

Syntheses of Acylurea Derivatives as Model Compounds for a Highly Specific Organic Reaction

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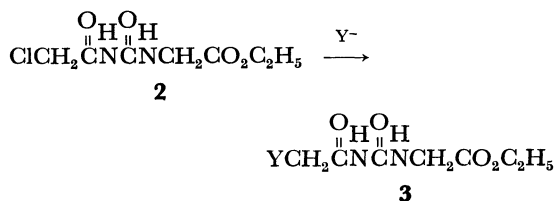
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Some types of acylurea derivatives were prepared as model compounds for a highly specific organic reaction by molecular association. When ethyl chloroacetate was treated successively with *o*-aminobenzenethiol (**4**) and chloroacetyl isocyanate (**1**) under mild conditions, triacylurea derivative (**9**) was obtained in total 84% yield. It was found that the use of "amino acid amide and oxalyl chloride" method led to the formation of diacylurea derivative (**11**) in high yield.

Increasing attention has recently been drawn to "molecular interaction" between proteins themselves and between proteins and nucleic acids or lipids in the field of biochemistry. The purine and pyrimidine bases in coenzymes and nucleic acids may play an important role in the control of enzyme reactions by forming hydrogen bonding and charge-transfer complexes with each other or with other biochemical macromolecules in living cells. Acylurea derivatives are regarded as a sort of open chain analogue of the pyrimidine bases. The present paper deals with the fundamental studies on syntheses of acylurea derivatives as model compounds which lead to a specific organic reaction by an intermolecular association.

In preparing acylurea derivatives it was found that the use of acyl isocyanates as carbamoylating reagents is the most effective. The desired acylurea derivatives were obtained in high yields by treatment with amines under mild conditions. Chloroacetyl isocyanate (**1**)¹ readily reacted with ethyl glycinate at 0°C in ether to give 5-chloroacetylhydantoic acid ethyl ester (**2**) in 94% yield.

Nucleophilic substitution at the terminal carbon of **2** was investigated for an introduction of a functional group which can be utilized in the formation of the next acylurea linkage. The aminated product (Y = NH₂) (**3**) could not be isolated by the use of Gabriel



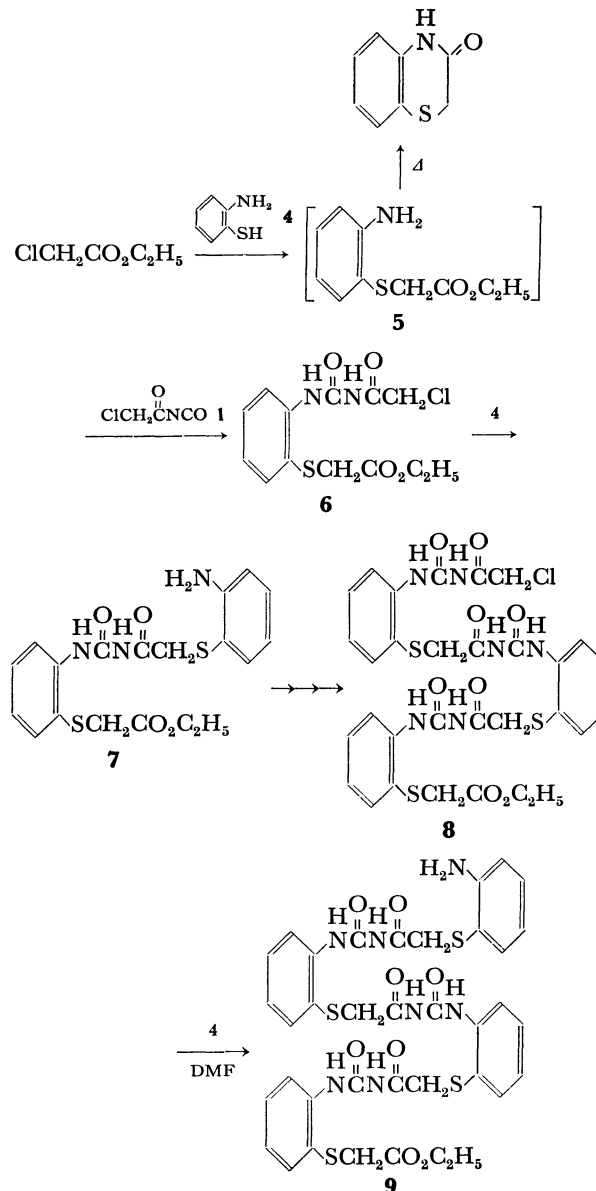
or Sommelet method or by treatment with ammonia²⁾ in methanol. However, it was found that **2** easily underwent nucleophilic substitution by thiols. Treatment of **2** with benzenethiol, *o*-aminobenzenethiol (**4**), 4-pyridinethiol, and thiobenzoic acid at room temperature in the presence of triethylamine gave the corresponding sulfides in 96, 96, 95, and 88% yields, respectively. Physical properties and analytical data of these sulfides are listed in Table 1. It is of special interest to note

1) A. J. Speziale and L. R. Smith, *J. Org. Chem.*, **27**, 3742 (1962).

