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KINETICS OF REACTIONS OF THIOUREA, PHENYLTHIOUREA, AND *p*-TOLYLTHIOUREA WITH SUBSTITUTED PHENACYL BROMIDES IN ETHANOL : STRUCTURE-REACTIVITY CORRELATION

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ABSTRACT

The kinetics of formation of thiazoles, from reactions of thiourea, phenylthiourea, and *p*-tolylthiourea with substituted phenacyl bromides, have been studied at four different temperatures (30–45°). The reactions are second order in the temperature range studied. Specific reaction rates and other thermodynamic parameters are reported. Isokinetic relationship is valid for the three reaction series and the values of isokinetic temperature (β) have been calculated. Justification of the Fairclough-Hinshelwood relationship implies that the reaction series is both energy and entropy controlled. The series is compatible with Exner's criterion showing that the same mechanism operates in each series. The rate constants at 40° have been correlated with the Hammett substituent constants, and the corresponding reaction constants computed. The values of the reaction constant are discussed in terms of the uncommon reactant in each series. Based upon the kinetic data and the discussion, two alternative mechanisms for the formation of thiazoles are proposed.

INTRODUCTION

THE reaction of an α-halo ketone with a thioamide has been the most important method for thiazole synthesis ever since it was originally introduced by Hantzsch and coworkers[1]. Ready access to a wide selection of the required reactants has made this method broadly applicable. By proper choice of reactants, thiazoles with alkyl, aryl, or heterocyclic substituents (attached to any of the three carbons of the thiazole nucleus) have been prepared. Thus when the thioamide reactant is a thiourea, a 2-aminothiazole results in excellent yields[1]. Some workers[2,3] have studied the thiazole synthesis kinetically. Okamiya[2] studied the reactions of thiobenzamides with phenacyl bromides. Behera *et al.*[3] reported the reactions of aryl thioureas with phenacyl bromide. The present investigation was undertaken to work out the mechanism of thiazole formation[4]. The effect of the change of substituents in either of the reactants has been studied.

EXPERIMENTAL

Thiourea (GR, Sarabhai M.) was used as such. Phenylthiourea and *p*-tolylthiourea were prepared and purified by the known methods[5]. Phenacyl bromides were prepared and purified by crystallization from ethanol[6-8]. Absolute ethanol was prepared by the usual method[9].

The rates of reaction were followed conductometrically in the temperature range 30–45° (± 0·05°). Equimolar solutions (M/50) of each of thiourea (or phenylthiourea, or *p*-tolylthiourea) and phenacyl bromide (or a substituted phenacyl bromide) were put into the conductivity cell and the conductivity measured at different time intervals. The temperature of the thermostat was finally raised to 60° to ensure completion of reaction. The infinity reading was taken after readjustment of the temperature. The reaction rates were calculated by the method described by Frost and Pearson[10]. The products of the reaction were in agreement with the standard u.v. spectrum of 2-amino-4-phenylthiazole.

RESULTS AND DISCUSSION

The reaction series obey second order rate equation, first order each in thiourea and phenacyl bromide. The second order rate constants at four different temperatures for the three reaction series are given in Tables I–III. The values are the average of at least two runs and are correct to ± 2%. The Arrhenius activation energy had an accuracy of ± 0·50 kcal/mole. The values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were calculated at 30°. Probable error limits for the $\Delta S^{\ddagger}$ values are ± 0·80 e.u.

The activation parameters are related by Fairclough–Hinshelwood relationship[11] and the isokinetic relationship[12]. The computed values of β and $\Delta H_{\beta}^{\ddagger}$ are recorded in the respective tables for the series.

The above two linear relationships imply that the reaction series are both energy and entropy controlled. In other words they are neither isoenthalpic nor isoentropic. Another conclusion that may be drawn is that all the derivatives in each series react with a similar mechanism.

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TABLE I

Second order rate constants and activation parameters for the reactions of thiourea and phenacyl bromides
[Thiourea] = M/100; [Phenacyl bromide] = M/100; Solvent: Absolute ethanol.

