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KINETIC STUDY OF THE THERMALLY INITIATED CYCLOCONDENSATION OF SOME 1,3-DIMETHYL-4-ALKYLAMINO-5-NITROSOURACILS

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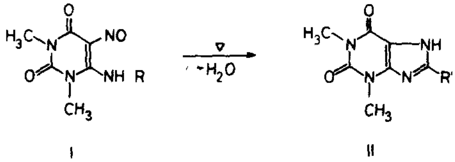
The isothermal and non-isothermal DSC method was used to investigate the influence of changes in structure of 1,3-dimethyl-4-alkylamino-5-nitrosouracils on the 8-substituted theophyllines originating in the cyclocondensation reaction. The evaluation of the optimum reaction mechanism obtained on the basis of the corresponding model functions by using the integral method of Coats and Redfern is discussed. Significant differences, depending on the nature of the substituents, were observed in the course of the reaction.

The thermoanalytical methods have become indispensable in the study of thermal properties of substances. In most cases these methods are used to investigate the thermal decompositions of inorganic compounds, organic polymers, etc. [1–3]. The results of such studies also contribute to characterization of the processes of destruction taking place in the course of heating.

The study of substances from which qualitatively different products originate on heating is an equally important field of use of these methods, though a relatively small number of papers are concerned with these problems [4–6]. The thermally initiated cyclocondensation of 1,3-dimethyl-4-alkylamino-5-nitrosouracils (I), which is the basis of one of the methods of synthesis of the 8-substituted theophyllines (II) [7], is one such process:



(1)

We recently published the results of a thermochemical study of this reaction in the solid state by means of the DSC method [8, 9]. The present paper deals with the

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influence of changes in the structure of the starting substance (I) on the kinetics of the above reaction under isothermal and non-isothermal conditions.

Experimental

The derivatives of 1,3-dimethyl-4-alkylamino-5-nitrosouracil (I) (where alkyl $R = CH_3$, C_2H_5, *iso*-C_4H_9, $(CH_2)_2C_6H_5$, $(CH_2)_2OH$, and $(CH_2)_3OH$) were prepared by nitrosation of I with propyl nitrite in methanol. The structures of the prepared compounds were confirmed by spectral methods (UV, IR and ^{1}H NMR) and elemental analysis. The isothermal and dynamic records (10 deg min^{-1}) were obtained with a DSC-2 calorimeter (Perkin-Elmer).

The measurements were carried out in nitrogen atmosphere, the flow rate being 20 cm^3 min^{-1}. Indium and lead were used as standards for calibrating the temperature.

Results and discussion

The kinetics of cyclocondensation reaction (1) was investigated for the six different derivatives of I under isothermal and non-isothermal conditions (Table 1). In both cases, we used kinetic functions in integral from (Table 2). These functions are convenient for describing reactions in the solid state [1, 10].

Table 1 Temperatures and temperature interval used for isothermal and dynamic study of cyclocondensation reaction [1]

No.	Compound R	Isothermal study T, K	Non-isothermal study[a]		
			T_i^b	T_p	T_f
1	CH_3	408, 410, 413, 415, 418	404	423	439
2	C_2H_5	375, 380, 385	369	403	416
3	*iso*C_4H_9	370, 375, 380	368	391	407
4	$(CH_2)_2C_6H_5$	395, 400	390	425	432
5	$(CH_2)_2OH$	400, 405, 408, 410	399	423	431
6	$(CH_2)_3OH$	370, 373, 375, 378	365	391	406

[a] Heating rate was 10 deg min^{-1}

[b] T_i, T_p, T_f denote the initial, maximum and final temperatures of the DSC peak of the reaction, respectively

Table 2 Functions $g(\alpha)$ used in kinetic analysis

$g(\alpha)$	Symbol	Rate controlling process
$-\ln(1-\alpha)$	F_1	Random nucleation, unimolecular decay law
$-\ln(1-\alpha)^n$	A_n	Avrami–Erofeev equation. Random nucleation and subsequent growth (n = 2, 3, 4)
α^2	D_1	One-dimensional diffusion
$\alpha+(1-\alpha)\ln(1-\alpha)$	D_2	Two-dimensional diffusion
$[1-(1-\alpha)^{1/3}]^2$	D_3	Three-dimensional diffusion (Jander function)
$1-2/3\alpha-(1-\alpha)^{2/3}$	D_4	Three-dimensional diffusion (Ginstling–Broushtein function)
$1-(1-\alpha)^{1/m}$	R_m	Phase boundary reaction (m = 2, 3)
$\ln\left(\frac{\alpha}{1-\alpha}\right)$	A_u	Autocatalytic reaction (Prout–Tompkins function)

