The Reaction of Nitriles with Phosgene. V[1]. Cyclization Reactions of *N*-(α-Chlorobenzylidene)carbamoyl Chloride

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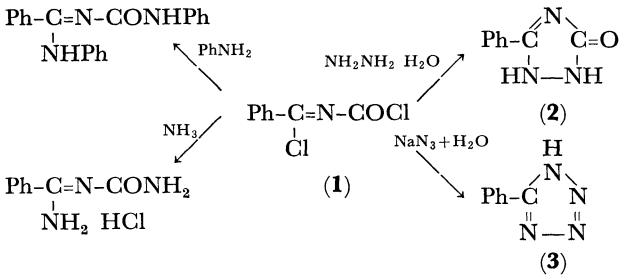
N-(α-Chlorobenzylidene)carbamoyl chloride (**1**) reacts with hydrazine hydrate to give 3-phenyl-1,2,4-triazolone (**2**), with sodium azide in the presence of water to give 5-phenyltetrazole (**3**), and with aliphatic nitriles in the presence of hydrogen chloride to give 6-chloro-2-phenyl-5-substituted-4(3*H*)-pyrimidones (**5**) and 4,6-dichloro-2-phenyl-5-substituted pyrimidines (**6**). However, the reaction of **1** with trichloroacetonitrile or pivalonitrile in the presence of hydrogen chloride did not give the expected triazines.

N-(α-Chlorobenzylidene)carbamoyl chloride (**1**) was prepared first by the reaction of benzoyl isocyanate with phosphorous pentachloride.[2] However, in the course of our work on the reaction of nitriles with phosgene, the carbamoyl chloride (**1**) has been found to be easily obtainable by the reaction of benzonitrile with phosgene in the presence of hydrogen chloride.[3] The carbamoyl chloride (**1**) has two reactive chlorine atoms in the molecule and thus can be expected to be useful as a precursor for the synthesis of nitrogen heterocycles. The Netherland patent claims that the carbamoyl chloride (**1**) reacts with amidines to give 2-hydroxy-6-phenyl-4-substituted-*s*-triazines.[4] In this paper we will report some cyclization reactions of the carbamoyl chloride (**1**) with some nucleophiles.

The reaction of the carbamoyl chloride (**1**) with excess aniline or ammonia gave *N*-phenyl-*N'*-anilinoformyl benzamidine and *N*-carbamoyl benzamidine hydrochloride respectively. On the other hand, the treatment of the carbamoyl chloride (**1**) with hydrazine hydrate gave the compound formulated as $C_8H_7N_3O$, which was confirmed to be 3-phenyl-1,2,4-triazolone (**2**) on the basis of the IR, NMR, and mass spectra.

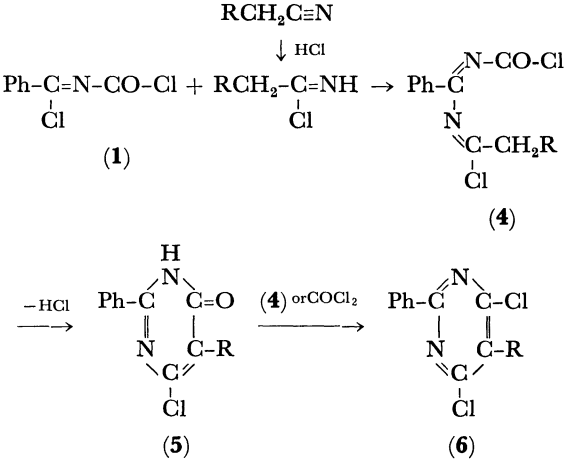
When the carbamoyl chloride (**1**) was allowed to react with sodium azide in aqueous acetone, 5-phenyltetrazole (**3**) was obtained, with the evolution of carbon dioxide. However, the reaction did not occur under anhydrous conditions, such as those in anhydrous THF.