Phenacyl bromide	k litre mole^{-1} sec^{-1}				E_a	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	log PZ
	30°	35°	40°	45°	kcal/mole	kcal/mole	e.u.	
p-Bromo	0·492	0·883	1·517	2·624	20·88	20·28	6·94	14·751
p-Chloro	0·374	0·684	1·222	2·118	21·91	21·31	9·79	15·375
Unsubstituted	0·225	0·486	0·897	1·607	23·42	22·82	14·02	16·298
p-Methyl	0·172	0·349	0·671	1·274	25·42	24·82	19·84	17·569
p-Methoxy	0·156	0·321	0·618	1·208	25·97	25·37	21·46	17·923

$\beta = 355{\cdot}4°K$ $\quad \Delta H_0^{\ddagger} = 17{\cdot}82$ kcal/mole $\quad \rho = 0{\cdot}718$

TABLE II

Second order rate constants and activation parameters for the reactions of phenylthiourea and phenacyl bromides
[Phenylthiourea] = M/100; [Phenacyl bromide] = M/100; Solvent: Absolute ethanol

Phenacyl bromide	k litre mole^{-1} sec^{-1}				E_a	$\Delta H^{\ddagger}$	$-\Delta S^{\ddagger}$	log PZ
	30°	35°	40°	45°	kcal/mole	kcal/mole	e.u.	
p-Bromo	0·404	0·650	0·989	1·501	16·76	16·16	7·05	11·694
p-Chloro	0·327	0·529	0·821	1·282	17·27	16·67	5·79	11·970
Unsubstituted	0·245	0·406	0·641	1·014	18·13	17·53	3·52	12·465
p-Methyl	0·181	0·309	0·499	0·827	19·24	18·64	0·46	13·134
p-Methoxy	0·166	0·284	0·472	0·771	19·57	18·97	−0·46	13·335

$\beta = 369{\cdot}6°K$ $\quad \Delta H_0^{\ddagger} = 18{\cdot}8$ kcal/mole $\quad \rho = 0{\cdot}592$

TABLE III

Second order rate constants and activation parameters for the reactions of p*-tolylthiourea and phenacyl bromides*
[*p*-Tolylthiourea] = M/100; [Phenacyl bromide] = M/100; Solvent: Absolute ethanol

Phenacyl bromide	k litre mole^{-1} sec^{-1}				E_a	$\Delta H^{\ddagger}$	$-\Delta S^{\ddagger}$	log PZ
	30°	35°	40°	45°	kcal/mole	kcal/mole	e.u.	
p-Bromo	0·597	0·813	1·076	1·421	11·33	10·73	24·19	7·948
p-Chloro	0·462	0·646	0·881	1·211	12·28	11·68	21·57	8·521
Unsubstituted	0·327	0·473	0·679	0·944	13·42	12·82	18·49	9·193
p-Methyl	0·232	0·347	0·502	0·731	14·78	14·18	14·69	10·025
p-Methoxy	0·216	0·326	0·476	0·690	15·14	14·54	13·64	10·254

$\beta = 366{\cdot}9°K$ $\quad \Delta H_0^{\ddagger} = 19{\cdot}6$ kcal/mole $\quad \rho = 0{\cdot}658$

However, the Exner's criterion[13] was also applied to strengthen this conclusion.

The applicability of the Exner's criterion is difficult when the isokinetic temperature lies within the temperature range of kinetic measurements[4]. But as the β values in each of the present reaction series lie well away from the range of study, the above criterion is applicable. Plots of log k (40°) *versus* log k (30°) were drawn for all the three reaction series and straight lines were obtained. Thus the series are compatible with the Exner's criterion and follow identical mechanism (under the experimental conditions described).

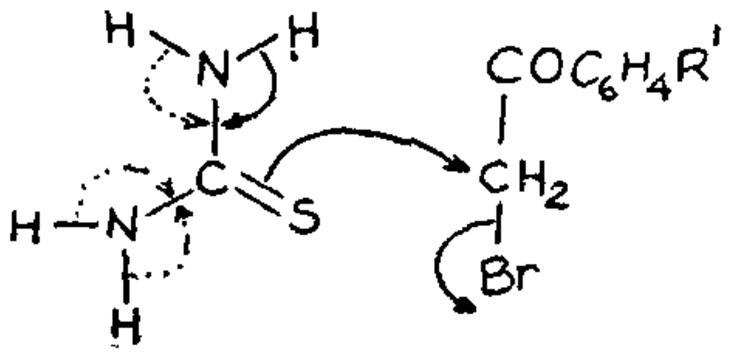
Structure–Reactivity Correlation

The satisfaction of the isokinetic relationship and the Exner's criterion enables us to correlate the structure with reactivity. The results of the structure-reactivity correlation with different scales of substituent constants were as follows :