Isothermal analysis

The kinetic analysis of the thermal decompositions of solid substances in the isothermal regime involves the use of the known form of the kinetic equation

$$g(\alpha) = kt$$

where $g(\alpha)$ is a function characterizing the physico-geometrical model with the pertinent mechanism of the process, α is the degree of transformation of the solid substance at the instant t, and k is the rate constant obeying the Arrhenius equation $k = A\exp(-E/RT)$ (A = frequency factor, E = activation energy, and R = gas constant) [10, 11].

1. 1,3-Dimethyl-4-methylamino-5-nitrosouracil

It is obvious from the plot of α against t for different temperatures that the shape of the curve is sigmoidal (Fig. 1). The plot of $\ln[-\ln(1-\alpha)]$ against $\ln t$ indicates [12] that the reaction is not isokinetic in the investigated temperature interval (Fig. 2). On the basis of testing of the mentioned model functions $g(\alpha)$, we have found that the course of the reaction at 418 K is best described by a first-order equation or autocatalytic equation (A_u), while the Avrami–Erofeev equation (A_n, $n=3$) is the most suitable at 408 K. This fact has been confirmed by comparing the experimental values with theoretical ones on the basis of the plot of α against $t/t_{0.5}$ according to [13]. The deviations from the theoretical relationship (Fig. 3) increase with increasing temperature.

As recently reported [8] for this compound, it has been established through visual observation in a Kofler microscope that the reaction does not take place in the solid state, but in the melt, because the starting substance melts before the reaction proper, which may also be observed via the colour change produced by a change in the structure.

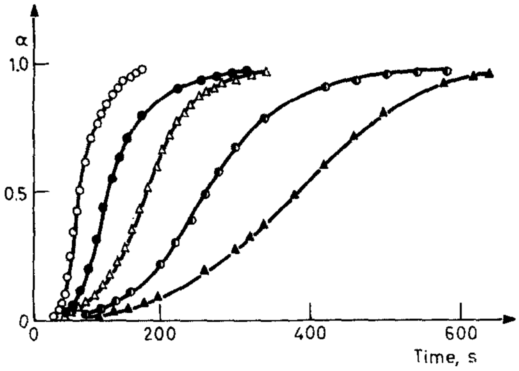

Fig. 1 Variation of α with time for methyl derivative at different temperatures, ○ 418 K, ● 415 K, △ 413 K, ◑ 410K, ▲ 408 K

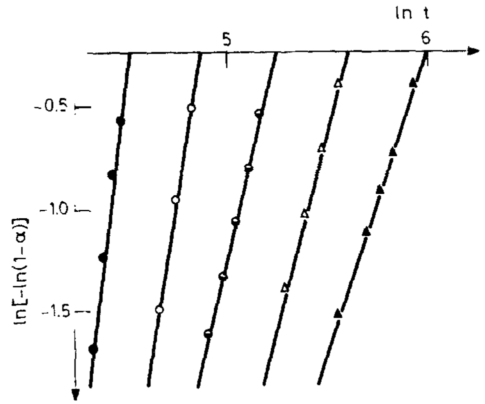

Fig. 2 Plot of $\ln[-\ln(1-\alpha)]$ vs. $\ln t$ for the cyclocondensation of the methyl derivative, ● 418 K, ○ 415 K, ◑ 413 K, ▽ 410 K, ▲ 408 K

Similar systems were described by Rogers [14],who stated that the sigmoidal shape of the isothermal α vs t curves should not always correspond to an autocatalytic process or a nucleation-growth process, but could also characterize systems which melted with decomposition. The activation energy value determined on the basis of the kinetic analysis he proposed was 173 kJ mol^{-1}.

2. 1,3-Dimethyl-4-ethylamino-5-nitrosouracil

In contrast with the preceding derivative, the curve expressing the dependence of α on t is not sigmoidal (Fig. 4). The testing of the functions $g(\alpha)$ has shown that in this case the course of the reaction is best described by the equation of volume contraction (R_3) for α(0.03–0.90). The plot of $\ln[-\ln(1-\alpha)]$ against $\ln t$ has confirmed the isokinetic character of the process.