2) In this case, chloroacetamide and hydantoic acid ethyl ester were obtained. This may be explained as nucleophilic attack of ammonia on the carbonyl carbon of chloroacetyl group in **2**.

that the thiols did not attack the carbonyl carbon of the chloroacetyl group in **2**.

On this basis, it was expected that the successive use of thiols containing the N-H bonds and of **1** would lead to the formation of the desired *polyacylurea* derivatives. An oily product (**5**), easily obtained by the reaction of ethyl chloroacetate with **4** and triethylamine at room temperature, decomposed to give 2*H*-1,4-benzo-



Y	Mp, °C	Recrystallization Solvent	Calcd, %				Found, %			
			C	H	N	S	C	H	N	S
C ₆ H ₅ S	110—111	Ether	52.70	5.44	9.46	10.80	52.92	5.14	9.31	11.07
<i>o</i> -NH ₂ C ₆ H ₄ S	120—121	Benzene	50.16	5.50	13.50	10.28	50.30	5.46	13.59	10.00
	129—130	Ethanol	51.85	4.97	8.64	9.87	51.91	5.05	8.71	9.82
	144—145	Acetone	48.48	5.09	14.14	10.76	48.39	4.94	14.20	11.03

$$\begin{array}{c}
 \text{O} \\
 \parallel \\
 \text{ClCH}_2\text{CNCNCO} \xrightarrow[\text{DMF}]{\text{N}_3\text{H}-\text{C}_6\text{H}_4-\text{C}(=\text{O})\text{NH}_2} \\
 \mathbf{1}
 \end{array}$$

$$\begin{array}{c}
 \text{O} \quad \text{O} \quad \text{O} \\
 \parallel \quad \parallel \quad \parallel \\
 \text{ClCH}_2\text{CNCN}-\text{C}_6\text{H}_4-\text{C}(=\text{O})\text{NH}_2 \xrightarrow[\text{CH}_3\text{CN}]{(\text{COCl})_2} \\
 \mathbf{10}
 \end{array}$$

$$\begin{array}{c}
 \text{O} \quad \text{O} \quad \text{O} \\
 \parallel \quad \parallel \quad \parallel \\
 \left[\text{ClCH}_2\text{CNCN}-\text{C}_6\text{H}_4-\text{C}(=\text{O})\text{NCO} \right] \xrightarrow[\text{CH}_3\text{CN}]{\text{H}_2\text{NCH}_2\text{CO}_2\text{C}_2\text{H}_5} \\
 \mathbf{11}
 \end{array}$$

5) W. A. Jacobs and M. Heidelberger, *ibid.*, **39**, 2438 (1917).

Reaction of 2 with Benzenethiol. To a solution of **2** (2.23 g, 0.01 mol) in 40 ml of acetone was added dropwise a solution of benzenethiol (1.10 g, 0.01 mol) and triethylamine (1.01 g, 0.01 mol) in 10 ml of acetone with stirring at room temperature. Stirring was continued for 1 hr at room temperature. After the reaction mixture had been concentrated *in vacuo* to dryness, the residual solid was treated with water for removal of triethylamine hydrochloride. The resulting crystals were collected by filtration, washed repeatedly with water and dried over phosphorus pentoxide *in vacuo* to give 2.85 g (96%) of **3** ($Y=C_6H_5S$). Recrystallization from ether gave white needles.

By a similar procedure the corresponding sulfides were obtained from other thiols. Physical properties and analytical data of these sulfides are listed in Table 1.

Preparation of 2H-1,4-Benzothiazin-(4H)-one. A solution of **4** (2.50 g, 0.02 mol) and triethylamine (2.02 g, 0.02 mol) in 20 ml of ether was added to a solution of ethyl chloroacetate (2.45 g, 0.02 mol) in 20 ml of ether with stirring at room temperature. A slightly exothermic reaction took place immediately and triethylamine hydrochloride precipitated. Stirring was continued for 1 hr at room temperature. After the reaction mixture had been filtered off, the filtrate was evaporated *in vacuo*. Residual oil (**5**) gave crystals of 2H-1,4-benzothiazin-3(4H)-one (3.14 g, 95%) with loss of ethanol when heated under reduced pressure. Recrystallization from acetone gave pure colorless needles, mp 175.0–175.5°C (lit.⁶) mp 176°C). (Found: C, 58.85; H, 4.15; N, 8.44; S, 19.70%).

Similarly, the oil (**5**) gave 2H-1,4-benzothiazin-3(4H)-one in 40% yield when allowed to stand for 6 days at room temperature.

