KINETICS OF CYCLIZATION OF 1-PHENYL-3-(1,2-DIMETHYL-3-OXO-1-BUTENYL)UREA AND ETHYL 2-METHYL-3-N-(N'-PHENYLUREIDO)-2-BUTENOATE

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Received October 15th, 1980

1-Phenyl-3-(1,2-dimethyl-3-oxo-1-butenyl)urea (*III*) has been prepared by reaction of phenyl isocyanate with 4-amino-3-methyl-3-penten-2-one (*I*). Ethyl 2-methyl-3-N-(N'-phenylureido)--2-butenoate (*V*) has been prepared by analogous reaction with ethyl 3-amino-2-methyl-2-butenoate (*II*). Kinetics have beeen measured of acid and base catalyzed cyclization of *III* and that of base catalyzed cyclization of *V* giving 1-phenyl-4,5,6-trimethylpyrimidin-2(1*H*)-one (*IV*) and 3-phenyl-5,6-dimethyluracil (*VI*), respectively. In acid medium the compound *V* is only hydrolyzed. The base catalyzed cyclization of *III* is faster than that of *V* by almost two orders of magnitude.

Several reports have already been published dealing with kinetics and mechanism of cyclization of β-ureido- and β-thioureido esters giving uracil and thiouracil derivatives[1-4]. So far, however, we have not found any communication dealing with cyclization of β-ureido ketone to derivatives of 2-hydroxypyrimidine. This fact is, *inter alia*, due to that usual way of preparation of these substances (acid catalyzed reaction of a diketone with urea or thiourea derivatives) does not allow to isolate the intermediate β-ureido ketone because of its high reactivity in the given medium[5].

Therefore, we prepared 1-phenyl-3-(1,2-dimethyl-3-oxo-1-butenyl)urea (*III*) by reaction of phenyl isocyanate with 4-amino-3-methyl-3-penten-2-one (*I*) and studied kinetics and mechanism of its reactions in acid and basic media. For comparison we also prepared the corresponding ethyl 2-methyl-3-N-(N'-phenylureido)-2-butenoate (*V*) and studied kinetics of its reactions under similar conditions.

EXPERIMENTAL

Reagents

4-Amino-3-methyl-3-penten-2-one (I): 10 g (0·09 mol) 3-methyl-2,4-pentanedione (prepared by methylation of 2,4-pentanedione with methyl iodide[6,7]) was mixed with 10 ml 25% aqueous ammonia. After a while a substance separated which was isolated and crystallized from benzene and ethyl acetate. Yield 7 g (71%), m.p. 111·5–112·5°C. For $C_6H_{11}NO$ (113·2) calculated:

63·66% C, 9·79% H, 12·37% N; found: 63·50% C, 10·03% H, 12·66% N. ^{1}H NMR spectrum $\delta(CH_3)$ 1·8; 1·94 and 2·11.

1-Phenyl-3-(1,2-dimethyl-3-oxo-1-butenyl)urea (III): 2·3 g (0·02 mol) compound *I* was dissolved in 15 ml benzene, treated with 2·9 ml (0·027 mol) phenyl isocyanate, and heated at 50°C for 10 min. The separated solid (2·95 g; 63%) was crystallized from benzene, m.p. 133—136°C. For $C_{13}H_{16}N_2O_2$ (232·3) calculated: 67·22% C, 6·94% H, 12·06% N; found: 67·52% C, 6·99% H, 12·36% N. ^{1}H NMR spectrum: $\delta(CH_3)$ 1·88 and 2·20; $\delta(C_6H_5)$ 6·94—7·69; $\delta(C_6H_5$—NH) 12·41; (δ(CO—NH—C=) 9·85.

1-Phenyl-4,5,6-trimethylpyrimidin-2(1H)-one (IV): 0·5 g *III* was dissolved in 10 ml methanol at 50°C and treated with one drop 1 mol l^{-1} sodium methoxide. Methanol was distilled off in vacuum, and the substance separated in the distillation flask was treated with 2 ml benzene in which it dissolved on boiling. Addition of 2 ml cyclohexane caused the substance to crystallize from the solution. Repeated crystallization from benzene–cyclohexane mixture gave 0·28 g product, m.p. 151—154°C. For $C_{13}H_{15}N_2O$ (214·3) calculated: 72·86% C, 7·05% H, 13·07% N; found: 73·15% C, 6·82% H, 13·32% N.