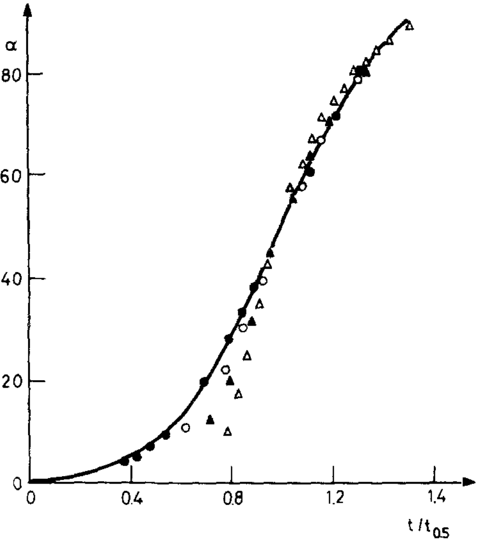

Fig. 3 Reduced time plots for reaction (1) of the methyl derivative, — master curve, A_3, ● 408 K, ○ 410 K, ▲ 415 K, ▽ 418 K

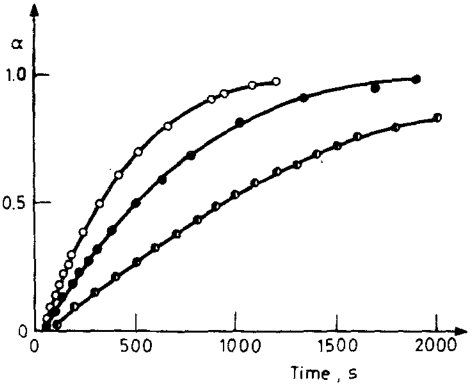

Fig. 4 Variation of α with time for the ethyl derivative, ○ 385 K, ● 380 K, ◑ 375 K

Thus, it appears that even a small change in the structure evidently affects the crystalline order or the interactions of the molecules, which results in a higher stabilization from the point of view of the $s-l$ phase transition of the original compound. On the other hand, the structural arrangement must be advantageous for the cyclocondensation reaction, which then takes place in the solid state, too.

3. 1,3-Dimethyl-4-isobutylamino-5-nitrosouracil

In order to show the influence of a more complicated structure, we investigated this isobutyl derivative. In this case the structure is more voluminous and branched, and we may assume that the arrangement in the solid state is less symmetrical and that the accessibility of the groups participating in reaction (1) may be better if they are located in the surface (steric hindrance). It is worth noting that it is rather difficult to investigate the reaction to the full extent because the slope of the α vs t curve assumes small values at lower temperatures, which gives rise to considerable errors at higher values of α. For this reason, we have taken into account only the relationships obtained at 375 K and 380 K. Besides the surface-controlled reaction (R_m), the first-order equation (F_1) is also in force, especially at lower values of α, and according we cannot eliminate the possibility of a mixed mechanism, as found in [15].

4. 1,3-dimethyl-4-(2-phenylethylamino)-5-nitrosouracil

The presence of the relatively voluminous substituent facilitates the surface reaction, which may be due to the considerable stability of the starting substance with respect to melting. In fact, microscopic observation has not revealed any formation of the melt in the course of the reaction. It follows from Table 3 that the lowest reaction enthalpy appears in this case, which may result from a small change in the symmetry of the arrangement of the molecules of the starting substance and product. In this connection, we should like to call attention to the smallest change in reaction entropy.

On the basis of testing, the course of the reaction may be described by the equation of area contraction (R_2) for $\alpha(0.10\text{–}0.95)$. The activation energy value thus found is 265 kJ mol^{-1}.

5. 1,3-Dimethyl-4-(2-hydroxyethylamino)-5-nitrosouracil

In order to examine to what degree the polarity or electron effects may influence the course of the reaction, we also prepared hydroxy derivatives.