Plots of log k against σ^+ values of Brown–Okamoto[14] were not linear, instead a curve with an upward concavity was obtained. The use of Yukawa–Tsuno equation[15] also was of little help, although the above concavity reduced gradually as the weightage to the conjugative effects was decreased. The best possible fits were achieved only with the Hammett σ values[16]. This shows that the effects of the substituents in these reaction series are of the same nature as their acid-strengthening effect on benzoic acids, and that there are no additional resonance effects. Plots of log k(40°) *versus* σ were drawn. The slopes (calculated by the method of least squares) of the lines give the reaction constant (ρ) values for the three reaction series.

The ρ values (given in the respective Tables) are positive, showing that the reactions proceed with a mechanism in which electrons are withdrawn by the substituents from the reaction site (methylene of phenacyl bromide). Thus, the reaction site is made more and more electrophilic as the substituents are changed in the order p-CH_3O, p-CH_3, H, p-Cl, p-Br. The values of ρ being less than unity, the effects of substituents in these reactions are not as strong as their corresponding acid-strengthening effect on benzoic acids.

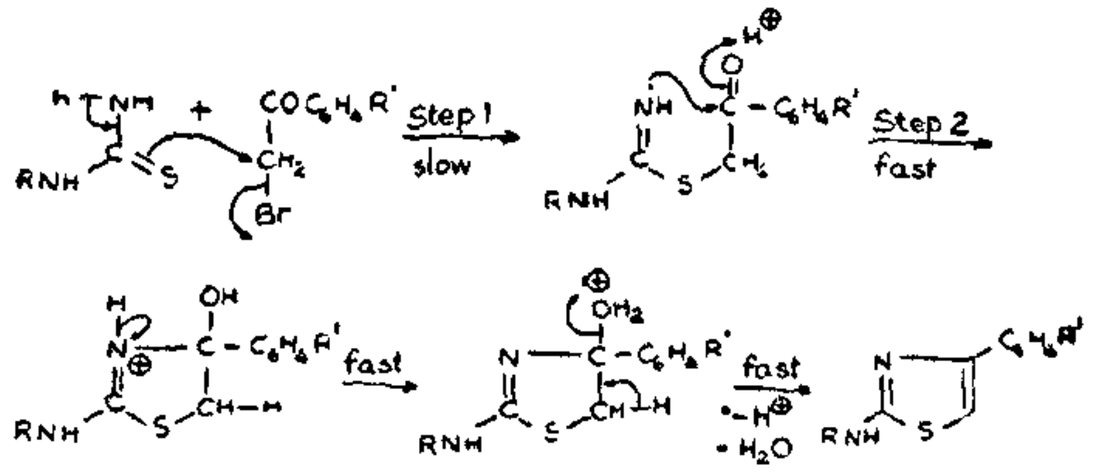
The variation of ρ values among the three reaction series reflects the response (to accept attack) of the reactant other than phenacyl bromide (namely, the thioureas). Among the three thioureas, the ρ value for the reaction of unsubstituted thiourea with phenacyl bromides is the highest. This shows that the reaction proceeds more conveniently with thiourea than with the substituted thioureas. There are two possible explanations. Firstly, there are four H atoms in thiourea and any one of them can leave as a proton and aid in the initial attack of sulphur on the methylene of phenacyl bromide. Thus



