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Abstract

Full Text

Chemistry

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On the Structural Directionality of the Reaction of Diketene with Monosubstituted Ureas

(Presented by Academician B. A. Kazanskii, May 12, 1964)

It is known that alkylureas are acylated by acetic anhydride and similar electrophilic reagents ([1], [2]) strictly selectively at the unsubstituted amino group, although *a priori* one might also assume another direction of the reaction involving the more basic substituted end of the molecule.

In the present work, using diketene as an example, we succeeded in carrying out the acylation of alkylureas in both theoretically possible directions and in tracing the influence of various factors on the course of the reaction. It was found that alkylureas add diketene with formation of a mixture of isomeric ureides (I) and (II), which, for convenience of separation and identification, were converted into the corresponding uracils (III) and (IV) (see Table 1).

$$\mathrm{RNHCONH_2} + \begin{array}{c} \mathrm{CH_2{=}C{-}CH_2} \\ \quad\;\; | \quad\; | \\ \mathrm{O{-}CO} \end{array} \longrightarrow \begin{cases} \mathrm{RNHCONHCOCH_2COCH_3}\ (I) \longrightarrow (III), \\ \mathrm{H_2NCONRCOCH_2COCH_3}\ (II) \longrightarrow (IV). \end{cases}$$

(III) uracil ring with R at N, CH_3 substituent (IV) isomeric uracil ring with R at the other N, CH_3

In pyridine solution, acetoacetylation proceeds rather selectively at the unsubstituted amino group, without being accompanied by cyclization of ureide (I) into uracil (III). In chlorobenzene medium with the addition of catalytic amounts of pyridine, the direction of the reaction is partly shifted in favor of the isomeric ureide (II). In boiling acetic acid medium, appreciable amounts of both isomeric uracils (III) and (IV) are formed, the ratio of which depends to some extent on the size of the alkyl radical. Enlargement of the latter adversely affects the reactivity of the substituted end of the alkylurea and lowers the yield of 3-alkyluracil (IV).

The clearly expressed directionality of the reaction in pyridine medium toward formation of acetoacetyl derivatives at the unsubstituted amino group (I) can be explained by the fact that, in this case, diketene reacts with the alkylurea in the form of a pyridine complex with a sterically hindered electrophilic center

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pyridine–diketene complex with alkylurea, showing electron shifts $\longrightarrow I$

Under all the conditions we studied, phenylurea condenses with diketene strictly selectively at the unsubstituted nitrogen, evidently because of the large difference in the basicity of its amino groups. Acetoacetylation of phenylurea in pyridine solution does not stop at the stage of addition of one molecule of diketene and leads to a substance of undetermined structure, also formed in the interaction of diketene with 3-phenylureidoacetoacetic acid.

The structures of 1-*n*-butyl-, 3-*n*-butyl-, 1-ethyl-, and 1-phenyl-6-methyluracils were confirmed by counter synthesis, starting from *n*-butylamide of acetoacetic acid or acetoacetylurethane ([3]), according to the following schemes:

$$\text{n-C}_4\text{H}_9\text{NHCOCH}_2\text{COCH}_3 \xrightarrow{\text{H}_2\text{NCONH}_2}$$

$$\text{C}_2\text{H}_5\text{OOCNHCOCH}_2\text{COCH}_3 \xrightarrow{\text{RNH}_2} \text{C}_2\text{H}_5\text{OOCNHCOCH=CCH}_3 \longrightarrow$$

$$R = n\text{-}C_4H_9,\ C_2H_5,\ C_6H_5$$

Isomeric N-alkyluracils differ distinctly from one another in R_f and in UV spectra (see Table 1), which can serve as convenient methods for their identification.

Experimental Part

Interaction of alkylureas with diketene in pyridine. To 0.01 mole of alkylurea in 20 ml of pyridine was added 1.5 ml ($\sim$ 0.014 mole) of diketene; the reaction proceeded with heating, and the temperature rose to $\sim 60^\circ$; after standing for 12 hr at $\sim 20^\circ$, the mixture was evaporated in vacuo to dryness. The residue was boiled for 6 hr with 20 ml of acetic acid and, after removal of the solvent, the remaining mixture of uracils was chromatographed on Al_2O_3 of activity III. With a mixture of chloroform and methanol (50 : 1), 6-methyl-4-alkyluracil was first eluted, and then 6-methyl-1-alkyluracil.

