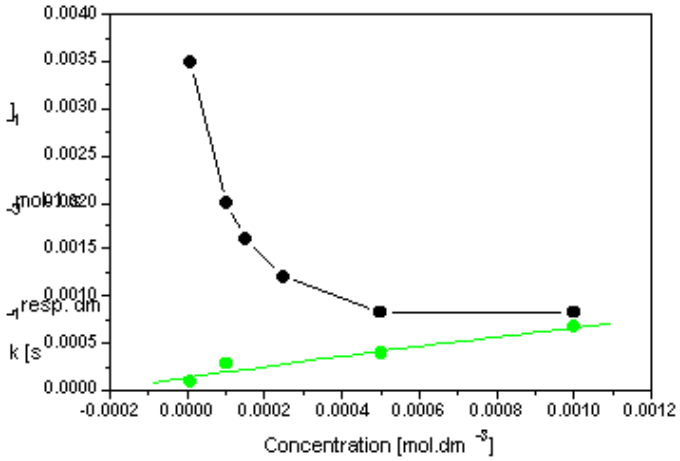


Fig. 7. *Rate constant - catalyst concentration relationship for formation of enamine ✹*

Rate constant - catalyst concentration relationship for transformation of 8 ® 9 ✹

The reverse is true for 4-aminosalicylic acid reactions. The transition rate 8 ® 9 is higher than that for the formation of enamine 8 at low concentrations of catalyst. Enamine reacts immediately giving imine under these conditions. It is possible to isolate enamine 8 from the reaction mixture only if the reaction rate of transformation 8 ® 9 is lower than that of formation of enamine 8 (Figure 8).

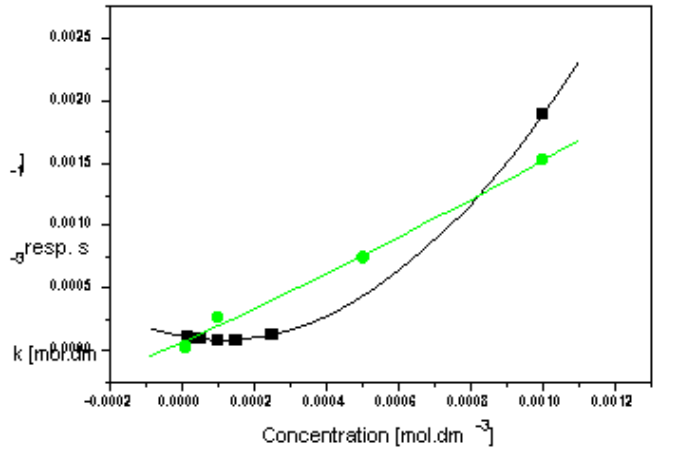


Fig. 8. *Rate constant - catalyst concentration relationship for formation of enamine ■*

Rate constant - catalyst concentration relationship for transformation of 8 ® 9 ✹

Experimental section

Preparation of compounds

4-Oxo-chromene-3-carboxaldehydes [16], 3-aminosalicylic acid [17] and 5-aminosalicylic acid [18] were prepared according to the reported methods, as indicated. Commercial chemicals (solvents, 4-aminosalicylic acid, 4-aminobenzoic acid, 4-aminohippuric acid and 4-toluenesulfonic acid) were used after purification and drying.

3-Arylaminomethylene-2-hydroxy-4-oxochromane 7

Method A. An aromatic amino acid **6** (1.148 mmol) was added to a stirred solution of 6-substituted 4-oxochomene-3-carboxaldehyde **1** (1.148 mmol) and 4-toluenesulfonic acid (0.029 mmol) in 6 ml dry toluene or benzene, and the solution was stirred at room temperature for 12 hours. The yellow precipitate was filtered off, washed with water and dried.

Method B. An aromatic amino acid **6** (1.148 mmol) was added to a boiling and stirred solution of 6-substituted 4-oxochomene-3-carboxaldehyde **1** (1.148 mmol) and 4-

toluenesulfonic acid (0.029 mmol) in 6 ml dry toluene or benzene, and the solution was refluxed for 10 hours. The yellow precipitate was filtered off, washed with water and dried.