Scheme 1

Recently several reactions concerning the electrophilic attack on the α-methylene of the C=N group have been reported.[5-7] In our previous papers,[7,8] we reported the preparation of 6-chloro-2,5-disubstituted-4(3*H*)-pyrimidones (**7**) by the reaction of aliphatic nitriles with phosgene in the presence of hydrogen chloride, in which *N*-(chloroformyl)-*N'*-(α-chloroalkylidene)alkylamidine was proposed as an intermediate. We assumed that the presence of hydrogen chloride promotes the polarization of the C=N bond in the intermediate, thus making the α-methylene more nucleophilic.

In view of these speculations, the carbamoyl chloride (**1**) can be expected to react with aliphatic nitriles in the presence of hydrogen chloride to afford 6-chloro-2-phenyl-5-substituted-4(3*H*)-pyrimidones (**5**) through *N*-(chloroformyl)-*N'*-(α-chloroalkylidene)-benzamidine (**4**), as is snown in Scheme 2. As expected, we have found the cyclization reaction of the carbamoyl chloride (**1**) with aliphatic nitriles in the presence of hydrogen chloride.



Scheme 2

When the carbamoyl chloride (**1**) was allowed to react with acetonitrile in the presence of hydrogen chloride (molar ratio 1 : 2 : 2) in a sealed glass tube at 60°C and the products were subjected to chromatographic separation, 6-chloro-2-phenyl-4(3*H*)-pyrimi-

1) Part IV, S. Yanagida, M. Ohoka, and S. Komori, *J. Org. Chem.*, **34**, 4127 (1969).

2) R. Neidlein and W. Haussmann, *Tetrahedron Lett.*, **1965**, 2423; *Chem. Ber.*, **99**, 239 (1966).

3) S. Yanagida, H. Hayama, M. Yokoe, and S. Komori, *J. Org. Chem.*, **34**, 4125 (1969).

4) Farbenfabriken Bayer A.-G., Neth. Appl. 301742 (1965). *Chem. Abstr.*, **64**, 8211 (1966).

5) A. J. Speziale and L. R. Smith, *J. Org. Chem.*, **27**, 4361 (1962).

6) H. Eilingsfeld, M. Seefelder, and H. Weidinger, *Chem. Ber.*, **96**, 2899 (1963).

7) S. Yanagida, M. Ohoka, M. Okahara, and S. Komori, *J. Org. Chem.*, **34**, 2972 (1969).

8) S. Yanagida, M. Ohoka, M. Okahara, and S. Komori, *Tetrahedron Lett.*, **1968**, 2351.

Table 1. The reaction of the carbamoyl chloride (**1**) with aliphatic nitriles

Run No.	R	Molar ratio 1 : RCN : HCl	Reaction time (hr) 30—35°C	60—65°C	Yield (%) 5	6	7
1	H	1 : 2 : 1.6	0	180	3.9	5.4	12
2	H	1 : 2 : 1.8	190	0	7.6	3.6	0
3	CH_3	1 : 2 : 1.7	0	220	8.2	trace	5.3
4	CH_3	1 : 2 : 2.0	170	290	1.8	23	trace
5	C_2H_5	1 : 2 : 2.0	170	240	15	9.4	0
6	C_3H_7	1 : 2 : 2.3	310[a]	300	19	9.4	trace
7	C_3H_7	1 : 2 : 2.3	190	0	13	trace	0
8	C_4H_9	1 : 2 : 2.2	160	260	24	5.0	trace

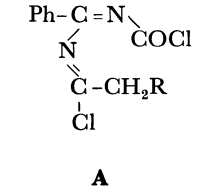
a) At room temperature.

done (**5a**), 4,6-dichloro-2-phenylpyrimidine (**6a**), 6-chloro-2-methyl-4(3*H*)-pyrimidone (**7a**), benzonitrile, and a tarry product were isolated. They were confirmed on the basis of the IR, NMR, and mass spectra, and by elemental analysis. It is known that the carbamoyl chloride (**1**) decomposes to benzonitrile and phosgene by heating.[3] Thus, the formation of **7a** is apparently due to the reaction of acetonitrile with the phosgene thus formed and hydrogen chloride.