Interaction of phenylurea with diketene in pyridine. To 20.4 g of phenylurea in 70 ml of pyridine was added dropwise 22.5 ml of diketene, maintaining the temperature at 60–65°. After standing for 24 hr at $\sim 20^\circ$, the precipitated solid was filtered off and 16.3 g of a product of undetermined structure, m.p. 205–206° (from 50% acetic acid), was obtained. The mother liquors were evaporated and the residue treated with acetic acid as described above. This gave 10.1 g (33%) of 6-methyl-1-phenyluracil, m.p. 272–274° (from aqueous acetic acid).

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Preparation of 3-ethylureidoacetoacetic acid. To 1.76 g of ethylurea in 20 ml of pyridine was added 1.7 ml of diketene; the temperature of the reaction mass rose to 60°. On standing for 12 hr at ∼ 20°, 2.2 g (65%) of 3-ethylureidoacetoacetic acid precipitated, m.p. 150–151° (from benzene).

Found %: C 48.71; 48.85; H 6.91; 6.96; N 16.20; 16.00.
$C_7H_{12}O_3N_2$. Calculated %: C 48.83; H 7.03; N 16.27.

λ_{max} 218 and 290 mμ, ε 5260 and 10 400 (in alcohol), 2,4-dinitrophenylhydrazone, m.p. 212–213° with decomposition (from a mixture of chloroform and methanol).

Found %: N 23.96; 23.90.
$C_{13}H_{16}O_6N_6$. Calculated %: N 23.86.

Interaction of *n*-butylurea with diketene in chlorobenzene in the presence of pyridine. A mixture of 20 ml

Table 1

Starting RNH$_2$	Products 1-R-4-OH	Solvent for crystallization	Found, % C	Found, % H	Found, % N	Empirical formula	Calculated, % C	Calculated, % H	Calculated, % N	λ_{max}, cm^{-1}, in spirit	λ_{max}, cm^{-1}, in CHCl$_3$	TLC R_f, Al_2O_3 II act.: acetone–water 30:1	TLC R_f, Al_2O_3 II act.: ethyl methyl ketone 30:2	Yield of isomer, % of theory: pyridine	Yield of isomer, % of theory: chlorobenzene + pyridine	Yield of isomer, % of theory: acetic acid
R = *n*-butyl	R = *n*-butyl, R′ = H	M.p. 179–180 (4)	59.16	7.74	15.37	$C_9H_{16}O_3N_2$	59.32	7.74	15.37	260	270	0.67	0.63	11	38	33
R = *n*-butyl	R = H, R′ = *n*-butyl	M.p. 133–136	59.31	7.92	15.02	$C_9H_{16}O_3N_2$	59.32	7.74	15.37	268 200	156	0.12	0.68	71	44	50
R = ethyl	R = ethyl, R′ = H	M.p. 197–198 (5)	54.69	7.68	18.12	$C_7H_{14}O_3N_2$	54.53	7.54	18.17	260	270 166	0.66	0.58	13	—	42
R = ethyl	R = H, R′ = ethyl	M.p. 195–196 (3)	54.47	7.46	18.17	$C_7H_{14}O_3N_2$	54.53	7.54	18.17	267.5 210	169	0.62	0.10	68	—	45