The α vs t curve to a certain extent exhibits a sigmoidal character (Fig. 5). In this case, the reaction can be satisfactorily described by the Avrami–Erofeev mechanism for $\alpha(0.10\text{–}0.97)$. It has been found from the plot of $\ln[-\ln(1-\alpha)]$ against $\ln t$ that the process is not isokinetic. The slope values obtained from this relationship vary with increasing temperature in the range between 1.9 and 2.7. The reduced time values confirm this fact (Fig. 6). The course of the reaction is described by the model function A_2 at 400 K, and by the model function A_3 at 410 K. Thus, it seems that a change occurs in the reaction mechanism, which may be caused, to a certain extent by interactions of the corresponding OH groups of the substituent. However, we cannot rule out an autocatalytic process, due to the fact that the gradually formed product brings about a change in the arrangement of the system or induces the pertinent reaction. For this reason, this reaction was investigated after adding the product (5.5 mass%) to the starting substance. A comparison with the reaction

Table 3 Values of E (kJ mol^{-1}) and log A (s^{-1}) as well as the corresponding correlation coefficients r obtained from the dynamic DSC curve[a]

Compound, R	CH_3			C_2H_5			*iso*-C_4H_9			$(CH_2)_2C_6H_5$			$(CH_2)_2OH$			$(CH_2)_3OH$		
$g(\alpha)$	E	log A	r	E	log A	r	E	log A	r	E	log A	r	E	log A	r	E	log A	r
R_1	364	43	0.958	170	20	0.985	211	26	0.967	218	27	0.974	252	29	0.974	317	37	0.990
R_2	398	47	0.971	184	22	0.993	234	29	0.981	240	30	0.986	274	32	0.985	342	40	0.995
R_3	412	49	0.976	190	22	0.995	244	30	0.986	250	31	0.990	283	33	0.989	353	42	0.996
F_1	446	53	0.985	203	25	0.997	267	34	0.993	273	35	0.996	306	36	0.993	379	45	0.996
A_2	219	25	0.985	98	11	0.997	130	16	0.993	133	16	0.996	149	17	0.992	186	21	0.996
A_3	144	16	0.984	63	6	0.996	85	9	0.993	87	10	0.995	97	10	0.992	122	13	0.996
A_4	106	11	0.984	46	4	0.996	62	6	0.968	63	6	0.995	71	7	0.992	90	9	0.996
D_1	735	—	0.959	347	43	0.986	428	55	0.986	442	57	0.973	510	62	0.975	640	—	0.990
D_2	773	—	0.966	363	45	0.990	454	58	0.976	468	60	0.982	535	64	0.981	640	—	0.997
D_3	830	—	0.976	386	47	0.995	494	63	0.986	506	65	0.990	572	69	0.989	713	—	0.995
D_4	791	—	0.969	370	45	0.992	466	59	0.980	480	61	0.985	547	65	0.984	683	—	0.993
$-\Delta H_R^b$	212 ± 7			219 ± 5			224 ± 9			235 ± 14			190 ± 5			178 ± 6		

[a] The listed values are average values of three measurements at least, range of α values (0.001–0.990)

[b] Reaction enthalpy (kJ mol^{-1}), see Ref. [8]

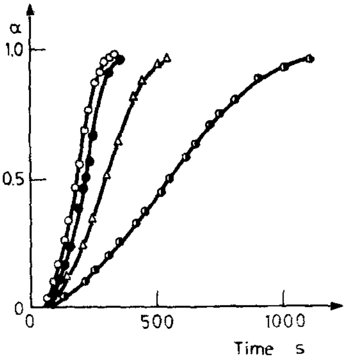

Fig. 5 Variation of α with time for the hydroxyethyl derivative, ○ 410 K, ● 408 K, △ 405 K, ◑ 400 K

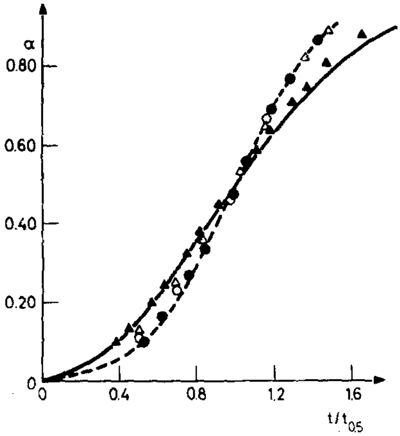

Fig. 6 Reduced time plots for reaction (1) of the hydroxyethyl derivative, – – – master curve, A_3, — master curve A_2, ▲ 400 K, ▽ 405 K, ○ 408 K, ● 410 K

without any addition of the product, performed under identical conditions, showed that the value of the rate constant increased and was almost doubled.