Preparation of 6. To a stirred solution of ethyl chloroacetate (2.45 g, 0.02 mol) in 20 ml of ether was added a solution of **4** (2.50 g, 0.02 mol) and triethylamine (2.02 g, 0.02 mol) in 20 ml of ether at room temperature. Work-up of the reaction mixture as described above gave the oil (**5**). To a solution of this oil in 30 ml of dichloromethane was added a solution of **1** (2.40 g, 0.02 mol) in 20 ml of dichloromethane with stirring at room temperature. Stirring was continued for 30 min at room temperature. After removal of dichloromethane, the resulting solid was treated with ether. A white precipitate of **6** (6.30 g, 95%) was collected by filtration and recrystallized from ethanol to give white needles, mp 146.0–146.5°C.

Found: C, 47.43; H, 4.72; N, 8.73; S, 9.94%. Calcd for $C_{13}H_{15}ClN_2O_4S$: C, 47.21; H, 4.57; N, 8.47; S, 9.68%.

Preparation of 9 and 7. A solution of **4** (0.63 g, 0.005

mol) and triethylamine (0.51 g, 0.005 mol) in 10 ml of DMF was added to a solution of **8** (3.74 g, 0.005 mol) in 30 ml of DMF with stirring at room temperature. Colorless crystals of triethylamine hydrochloride were soon formed. Stirring was continued for 1 hr at room temperature. After evaporation of DMF, the residue was treated with water. The resulting solid was collected by filtration, washed with water, and dried over phosphorus pentoxide *in vacuo* to afford **9** (4.10 g, 98%). Slow addition of ether in small portions to a solution of **9** in dichloromethane gave a white powder, mp 122.0–122.5°C. IR (KBr): 3220 (N–H), 3135 (N–H), 1738 (C=O), 1722 (C=O), 1715 (C=O), 1706 (C=O), 1700 (C=O), and 1696 (C=O) cm^{-1} (see Fig. 1). NMR ($CDCl_3$): τ 8.85 (t, 3H, $J=7.0$ Hz, CH_3), 6.50 (s, 8H, $-S-CH_2-CO-$), 5.93 (q, 2H, $J=7.0$ Hz, $-O-CH_2-CH_3$), and 2.42–3.40 (m, 16H, aromatic protons).

Found: C, 53.37; H, 4.68; N, 11.60; S, 15.18%. Calcd for $C_{37}H_{37}N_7O_8S_4$: C, 53.16; H, 4.46; N, 11.73; S, 15.31%.

Similarly, **7** was obtained in 97% yield by treatment of **6** with **4** and triethylamine in acetone at room temperature. Recrystallization from ethanol gave an analytically pure sample, mp 124.5–125.0°C. IR (KBr): 3405 (N–H), 3325 (N–H), 3225 (N–H), 3110 (N–H), 1736 (C=O), 1712 (C=O), and 1682 (C=O) cm^{-1} (see Fig. 1). NMR ($CDCl_3$): τ 8.87 (t, 3H, $J=7.0$ Hz, CH_3), 6.58 (d, 2H, $J=9.0$ Hz, $-S-CH_2-CO-$), 6.50 (d, 2H, $J=10.0$ Hz, $-S-CH_2-CO-$), 5.97 (q, 2H, $J=7.0$ Hz, $-O-CH_2-CH_3$), and 2.42–3.40 (m, 8H, aromatic protons).

Found: C, 54.10; H, 4.94; N, 10.04; S, 15.12%. Calcd for $C_{19}H_{21}N_3O_4S_2$: C, 54.41; H, 5.05; N, 10.02; S, 15.26%.

Preparation of 11. Oxalyl chloride (1.45 g, 0.012 mol) and **10** (2.56 g, 0.01 mol) were refluxed in 30 ml of acetonitrile for 1 hr. Vigorous evolution of hydrogen chloride and carbon monoxide was observed. After the reaction mixture had been concentrated *in vacuo* to dryness for complete removal of the excess of oxalyl chloride, the dark red residue was dissolved in 30 ml of acetonitrile. To this solution was added a solution of ethyl glycinate (1.03 g, 0.01 mol) in 10 ml of acetonitrile at room temperature with stirring. A slightly exothermic reaction soon took place. Stirring was continued for 30 min at room temperature. After evaporation of the solvent, the residue was treated with ether. The pale yellow crystals of **11** (2.65 g, 70%) were collected by filtration. Repeated recrystallization from DMF-ethanol gave analytically pure colorless plates, mp 323–325°C (dec.). IR (KBr): 3270 (N–H), 3125 (N–H), 1748 (C=O), 1724 (C=O), 1705 (C=O), 1692 (C=O), and 1675 (C=O) cm^{-1} .

Found: C, 47.35; H, 4.69; N, 14.70%. Calcd for $C_{15}H_{17}ClN_4O_6$: C, 46.78; H, 4.45; N, 14.56%.

6) A. W. Hofmann, *Ber.*, **13**, 1234 (1880).