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Starting RNH$_2$	Products R	R′	M.p., °C	Solvent for crystallization	Found, % C	Found, % H	Found, % N	Empirical formula	Calculated, % C	Calculated, % H	Calculated, % N	λ_{max}, mμ in spirit*	ν, cm^{-1} in CHCl$_3$*	TLC R_f, Al_2O_3 II act.: acetone–water 30:1	TLC R_f, Al_2O_3 II act.: ethyl methyl ketone 30:2	Yield of isomer, % of theory: pyridine	Yield of isomer, % of theory: chlorobenzene + pyridine	Yield of isomer, % of theory: acetic acid
R = *n*-hexyl	R = *n*-hexyl	H	162–163	Heptane–isopropanol	62.39 62.36	8.36 8.36	13.64 13.64	$C_{11}H_{18}O_2N_2$	62.83 62.83	8.63 8.63	13.32 13.32	260.5 260	1720 1660	0.74 0.74	0.70 0.70	14 14	—	26
R = *n*-hexyl	R = *n*-hexyl	H	108–109	Heptane–benzene	62.19 62.19	8.72 8.72	13.44 13.44	$C_{11}H_{18}O_2N_2$	62.83 62.83	8.63 8.63	13.32 13.32	268 970	1697 1652	0.62 0.62	0.11 0.11	66 66	—	52
R = phenyl	R = phenyl	H	272–274 (3)	Aqueous acetic acid	65.04 65.04	5.52 5.52	13.77 13.77	$C_{11}H_{12}O_3N_2$	59.99 59.99	5.49 5.49	12.72 12.72	263.5 980	1719 1690 1602	0.31 0.31	0 0	33** 33**	72	87

* Upper values are for λ, lower values for ε.
** Together with a compound of undetermined structure (see experimental section).

chlorobenzene, 1.16 g of *n*-butylurea, and 0.2 ml of pyridine were heated to 87°, and 1.5 ml of diketene was added; the temperature of the reaction mixture rose to 100°. After 12 h it was evaporated and treated with acetic acid, as described above. The resulting mixture of uracils was separated by chromatography on Al_2O_3.

Reaction of phenylurea with diketene in chlorobenzene in the presence of pyridine. To a solution of 1.36 g of phenylurea in 20 ml of chlorobenzene and 1.5 ml of diketene at 85° was added 0.2 ml of pyridine; the temperature rose to 100°. The mixture was left for 12 h; the precipitate that separated was filtered off, giving 1.6 g (72%) of 3-phenylureidoacetoacetic acid with mp 143–144° (from benzene). λ_{max} 248.5 mμ, ε 6890 (in alcohol), ν 1721, 1652, 1610, 1560 cm^{-1}; gives a coloration with ferric chloride.

Found, %: C 59.97; 60.14; H 5.48; 5.48; N 12.55; 12.51.
$C_{11}H_{12}O_3N_2$. Calculated, %: C 59.99; H 5.49; N 12.72.

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On boiling with acetic acid, phenylureide is quantitatively cyclized to 1-phenyl-6-methyluracil.

Reaction of 3-phenylureidoacetoacetic acid with diketene in pyridine. To 1.1 g of 3-phenylureidoacetoacetic acid in 3.5 ml of pyridine was added 0.5 ml of diketene. After completion of the exothermic reaction, the precipitate that separated was filtered off and washed with ether. This gave 0.4 g of the above-described substance of undetermined structure with mp 202–204°.

Reaction of alkylureas with diketene in acetic acid. A mixture of 0.01 mole of alkylurea and 1.5 ml of diketene was boiled for 6 h in 20 ml of acetic acid. After removal of the solvent, the remaining mixture of isomeric N-alkyluracils was chromatographed on Al_2O_3, as described above.

Reaction of phenylurea with diketene in acetic acid. A mixture of 2.72 g of phenylurea, 4 ml of diketene, and 60 ml of acetic acid was boiled for 6 h, evaporated to dryness, and the residue was treated with ether and filtered, giving 3.5 g (87%) of 6-methyl-1-phenyluracil.

Preparation of *n*-butylamide of acetoacetic acid. To a solution of 20 ml of diketene in 90 ml of benzene was added 14.6 g of *n*-butylamine in 90 ml of benzene; the mixture was boiled for 6 h and evaporated, and the residue was recrystallized from hexane to give 11 g of *n*-butylamide of acetoacetic acid, mp 35–36°.

Found, %: N 8.74; 8.69.
$C_8H_{15}O_2N$. Calculated, %: N 8.91.

Preparation of 6-methyl-3-*n*-butyluracil from *n*-butylamide of acetoacetic acid. A mixture of 1.6 g of *n*-butylamide of acetoacetic acid and 1.8 g of urea was heated for 3 h at 170–185°. After cooling, it was treated with dilute hydrochloric acid and extracted with chloroform, giving 1.08 g of an oil from which, upon chromatography on Al_2O_3 as indicated above, 0.05 g of 6-methyl-3-*n*-butyluracil with mp 179–180° was isolated.

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