6. 1,3-Dimethyl-4-(3-hydroxypropylamino)-5-nitrosouracil

Because of the lengthening of the chain, an evident decrease in the electron-withdrawing effect of the OH group is manifested. In the α(0.06–0.80) range, the reaction may be described well by the function R_2 or R_3. Moreover, the reaction in the investigated temperature region is not an isokinetic process.

Therefore, we cannot rule out a combination of the mechanisms A_n and R_m.

Non-isothermal analysis

As reported by Kassman [16], a comparison of the different integral methods has shown that a quite simple and precise method for obtaining the kinetic parameters of a reaction is the integral method of Coats and Redfern [17]:

$$\ln\left\{\frac{g(\alpha)}{T^2}\right\} = \ln\frac{AR}{aE}\left(1-\frac{2RT}{E}\right)-\frac{E}{R}\frac{1}{T}$$

where a is the rate of heating. The obtained linear relationship between $\ln(g(\alpha)/T^2)$ and $1/T$ enables us to calculate the activation energy from the slope and the frequency factor from the intercept. In order to facilitate the kinetic analysis, we elaborated a programme for testing by the method of least squares the model functions $g(\alpha)$ given in Table 2, except for the Prout–Tompkins equation. The results thus obtained for all investigated derivatives are presented in Table 3. It is obvious from these results that the use of the correlation coefficient as criterion for the selection of an appropriate model function $g(\alpha)$ describing the reaction mechanism is not admissible [18, 19]. It results from this fact that the isothermal study of the course of reaction [20–22] is really a necessary condition, owing to which the non-isothermal methods lose one of the main virtues, i.e. the possibility of determining the kinetic parameters from a single curve.

In all cases, the shape of the α vs T curves is more or less sigmoidal. Good agreement of the kinetic parameters obtained under isothermal and non-isothermal conditions was found for the phenyl ethyl derivative. This reaction, proceeding in the dynamic or the isothermal regime, can be described very well by equation R_2 in the whole range of $\alpha(0.01–0.98)$. The values of E found for the non-isothermal and the isothermal regime are 240 kJ mol^{-1} and 265 kJ mol^{-1}, respectively.

As concerns the ethyl derivative, it is true that there is a consistence of the mechanism of the surface-controlled reaction (R_3) proceeding under isothermal and non-isothermal conditions. Nevertheless, the results of the non-isothermal measurements indicate the possibility of describing the reaction of this derivative by using the Avrami–Erofeev function. This means that the non-isothermal method is not of good use, even for the mutual comparison of the mechanisms valid for the individual derivatives. It goes without saying that the determined activation parameters are not consistent. This fact may be due to the thermal conductivities of the investigated samples or the thermal effects of the corresponding condensation reaction. These effects are smaller for the phenylethyl derivative than for the ethyl derivative, owing to which different temperature gradients may appear in the samples.

The interpretation of the results is much more complicated for those derivatives for which the reaction mechanism cannot be unambiguously described even for isothermal measurements. Thus, we may state that the individual "quasi-optimum" functions used for the given mechanisms were not consistent with one another in these cases.

On testing the Avrami–Erofeev functions ($n = 2, 3, 4$) under non-isothermal conditions, we obtained a double linear relationship with a break, and even with two breaks for the isobutyl derivative (Fig. 7). Similar breaks were observed in the Coats–Redfern relationships obtained for the thermal decomposition of the $ZnO - Al_2O_3$ system [23].

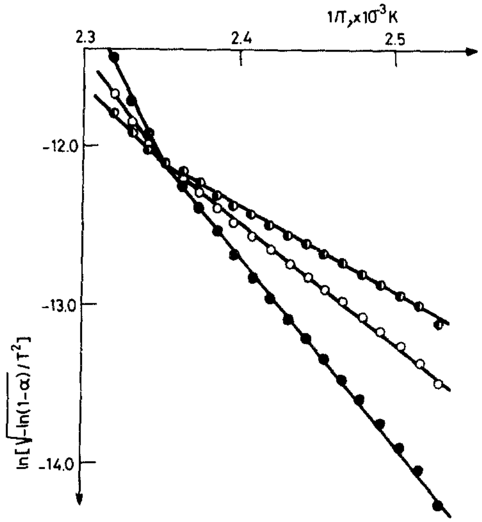

Fig. 7 Coats–Redfern plot (Avrami-Erofeev function) for phenylethyl derivative, ● A_2, ○ A_3, ◐ A_4, α range (0.01–0.98)