Ethyl 2-methyl-3-N-(N'-phenylureido)-2-butenoate (V): 29 g (0·2 mol) ethyl 2-methyl-3-oxobutanoate (prepared by methylation of ethyl 3-oxobutanoate[8]) was mixed with 50 ml ethanol, and gaseous ammonia was introduced in the solution for 7 days. Ethanol was distilled off in vacuum, and the residue was distilled through a column at 4 . 10^3 Pa. Two fractions were isolated boiling within 64—65°C and 74—75°C, respectively. The latter fraction (13 g) had m.p. 43—46°C. ^{1}H NMR spectrum indicates ethyl 3-amino-2-methyl-2-butenoate (*II*): δ(—CH_2—) 4·04; $\delta(CH_3$—C) 1·86 and 1·67; δ(—CH_2—CH_3) 1·23. The product *II* (2·5 g, 0 02 mol) was dissolved in 1 ml benzene and treated with 2·6 g (0·022 mol) phenyl isocyanate. The product separated within 2 h was crystallized from benzene (1·75 g; 38%), m.p. 121·5—124°C. For $C_{14}H_{18}N_2O_3$ (262·23) calculated: 64·11% C, 6·86% H, 10·68% N; found: 63·80% C, 7·11% H, 10·83% N. ^{1}H NMR spectrum δ(OCH_2—CH_3) 1·23; $\delta(CH_3$—C(=C)—NH) 1·80; $\delta(CH_3$—C(—$COOC_2H_5$)—NH) 2·34; δ(OCH_2—CH_3) 4·15; $\delta(C_6H_5)$ 6·94—7·63 δ(=C—NH) 9·79; δ(NH—C_6H_5) 10·90.

3-Phenyl-5,6-dimethyluracil (VI): 0·5 g (0·002 mol) *V* was dissolved in 2 ml 1 mol l^{-1} sodium methoxide. After 1 h, 0·4 ml 2 mol l^{-1} hydrochloric acid and 1 ml 2 mol l^{-1} acetic acid were added. The separated cyclizate *VI* was purified by vacuum sublimation at 160—180°C. Yield 0·32 g (75%), m.p. 241—243°C. For $C_{12}H_{12}N_2O_2$ (316·2) calculated: 66·65% C, 5·59% H, 12·95% N; found: 67·00% C, 5·36% H, 12·80% N. ^{1}H NMR spectrum: $\delta(CH_3)$ 1·79 and 2·09; $\delta(C_6H_5)$ 7·06—7·56.

Kinetic Measurements

The acid catalyzed cyclization of *III* in water: 2 ml aqueous hydrochloric acid (6 . 10^{-4}—5 . 10^{-3} mol l^{-1}) containing potassium chloride for adjustment of ionic strength (I = 0·5) was placed in a 1 cm quartz cell in a temperated (25°C) cell compartment of a Zeiss VSU-2P spectrophotometer. Then 1 drop of solution of *III* in 1-propanol (0·01 mol l^{-1}) was added, and value of the decreasing absorbance at 350 nm was measured. The rate constants were determined graphically from the relation $k_{obs} = -\log(A_t - A_\infty) + \text{const}$. The acid catalyzed cyclization of *III* in methanol was measured similarly to that in water. Ionic strength was adjusted at the value 0·5 by addition of methanolic solution of 1 mol l^{-1} potassium bromide. The analytical wavelength was 300 nm. The base-catalyzed cyclization of *III* was measured in acetatebuffers (acetic acid–sodium acetate 1 : 8 to 5 : 1) at I = 0·5 at λ = 340 nm. The spectra of the products obtained by cyclization of *III* in both hydrochloric acid and acetate buffers were measured in the same

media (0·1 mol l^{-1} hydrochloric acid; acetate buffer 1 : 4). In the both cases the spectra of the products were practically identical. This means that the cyclization of *III* in acid medium is not accompanied by any side reaction.

The base-catalyzed cyclization of *V* was measured in phosphate buffers (K_2HPO_4–KH_2PO_4 1 : 1 to 4 : 1) at 25°C. Ionic strength was adjusted at the value $I = 1$ by addition of solution of potassium chloride. One drop of methanolic solution of *V* (0·01 mol l^{-1}) was added to 2 ml buffer solution, and the absorbance decrease was measured at 300 nm.

The Other Methods Used

The dissociation constant of the protonated *IV* was measured spectrophotometrically[9] in formate and acetate buffers with the Zeiss VSU-2P apparatus at 340 nm at $I = 0{\cdot}1$. The found pK_a value is 3·78 ± 0·02. The dissociation constant of *VI* was measured in carbonate buffers at 300 nm at $I = 1$. The found pK_a value is 9·92 ± 0·02. The pH measurements of the buffers were carried out with a Radiometer Copenhagen PHM-4C apparatus at 25°C with a combined electrode GK 230 1C. The ^{1}H NMR spectra were measured with a Tesla BS 487 apparatus at 80 MHz using hexamethyldisiloxane as internal standard in solutions of hexadeuteriodimethyl sulphoxide or tetrachloromethane (for *II*) at room temperature.