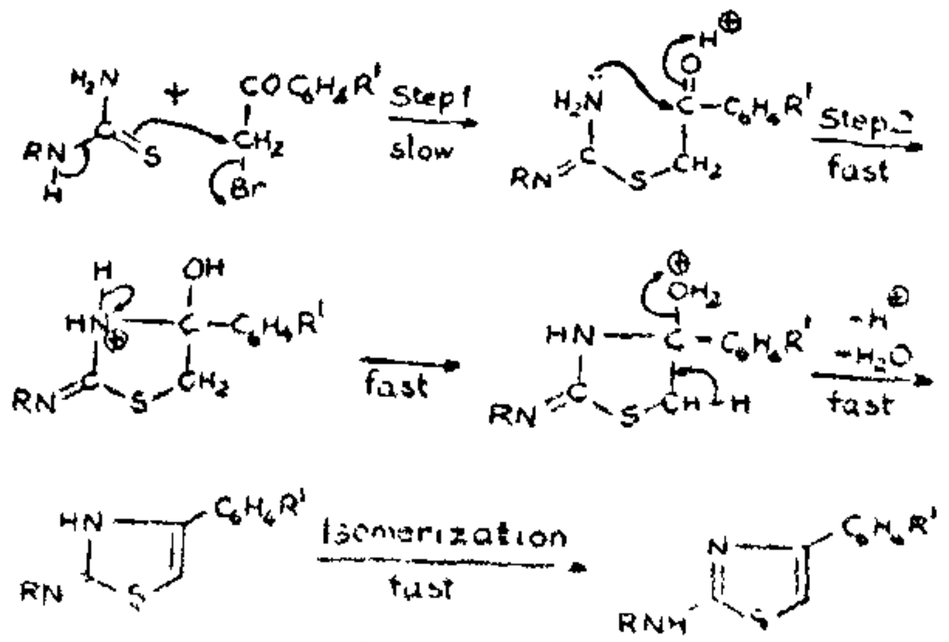
Only one H leaves (shown by solid arrow). The dashed arrows indicate the other three possibilities. In the case of the substituted thioureas, the position of one of the H atoms is occupied by the substituent and the probability of assistance by H is reduced to 75%. Secondly, it is possible that the smaller size (or lower molecular weight) of thiourea makes it more responsive to attack. It can easily orient itself according to the mechanistic requirements of the reaction. In view of both these possibilities the higher ρ value of p-tolylthiourea reaction as compared to that of the reaction of phenylthiourea, can be understood by taking into account the inductive effect. The inductive effect of p-tolyl is more positive than that of phenyl group. This makes the sulphur more nucleophilic and the initial attack is favourably accepted.

Mechanism

In the light of the foregoing discussions, the mechanisms shown in Scheme 1 and Scheme 2



SCHEME 1



SCHEME 2

are proposed. These alternative mechanisms are kinetically indistinguishable. The rate being second order, the first step is the slow and hence the rate-determining step. The probable subsequent steps are unimolecular and are fast, so that they do not affect the kinetics.

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STUDIES IN RUBIACEAE—III

Structure and Development of Ovule and Seed of *Oldenlandia gracilis* DC.

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A REVIEW[6] of the early embryological literature on Rubiaceae reveals that *Oldenlandia*, a genus with several species, have received little attention except for the contributions of Raghavan and Rangaswami[5] on *O. alata* and Farooq[2-3] on *O. corymbosa* and *O. nudicaulis*. There is thus scope for further work on more species of this genus. The present investigation deals with the structure of the ovule, development of the female gametophyte, endosperm, embryogeny and structure of seed of *O. gracilis* DC.

O. gracilis are slender erect herbs with small white flowers and elongate capsules. Flower buds and fruits were collected in July from the National Park, Bannerghatta, Bangalore District and fixed in Formalin-acetic-alcohol; *n*-Butanol series was used for dehydration and infiltration; Paraffin sections were cut at 8–10 μm and stained with Heidenhain's haematoxylin and counterstained with erythrosin.

The ovary is inferior, bicarpellary syncarpous and bilocular with numerous hemianatropous, unitegmic and tenuinucellate ovules borne on axile placentae. The nucellus is highly reduced and appears as a small papillate growth on the placenta. The integument initiates its growth as the female archesporium, represented by a single cell, differentiates hypodermally in the nucellus. The archesporial cell functions directly as the megasporocyte which lies directly under the nucellar epidermis consisting of only two cells (Fig. 1). The nucleus of the megasporocyte undergoes meiotic divisions resulting in a linear tetrad of megaspores (Fig. 2). By this time, the integument grows around crushing the nucellar epidermis. A narrow micropylar canal is formed. The integument which is 5–7 cells thick does not form an integumentary tapetum around the embryo sac.

The megaspore at the chalazal end of the tetrad functions while the upper three degenerate (Fig. 2). The functional megaspore after undergoing three successive free nuclear divisions gives rise to the 8-nucleate embryo sac (Figs. 3–5). In the mature embryo sac, the synergids are hooked. The two polar nuclei fuse before fertilization to form a large secondary nucleus which lies abutting the egg cell. The antipodals are organised into large cells and degenerate soon after fertilization. The embryo sac at the time of fertilization is slightly curved (Fig. 6).

Fertilization is porogamous. One of the synergids is destroyed during the entry of the pollen tube into the embryo sac. The primary