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

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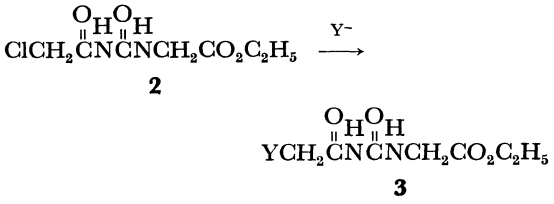
(Received May 14, 1971)

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 fundametal 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.

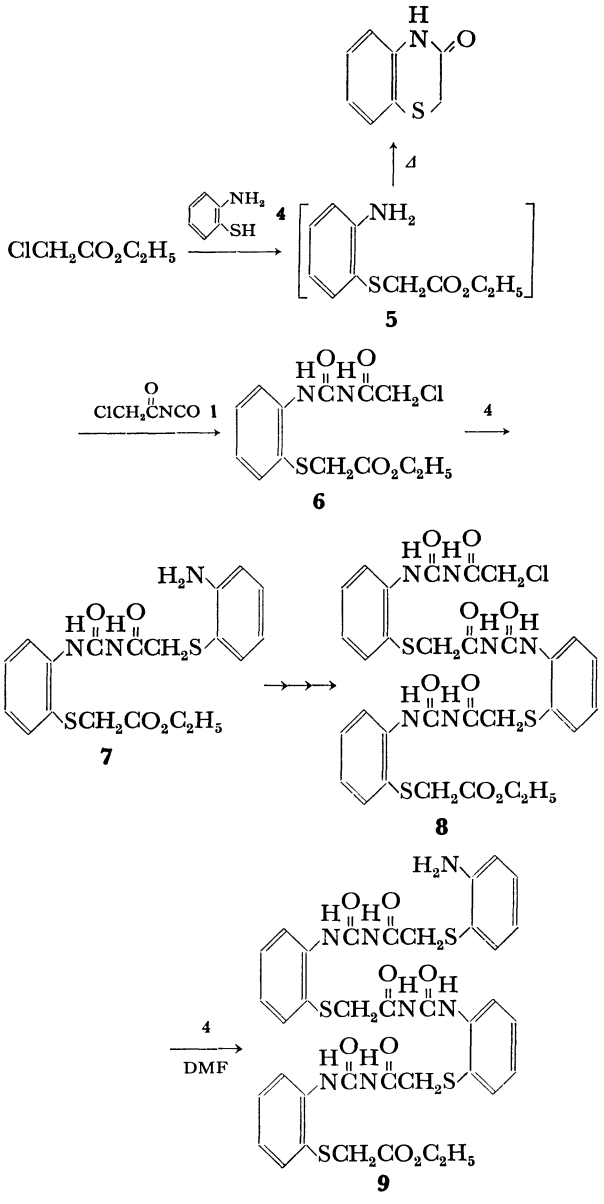
Nucleophilic substitution at the terminal carbon of **2** was investigated for an introduction of a functional group which can be utilized in the formation of the next acylurea linkage. The aminated product (Y= NH_2) (**3**) could not be isolated by the use of Gabriel



2 **3**

or Sommelet method or by treatment with ammonia[2] 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 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-



5 **6** **7** **8** **9**

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**.

Table 1. Physical properties and analytical data of **3**

Y	Mp, °C	Recrystallization Solvent	Calcd, %				Found, %			
			C	H	N	S	C	H	N	S
C_6H_5S	110—111	Ether	52.70	5.44	9.46	10.80	52.92	5.14	9.31	11.07
o-$NH_2C_6H_4S$	120—121	Benzene	50.16	5.50	13.50	10.28	50.30	5.46	13.59	10.00
$C_6H_5\overset{O}{\overset{\|}{C}}S$	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

thiazin-3(4*H*)-one in 95% yield when distilled. Thus, compound **5** was converted into the acylurea derivative (**6**), without isolation, on rapid treatment with **1**. Similarly, compound **6** reacted with **4** to afford the amine (**7**). It was found that triacylurea derivative (**9**) was prepared by treatment of **7** successively with **1** and **4**. All processes proceeded almost quantitatively at room temperature. Compound **9** could be isolated in total 84% yield. It should be noted that in contrast to the chloroacetylurea derivatives such as **6** and **8**, **9** is very soluble in organic solvents, especially in dichloromethane, benzene, and acetone. The protons of the methylene groups attached to the sulfur in **7** resonated as two doublets at τ 6.50 and 6.58. However, those of **9** resonated as a singlet at 6.50. The infrared spectrum of **9** showed broader absorptions than that of **7** (Fig. 1).