3-Arylaminomethylene-2-alkoxy-4-oxochromane 8

Method A. A solution of aromatic amino acid **6** (1.148 mmol) in 6 ml of an appropriate alcohol was added dropwise to a stirred solution of 6-substituted 4-oxochomene-3-carboxaldehyde **1** (1.148 mmol) and 4-toluenesulfonic acid (0.029 mmol) in 6 ml alcohol, and the solution was stirred at room temperature for 12 hours. The yellow precipitate was filtered off, washed with water and dried.

Method B. A hot solution of 4-aminobenzoic acid **6a** or 4-aminohippuric acid **6b** (1.148 mmol) in 6 ml ethanol was added dropwise to a stirred and boiling solution of 6-substituted 4-oxochromene-3-carboxaldehyde **1** (1.148 mmol) and 4-toluenesulfonic acid (0.029 mmol) in 6 ml of ethanol, and the solution was refluxed for 3 hours. The yellow precipitate was filtered off, washed with alcohol and recrystallized from alcohol.

3-Aryliminomethyl-4-oxochromene 9

A hot solution of 4-aminosalicylic acid **6c** or 3-aminosalicylic acid **6d** (1.148 mmol) in 6 ml ethanol was added dropwise to a stirred and boiling solution of 6-substituted 4-oxochromene-3-carboxaldehyde **1** (1.148 mmol) and 4-toluenesulfonic acid (0.029 mmol) in 6 of ml ethanol, and the solution was refluxed for 3 hours. The precipitate was filtered off, washed with diethyl ether and dried.

2-Alkoxy-3-[N-arylmethyl-N-arylaminomethylene]-4-oxochromane 10

A mixture of 4-oxochromane **8** (1.148 mmol) and K2CO3 (2.296 mmol) in 8 ml dry acetonitrile was stirred at room temperature for 3 hours. After then we added benzylbromide or 3-fluorobenzylchloride, respectively, (2.296 mmol) and the stirring was continued at 110 °C under reflux condenser for 5 hours. The acetonitrile was removed by distillation. Diethyl ether (30 ml) was added to the residue. The solid crude product was filtered off and recrystallized from ethanol.

Identification of compounds

The purity and structures of starting and prepared compounds were monitored by the microanalyses , ^{1}H NMR and IR spectroscopy and by the thin-layer chromatography. Melting points were determined using a Kofler hot stage and are uncorrected. IR spectra (ν , cm^{-1}) were taken in the region of ν = 400 - 4000 cm^{-1} on a Specord 75 IR (Zeiss, Jena) in paraffin oil. ^{1}H NMR spectra (δ , ppm, J, Hz) were measured on Spectrometer BS-487 (80MHz, Tesla) except for the compounds **8b-8d**, which spectra were taken on Spectrometer VXR-300 (300 MHz, Varian) in hexadeuteriodimethyl sulfoxide with tetramethylsilane as internal standard.

Kinetic measurements

Alcoholic solution (2 ml, c = 4x10-4 mol.dm-3) of 6-substituted 4-oxochromene-3-carboxaldehyde **1** was mixed with 2 ml of alcoholic solution of 4-toluenesulfonic acid (c = 4x10-4 mol.dm-3). This resultant solution together with 2 ml of alcoholic solution of aminosalicylic acid **6** (c = 2x10-4 mol.dm-3) was maintained at constant temperature 40.5 ° C. Solutions were mixed together. All measurements were performed in a 1cm thick absorption cell at 40.5 ° C.

The kinetics of reactions was monitored UV-VIS spectrophotometrically using the spectrometer Hewlett-Packard "Diode Array 8254". The rate constants were calculated by the Hewlett-Packard programme-assisted method of initial velocity and by fitting of experimental data to a parabola equation. Kinetic experiments were measured to the limiting equilibrium concentration.

Conclusion

6-Substituted 4-oxochromene-3-carboxaldehydes **1** with aromatic amino acids **6** yield enamines **7**, **8** or imines **9** in dependence upon reaction conditions. The results can be summarized as follows:

1. 2-Hydroxy-3-arylaminomethylene-4-oxochromanes **7** are formed in the reaction of aldehydes **1** with aromatic amino acids **6** in the presence of 4-toluenesulfonic acid as the catalyst in dry aprotic reaction media at room temperature or reflux, respectively.