On the basis of the finding made for the first derivative, according to which the melting precedes the reaction [8], we cannot rule out local melting [1], e.g. produced by self-heating for other compounds, because the reaction is strongly exothermic (in some cases even explosive) and hence can take place in the system of mixed phases. Thus, we may assume that it is a microheterogeneous process or a process involving a few steps which may be characterized by the observed breaks corresponding to different activation energy values. We cannot rule out a radical mechanism of the process, evidence of which would necessitate the use of one of the auxiliary methods, especially the EPR method.

On the other hand, the function describing the surface-controlled reaction was the most convenient for non-isothermal measurements. We may assume that this fact is caused by successive generation of the product in the direction of the temperature gradient, i.e. by gradual acceleration of the reaction. As concerns the general use of non-isothermal kinetic measurements, we must state that the results obtained are not usable even for relative comparison in a given series of substituents (e.g. methyl, ethyl, isobutyl). From the standpoint of testing of the isokinetic process, it appears that we may also assume a temperature-conditioned kinetic process for the cases in which an agreement of isothermal measurements with non-isothermal measurements has not been attained.

Conclusions

The cyclocondensations of six derivatives of 1,3-dimethyl-4-alkylamino-5-nitrosouracils, yielding the 8-substituted theophyllines, were studied by using the DSC method under isothermal and non-isothermal conditions. The kinetic analysis revealed that the course of this reaction can be affected:

a) by melting of the starting substance (e.g. the methyl derivative) or by local melting, which is difficult to detect;

b) by the nature of the substituent (electron and steric effects) and the convenient orientation of the groups giving rise to the product, or by the crystal structure.

The study of the kinetics has shown that the equations usually used in kinetic analysis seem to be only boundary cases derived on the basis of physico-geometrical models, which means that the real processes taking place in the solid phase do not strictly obey them, or a combination of these equations may be operative.

Besides isothermal analysis, a more thorough study of the mechanism of this reaction requires additional information about the structures of the pertinent compounds, obtained by X-ray analysis, about the influence of the distribution of particle sizes, etc. A similar kinetic analysis of this reaction in solution could contribute to the knowledge of the electronic and steric effects of the substituent and simplify the classification of the reaction into a certain reaction type from the viewpoint of organic chemistry (i.e. whether the reaction follows a polar or a radical mechanism).

On the other hand, as we are concerned with a strongly exothermic reaction, different behaviour is to be observed under non-isothermal conditions (formation of temperature gradients in the sample, self-heating), which ensues from an apparently different mechanism or a mechanism that is determined by dissimilar processes taking place on the surface and inside the system. It may be that in some cases the reaction takes place in several phases of the condensed system.

It appears that the use of non-isothermal methods is, in principle, not suited for more complicated mechanisms, especially if we want to investigate an autocatalytic process which has been experimentally demonstrated by addition of the product.

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Zusammenfassung — Der Einfluß von Veränderungen in der Struktur von 1,3-Dimethyl-4-alkylamino-5-nitrosouracilen auf die in einer Zyklokondensationsreaktion gebildeten, 8-substituierten Theophylline wurde mittels isothermer und nicht-isothermer DSC untersucht. Die optimalen, basierend auf entsprechenden Modellfunktionen bei Anwendung der Integralmethode von Coats und Redfern erhaltenen Reaktionsmechanismen werden diskutiert. Im Verlaufe der Reaktion wurden signifikante, von der Natur der Substituenten abhängende Unterschiede festgestellt.

Резюме — Для изучения изменения структуры 1,3-диметил-4-алкиламино-5-нитрозоурацилов в реакции циклоконденсации их с 8-замещенными теофиллинами, была использована изотермическая и неизотермическая ДСК. Обсуждена оценка оптимальных механизмов реакции, полученных на основании соответствующих модельных функций, найденных с помощью интегрального метода Коутса–Рэдферна. Отмечены заметные различия хода реакции в зависимости от природы заместителей.