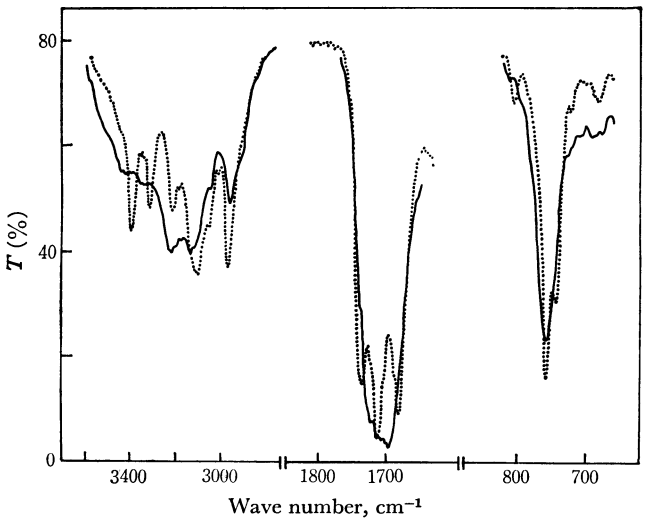
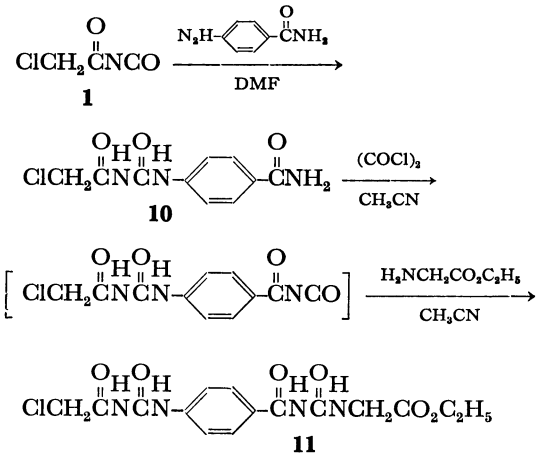


Fig. 1. Infrared spectra of **7** (·····) and **9** (——) in KBr disks.

Preparation of another type of polyacylurea derivatives was studied by the use of amino acid amides on the assumption that amides are easily converted into the corresponding acyl isocyanates[1] when treated with oxalyl chloride. Compound **1** reacted with *p*-aminobenzamide in DMF to give the corresponding acylurea derivative (**10**) in 88% yield. The diacylurea derivative (**11**) was prepared in 70% yield by treatment of **10** first with oxalyl chloride in refluxing acetonitrile and then with ethyl glycinate at room temperature. Compound **11** showed remarkably high decomposition point (323—325°C) and could be recrystallized from DMF-ethanol to give colorless plates.



From these results, it seems reasonable to conclude that polyacylurea derivatives could be prepared by the use of either "N–H bond-containing thiol and haloacyl isocyanate" method or of "amino acid amide and oxalyl chloride" method.

Experimental[3]

Materials. Chloroacetyl isocyanate (**1**) was prepared according to the method of Speziale.[1] Benzenethiol, ethyl chloroacetate, *o*-aminobenzenethiol, and *p*-aminobenzamide were all commercial materials and purified by distillation or recrystallization before use. Thiobenzoic acid, 4-pyridinethiol, and ethyl glycinate were prepared in the usual manner.

Preparation of 2 and 10. To a stirred solution of ethyl glycinate (2.10 g, 0.02 mol) in 30 m*l* of ether was added a solution of **1** (2.40 g, 0.02 mol) in 10 m*l* of ether under cooling at 0°C. After stirring had been continued for 1 hr at room temperature, the resulting precipitate of **2** (4.10 g, 94%) was collected by filtration and washed twice with a small amount of ether. Recrystallization from ether gave analytically pure colorless needles, mp 144—145°C (lit,[4] mp 145—146°C). (Found: C, 37.74; H, 4.70; N, 12.86%).

Similarly, **10** was obtained in 88% yield by the reaction of **1** with *p*-aminobenzamide in DMF. Recrystallization from DMF-water gave analytically pure colorless needles, mp 229—230°C (dec.) (lit,[5] mp 236—237°C (dec.)). (Found: C, 47.05; H, 3.84; N, 16.39%).

3) All melting points were uncorrected. The IR spectra were recorded with a Hitachi EPI-G3 Spectrophotometer. The NMR spectra were measured at 100 MHz with a Japan Electron Optics JNM-4H-100 Spectrometer. All the solvents used for reactions were purified by the usual methods.

4) A. H. Corwin and C. I. Damerel, *J. Amer. Chem. Soc.*, **65**, 1974 (1943).

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 m*l* 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 m*l* 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 cyrstals 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 m*l* of ether was added to a solution of ethyl chloroacetate (2.45 g, 0.02 mol) in 20 m*l* 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 2*H*-1,4-benzothiazin-3(4*H*)-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 2*H*-1,4-benzothiazin-3(4*H*)-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 m*l* of ether was added a solution of **4** (2.50 g, 0.02 mol) and triethylamine (2.02 g, 0.02 mol) in 20 m*l* 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 m*l* of dichloromethane was added a solution of **1** (2.40 g, 0.02 mol) in 20 m*l* 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 m*l* of DMF was added to a solution of **8** (3.74 g, 0.005 mol) in 30 m*l* 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%. Cacld 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 m*l* 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 m*l* of acetonitrile. To this solution was added a solution of ethyl glycinate (1.03 g, 0.01 mol) in 10 m*l* 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).