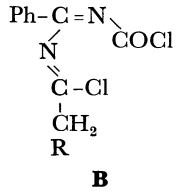
The reaction of **1** with aliphatic nitriles was extended to propionitrile, butyronitrile, valeronitrile, and capronitrile, giving the corresponding pyrimidine derivatives, **5b-e**, **6b-e**, and **7b-e**. (Table 1)

The treatment of **1** with 3-chloropropionitrile under comparable conditions, however, resulted in the isolation of a polymeric product which was similar in both appearance and quality to that obtained by the reaction of 3-chloropropionitrile with phosgene in the presence of hydrogen chloride.[7]

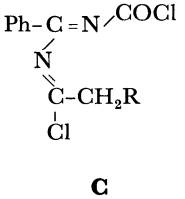
In order to avoid the side reactions and to increase the yield of **5**, the reaction was carried out at 30—35°C and finally the reaction temperature was raised to 60—65°C, as is shown in Runs 4, 5, 6, and 8 in Table 1. The formation of **7** was indeed diminished, as expected, but the dichloropyrimidines (**6**) were still forme din considerable amounts. In all the experiments the total yields of **5** and **6** were independent of the chain length of nitriles, but did not exceed 30%. It is assumed that the low yields are partly due to the configurations of the intermediate *N*-chloroformyl-*N'*-(α-chloroalkylidene)benzamidine (**4**) and/or the protonated one (**4'**). The intermediates **4** and/or **4'**, may have the following four configurations:



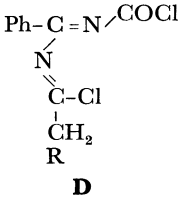
A



B



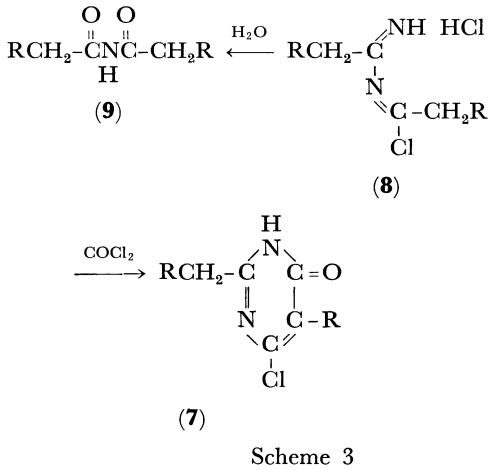
C



D

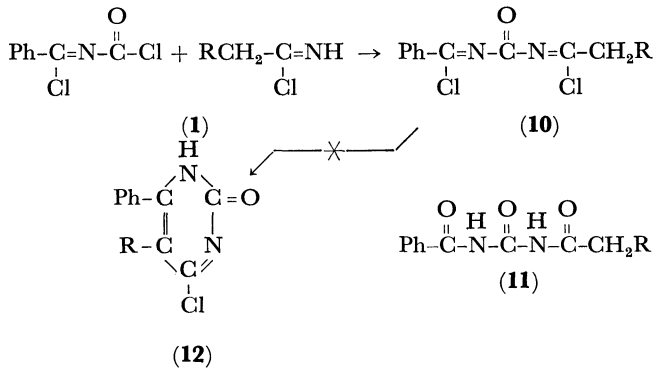
The protonation of **A**, **B**, **C**, and **D** would occur on a nitrogen bearing chloroalkylidene group.[7] It seems that **A** and protonated **A** are favorable configurations for the cyclization giving the **5** pyrimidones. However, judging from the facts that **6** did not produce under mild reaction conditions as is shown in Run 7 and that the pyrimidone **7** was formed only in traces in Runs 4, 6, and 8, non-cyclized intermediates which may exist in the **B**, **C**, and **D** and protanated **B**, **C**, and **D** forms may have a chlorinating ability and thus chlorinate **5** to give **6**, especially when the reaction temperature is raised. The chlorination by phosgene can not be neglected, either.