RESULTS AND DISCUSSION

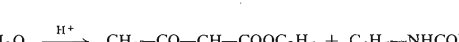
The acid catalyzed cyclization of *III* was studied in methanolic and aqueous hydrochloric acid. The reaction was pseudomonomolecular in the whole range studied, and the obtained k_{obs} values (for the both media) show linear dependence on the proton concentration. The k_{obs} value extrapolated to zero proton concentration differed but slightly from zero. The rate constant of the proton-catalyzed reaction in methanol ($k_{H^+} = 2{\cdot}60 \pm 0{\cdot}10$ l mol^{-1} s^{-1}) is almost three times higher than that in water ($k_{H^+} = 1{\cdot}04 \pm 0{\cdot}03$ l mol^{-1} s^{-1}). Even in diluted hydrochloric acid the hydrolysis of *III* is so slow that it cannot be proved experimentally.

Kinetics of the base catalyzed cyclization of *III* was measured in aqueous acetate buffers. Again the reaction was pseudomonomolecular, and the observed rate constants increased linearly with increasing activity of hydroxyl ion at the given ionic strength, being independent of the buffer concentration. This finding indicates a specific base-catalyzed reaction with the rate given by Eq. (*I*):

$$v = k_{obs}(III) = k_{OH^-} \cdot a_{OH}[III] \,. \qquad (I)$$

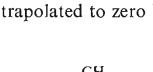
The value $k_{OH^-} = (1{\cdot}18 \pm 0{\cdot}05) \,.\, 10^6$ l mol^{-1} s^{-1}.

In aqueous hydrochloric acid medium hydrolysis of *V* only took place (*A*), no cyclization being observed.

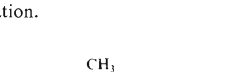


(*A*)

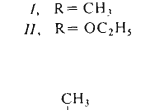
This result agrees with aminolyses of esters being base-catalyzed reactions[10]. The base-catalyzed cyclization was studied kinetically in phosphate buffers within pH 6·4 to 7·1. The reaction proceeded as pseudomonomolecular. Its velocity increased with increasing activity of hydroxyl ion, but also, to a smaller extent, with increasing concentration of monohydrogenphosphate ion. Influence of HPO_4^{2-} concentration on the reaction rate increases with increasing activity of hydroxyl ion. We suppose that the reaction is not a general base catalyzed reaction of the negatively charged intermediate (for the given catalysis type it is impossible to suggest any acceptable mechanism, and the found effect of HPO_4^{2-} on k_{obs} is small), but rather it is a specific influence of phosphate ions on activity coefficients of the starting substances and of the activated complex. Again the reaction is defined as a specific base catalyzed one. For calculation of the value $k_{OH^-} = (2{\cdot}9 \pm 0{\cdot}1) \cdot 10^4\ l\ mol^{-1}\ s^{-1}$ the values k_{obs} were extrapolated to zero buffer concentration.



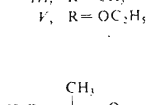
I, R = CH_3
II, R = OC_2H_5



III, R = CH_3
V, R = OC_2H_5



IV

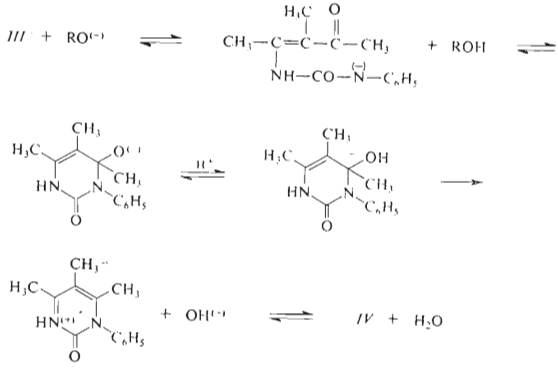


VI

Reactions of the two ureido derivatives (*III*, *V*) in acid medium are quite different. Whereas with the ester *V* the only products are phenylurea and ethyl 2-methyl-3-oxobutanoate (which are formed by the acid catalyzed hydrolysis of the starting substance), with the ketone *III* only cyclization was observed (no hydrolysis products could be found in the reaction mixture). This is due to β-ureido ketones tending extraordinarily to the acid catalyzed cyclization, the hydrolysis reactions (which take place with such derivatives of β-enamino ketones for which cyclization is impossible[11]) being practically insignificant.

The base catalyzed cyclization of *III* is by about two orders of magnitude faster than that of ester *V*. Generally, base-catalyzed reactions of amines with esters are faster than analogous reactions with ketones in which elimination of water must

take place which is usually rate-limiting[12]. In the base-catalyzed cyclization of *III* (Scheme 1) the rate-limiting step consists in the attack of carbonyl group by negatively charged nitrogen atom. The subsequent step is a rapid proton-transfer, and the last step cannot be rate-limiting, because it involves splitting off of hydroxyl ion from the neutral intermediate, the whole reaction being base-catalyzed (Scheme 1). As ketonic groups are much more reactive to nucleophiles than are ester groups, the cyclization of *III* is much faster than that of *V*.



SCHEME 1

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Translated by J. Panchartek.