2. 4-Aminohippuric **6b** and 4-aminobenzoic **6a** acids undergo the reaction with **1** in alcohols at room temperature or at reflux, respectively, to form 2-alkoxy-3-arylaminomethylene-4-oxochromanes **8a-e**.

3. Ethanole and 1-butanole are suitable reaction media for preparation of chromanes **8**, derived from aminosalicylic acids, in the presence of 4-toluenesulfonic as the catalyst at temperatures lower than 40° C.

4. The rate of formation of enamines **8f-r** and imines **9a, b** is proportional to the concentration of 4-toluenesulfonic acid. Only imines **9** were isolated from reaction mixture when a large excess (100 times excess) of catalyst was used.

5. Aminosalicylic acids **6** with 6-substituted 4-oxochromene-3-carboxaldehydes **1** yield imines **9** in the presence of catalyst in alcohols at reflux.

Acknowledgement. Financial support for this research was granted by the Slovak Grant Agency (Grant No 1/5058/98) and is gratefully acknowledged.

References

1. Ghosh, C. K. *J. Heterocycl. Chem.,* **1983**, *20*, 1437.

2. Sigg, I.; Haas, G.; Winkler, and Winkler, T. *Helv. Chim. Acta,* **1982**, *65*, 275.

3. Stankovicova, H., Fabian, W. M. F., and Lacova, M. *Molecules*, **1996**, *1*, 223.

4. Stankovicova, H., Fabian, W. M. F., and Lacova, M. *unpublished results.*

4. Kostka, K. *Roczniki Chem*., **1966**, *40*, 1638.

5. Fitton, A. O.; Frost, J. R.; Houghton, P. G.; Suschitzky, H. *J. Chem. Soc., Perkin Trans 1*, **1979**, 1691.

6. Devi, T. K.; Achaiah, G.; Reddy, V.M. *J. Indian Chem. Soc.*, **1988**, *65*, 567.

7. Kapoor, R. P.; Chhabra, V.; Sangita, G. C. P. *Indian J. Chem. Sect. B*, **1985,** *24B*, 539.

8. El-Shaaer, H. M. *PhD Thesis*, **1992**, Comenius University Bratislava.

9. Prousek, J.; Jurásek, A.; Kovác J. *Collect. Czech. Chem. Commun.*, **1980**, *45*, 1581.

10. Lácová, M.; Stankovicová H.; Odlerová, Ž. *II Farmaco*, **1995**, *50*, 885.

11. Králová, K.; Sersen, F.; Lácová, M.; Stankovicová, H. *Biol. Plant.*, **1996**, *38*, 397.

12. El-Shaaer, H. M.; Foltinová , P.; Lácová, M.; Chovancová, J.; Stankovicová, H. *II Farmaco*, **1998**, *53*, 224.

13. Fitton, A. O.; Frost, J. R.; Suschitzky, H. *Tetrahedron Lett.*, **1975**, 2099.

14. Fitton, A. O.; Houghton, P. G.; Suschitzky, H. *Synthesis*, **1979**, 337.

15. Nohara, A.; Umetani, T.; Sanno, Y. *Tetrahedron* , **1974**, *30*, 3553.

16. Beilstein, **1931**, *H14*, 577.

17. Beilstein, **1931**, *H14*, 579.

Table1. *Characteristic data of synthesized compounds*

Comp.	R1	R3	starting	M. p. / °C	Formula	Analysis Calc./Found			
			6a	Yield / %	Mr	%C	%H	%N	%X
7a	H	H	6a	217 - 220 76	C17H13NO5 311.29	65.59 65.53	4.29 4.03	4.51 4.48	- -
7b	CH_3	H	6a	339 - 342 78	C18H15NO5 352.32	66.46 66.38	4.65 4.60	4.31 4.33	- -
7c	CH_3	H	6b	235 - 239 70	C20H18N2O6 382.37	62.82 62.54	4.74 4.71	7.33 7.33	- -
7d	H	H	6c	231 - 234 92	C17H13NO6 326.29	62.39 62.04	4.01 3.98	4.28 4.29	- -
8a	H	Et	6a	289 - 291 92	C19H17NO5 340.56	67.01 67.07	5.38 5.15	4.11 4.14	- -
8b	Cl	Et	6a	318 - 320 90	C19H16NClO5 373.80	61.05 60.85	4.31 4.25	3.75 3.68	9.48 9.06