The treatment of the tarry residue obtained after column chromatographic separation with water gave a considerable amount of diacylamine (**9**) and a small amount of *N,N'*-diacylurea (**11**). The formation of **9** indicates the presence of *N*-(α-chloroalkylidene)-alkylamidine hydrochloride (**8**). As has been reported previously,[7] the pyrimidones **7** are formed by the reaction of **8** with phosgene. The isolation of **8** is now under investigation (Scheme 3).



Scheme 3

The isolation of **11** suggests the formation of *N*-(α-chlorobenzylidene)-*N'*-(α-chloroalkylidene)urea (**10**), which appears to be formed by the attack of the carbonyl carbon of **1** on the nitrogen atom of the imidoyl chloride (Scheme 4). The pyrimidone **12**, which may be formed by the intramolecular cyclization of **10**, was not isolated.



Scheme 4

In our preceding paper[3] we reported that the carbamoyl chloride (**1**) reacts with *p*-tolunitrile or benzonitrile in the presence of hydrogen chloride to give 2-chloro-4-phenyl-6-(*p*-tolyl)-*s*-triazine and 2-chloro-4,6-diphenyl-*s*-triazine respectively. Accordingly, it can be expected that **1** will react with aliphatic nitriles which have no α-hydrogen to give the corresponding triazines. However, the reaction of **1** with trichloroacetonitrile or pivalonitrile in the presence of hydrogen chloride gave only a small amount of 2-chloro-4,6-diphenyl-*s*-triazine, and the expected triazines were not obtained.

Experimental

All the melting points were determined on a Yanagimoto micromelting point apparatus and were corrected. The IR spectra were measured on a JASCO IR-E apparatus, the NMR spectra on a JEOL J.M. M-G-60 apparatus, and the mass spectra on a Hitachi RMU-6E apparatus.

N-(α-chlorobenzylidene)carbamoyl chloride was prepared from benzonitrile, phosgene, and hydrogen chloride according to our method.[3] The fraction with a bp of 85—90°C/1 mmHg was used.

Reaction of Aniline with ***1***. A solution of carbamoyl chloride **1** (1.0 g, 5 mmol) in 10 ml of benzene was added, drop by drop, to a solution of aniline (1.9 g, 20 mmol) in 15 *ml* of benzene under cooling in an ice-water bath. The precipitate thus formed was filtered and washed with cold water. After drying, they were recrystallized from aqueous acetone. The yield was almost quantitative (1.6 g, 100%), but the melting point was broad even after several recrystallizations. It began to melt around 159°C and melted completely below 172°C (lit,[9] 179—180°C) It was identified as *N*-phenyl-*N'*-anilinoformylbenzamidine on the basis of the following analytical results: IR(mull), 3200, 3070, 1695 and 1647 cm^{-1}; NMR(DMSO)(τ), 0.32(s, 1H), 0.55(s, 1H), 2.2—3.2(m, 15H); Mass(M^+) 315. Found: C, 76.30; H, 5.37; N, 13.42%. Calcd for $C_{20}H_{17}N_3O$, C, 76.17; H, 5.43; N, 13.33%,

Reaction of Ammonia with ***1***. The carbamoyl chloride **1** (1.8 g, 9.1 mmol) was stirred into an ethanol solution of ammonia under cooling. The precipitate thus formed was filtered, washed, dried, and recrystallized from a mixed solvent of methanol and isopropanol The yield was 49%. The melting point was also broad even after several recrystallizations. It began to melt around 167°C and melted completely below 185°C.(Lit,[10] 192—194°C). However, it was analyzed and identified as *N*-carbamoylbenzamidine hydrochloride on the basis of the following data: IR(mull), 3280, 3210, 1743 and 1671 cm^{-1}; Mass(M^+−HCl), 163. Found: C, 47.83; H, 5.05; N, 21.05; Cl, 18.09%. Cald for $C_8H_{10}N_3OCl$: C, 48.13; H, 5.05; N, 21.05; Cl, 18.09%.

Reaction of ***1*** *with Hydrazine Hydrate.* An acetone solution of hydrazine hydrate(0.25 g, 5 mmol) was mixed with the carbamoyl chloride **1** (0.5 g, 2.4 mmol) under cooling in an ice-water bath. The precipitate thus formed was treated as usual and recrystallized from acetone (58% yield). It was identified as 3-phenyl-1,2,4-triazolone (**2**) on the basis of the following data; mp 316.0—318.0°C (lit,[11] 321—322°C). Mass(M^+) 161, IR(KBr) *ca.* 3000, 1740 cm^{-1}, NMR (DMSO) (τ) *ca.* 2.25(m, 3H, *o*-H), −1.60(s, 1H, NH), −1.95(s, 1H, NH). Found: C, 59.50; H, 4.49; N, 26.29%. Calcd for $C_8H_7N_3O$: C, 59.62; H, 4.37; N, 26.07%.

Reaction of ***1*** *with Sodium Azide.* To a solution of sodium azide (0.16 g) in 1 m*l* of water we added a solution of the carbamoyl chloride **1** (0.5 g, 2.5 mmol) in 0.75 m*l* of acetone. The mixture was shaken in a water bath at 30°C. The precipitate thus formed was filtered, washed with acetone, and dried *in vacuo*. It was recrystallized from aqueous ethanol and identified as 5-phenyltetrazole (**3**) on the basis of the following analytical results: mp 217.0—219°C(dec)(lit,[12] 215°C(dec)). Mass(M^+) 146, IR(KBr) *ca.* 3000, 1560 cm^{-1}. Found: C, 58.00; H, 3.91; N, 38.53%. Calcd for $C_7H_6N_4$:C, 57.53; H, 4.14; N, 38.33%. Yield, 53%.

Reaction of ***1*** *with Aliphatic Nitriles in the Presence of Hydrogen Chlorides. General Procedure.* In a 20-m*l* glass tube we placed the carbamoyl chloride **1** (9.9 mmol), aliphatic nitrile (20 mmol), and chlorobenzene (2 g). Dry hydrogen chloride (16—17 mmol) was bubbled into the mixture under cooling. The tube was then stoppered, cooled in a dry ice-acetone mixture, sealed carefully, and allowed to stand at 30—35°C or heated to 60—65°C, as is shown in Table 1. After the end of the reaction, the reaction tube was chilled in dry ice-acetone mixture, and opened. The reaction mixture was concentrated under reduced pressure. In some cases, the removal of the hydrogen chloride gave the precipitate of the pyrimidone **5**. After the filtration of the precipitate, the mixture was concentrated as has been mentioned above. The resulting residue was chromatographed on silica gel. The dichloropyrimidines **6** were eluted with petroleum ether, the pyrimidones **5** with chloroform, and the pyrimidones **7** with a mixture of chloroform and ethanol. The pyrimidones **5** were purified by recrystallization from ethanol. The dichloropyrimidines **6** were purified by sublimation or recrystallization from aqueous ethanol. The analytical data are summarized in Tables 2 and 3.

The pyrimidones **7** were identified by comparison with authentic samples.

*Isolation of Diacylamines (****9****) and* N-*Benzoyl*-N'-*acylureas (****11****).* Oily products eluted with a mixture of chloroform and ethanol on the above-mentioned column chromatography were treated with aqueous acetone. The reaction mixture was then allowed to stand overnight. The resulting precipitates were filtered and sublimated under reduced pressure. Diacylamines **9** sublimed at 90°C under reduced pressure and *N*-benzoyl-*N'*-acylureas **11** at 140°C under the same conditions.

9) H. L. Wheeler, *J. Amer. Chem. Soc.*, **23**, 223 (1901).

10) K. R. Huffman and F. C. Schaefer, *J. Org. Chem.*, **28**, 1812 (1963).

11) G. Young and E. Witham, *J. Chem. Soc.*, **77**, 224 (1900).

12) A. Pinner, *Ann.*, **297**, 221 (1897).