8c	NO_2	Et	6a	298 - 305* 87	C19H16N2O7 384.35	59.38 58.95	4.20 4.23	7.28 6.98	- -
8d	CH_3	Et	6a	309 - 311* 85	C20H19NO5 353.37	67.98 67.67	5.42 5.34	3.96 3.84	- -
8e	H	Et	6b	228 - 230 81	C21H20N2O6 396.40	66.63 66.51	5.09 5.05	7.07 7.00	- -
8f	.H	Et	6c	215 - 219* 73	C19H17NO6 355.35	64.22 64.08	4.82 4.81	3.94 3.37	- -
8g	Cl	Et	6c	205 - 207* 84	C19H16NClO6 389.06	58.65 58.16	4.14 4.07	3.60 3.59	9.11 9.10
8h	NO_2	Et	6c	207 - 209* 79	C19H16N2O8 400.34	57.00 56.87	4.03 4.05	7.00 6.95	- -
8i	Br	Et	6c	206 - 210* 86	C19H16NBrO6 434.24	52.55 52.04	3.71 3.64	3.23 2.95	18.40 18.10
8j	CH_3	Et	6c	194 - 197* 73	C20H19NO6 369.37	65.03 64.78	5.18 5.18	3.79 3.83	- -
8k	Cl	n-Bu	6c	210 - 211* 86	C21H20NClO6 417.85	60.42 59.85	4.83 4.81	3.36 3.16	8.48 8.45
8l	Cl	n-Hex	6c	139 - 140* 56	C23H24NClO6 445.90	61.95 61.72	5.43 5.39	3.14 3.13	7.95 7.90
8m	Cl	n-Pr	6c	206 -208* 62	C20H18NClO6 403.82	59.49 59.15	4.49 4.39	3.47 3.45	8.78 8.75
8n	NO_2	i-Pr	6c	216 - 219* 58	C20H18N2O8 414.37	57.79 57.65	4.38 4.36	6.76 6.70	- -
8o	H	Et	6d	145 - 146 57	C19H17NO6 355.35	64.22 63.78	4.82 4.57	3.94 3.93	- -
8p	Cl	Et	6d	203 - 207 73	C19H16NClO6 389.06	58.65 58.24	4.14 4.36	3.60 3.43	9.11 8.90
8q	NO_2	Et	6d	172 - 175* 68	C19H16N2O8 400.34	57.00 56.91	4.03 3.99	7.00 6.95	- -
8r	H	i-Pr	6d	139 - 143 60	C20H19NO6 369.37	65.03 64.78	5.18 5.15	3.79 3.71	- -
8s	H	Et	6e	285 - 287* 62	C19H17NO6 355.35	64.22 63.87	4.82 4.76	3.94 3.72	- -

8t	CH_3	Et	6e	275 - 277*	C20H19NO6	65.03	5.18	3.79	-
				65	369.37	64.75	5.12	3.72	-
9a	H	-	6c	249 - 250	C17H11NO5	66.02	3.58	4.52	-
				51	309.28	65.57	3.56	4.21	-
9b	Br	-	6c	226 - 230	C17H10NBrO5	52.60	2.59	3.60	20.58
				49	388.17	52.15	2.44	3.32	20.60
10a	H	Et	6e	140 - 141	C33H29NO6	74.00	5.46	2.62	-
				70	535.60	73.94	5.51	2.38	-
10b	CH_3	Et	6c	120 - 122	C34H29NF2O6	70.05	4.95	2.39	6.49
				70	585.60	69.84	4.72	2.64	-b
10c	CH_3	Et	6a	133 - 134	C27H25NO5	73.12	5.68	3.16	-
				70	443.50	73.16	5.83	3.05	-

X= halogen

* decomposition

a **6a** - 4-aminobenzoic ; **6b** - 4-aminohippuric ; **6c** - 4 -aminosalicylic ; **6d** - 3-aminosalicylic ; **6e** - 5-aminosalicylic acids

b not analysed

Comments

During 1-30 September 1998, all comments on this poster should be sent by e-mail to ecsoc@listserv.arizona.edu with a0014 as the message subject of your e-mail. After the conference, please send all the comments and reprints requests to the author.