Table 2. Analyses of 6-chloro-5-alkyl-2-phenyl-4(3*H*)-pyrimidones (**5**)

Pyrimidones (**5**)	mp (°C)	IR (KBr) (cm^{-1})	NMR (in CF_3COOH) (τ)	Mass (70 eV) (M^+)	Elemental analysis[a] C%	H%	N%
5a	228.0—231.0	1680, 1550[b] 1535	1.9—2.6 (m, 5H, ring) 3.13 (s, 1H, CH)	206	58.11 (58.13)	3.30 (3.41)	13.53 (13.56)
5b	272.0—274.0	1642, 1565 1541	1.8—2.4 (m, 5H, ring) 7.58 (s, 3H, CH_3)	220	59.97 (59.87)	3.93 (4.11)	12.81 (12.70)
5c	219.0—220.0	1640, 1573 1540	1.8—2.5 (m, 5H, ring) 7.17 (q, 2H, CH_2) 8.68 (t, 3H, CH_3)	234	61.70 (61.41)	5.00 (4.73)	11.85 (11.94)
5d	195.0—197.0	1648, 1548	1.78 (m, 2H, *o*-ring)[c] 2.53 (m, 3H, m, *p*-ring) 7.35 (t, 2H, CH_2) 8.35 (m, 2H, CH_2) 8.94 (t, 3H, CH_3)	248	62.87 (62.78)	5.18 (5.27)	11.22 (11.26)
5e	194.0—196.0	1650, 1546	1.9—2.5 (m, 5H, ring) 7.18 (c, 2H, CH_2) 8.33 (c, 4H, CH_2CH_2) 8.98 (c, 3H, CH_3)	262	63.87 (64.00)	5.84 (5.76)	10.67 (10.66)

a) Values in parenthesis are calculated ones. b) Nujol. c) In $CDCl_3$.

Table 3. Analyses of 4,6-dichloro-5-alkyl-2-phenylpyrimidines (**6**)

Pyrimidines (**6**)	mp (°C)	IR (KBr) (cm^{-1})	NMR (in CCl_4) (τ)	Mass (70 eV) (M^+)	Elemental analysis[a] C%	H%	N%
6a	97.0[b] 98.0	1545, 1514[c]	1.60 (m, 2H, *o*-ring) 2.56 (m, 3H, *m,p*-ring) 2.82 (s, 1H, CH)	224	53.58 (53.36)	2.57 (2.69)	12.36 (12.45)
6b	111.0—[d] 113.0	1550, 1501, 1405	1.68 (m, 2H, *o*-ring) 2.62 (m, 3H, *m,p*-ring) 7.56 (s, 3H, CH_3)	238	55.43 (55.25)	3.29 (3.37)	11.55 (11.72)
6c	74.0—75.0	1556, 1500, 1406	1.72 (m, 2H, *o*-ring) 2.65 (m, 3H, *m,p*-ring) 7.17 (q, 2H, CH_2) 8.76 (t, 3H, CH_3)	252	57.17 (56.94)	3.94 (3.98)	11.20 (11.07)
6d	67.0—70.0	1551, 1505 1405	1.65 (m, 2H, *o*-ring) 2.61 (m, 3H, *m,p*-ring) 7.17 (t, 2H, CH_2) 8.33 (m, 2H, CH_2) 8.92 (t, 3H, CH_3)	266	58.73 (58.44)	4.56 (4.53)	10.47 (10.49)
6e	62.0—63.0	1556, 1507 1400	1.68 (m, 2H, o-ring) 2.62 (m, 3H, m,p-ring) 7.16 (c, 2H, CH_2) 8.48 (c, 4H, CH_2CH_2) 9.00 (c, 3H, CH_3)	280	59.73 (59.80)	4.97 (5.02)	10.00 (9.96)

a) Values in parenthesis are calculated ones. b) Lit.[13] 96°C. c) Nujol. d) Lit[14] 110°C

N-*Benzoyl*-N′-*acetylurea* ***11a*** was confirmed by the following analytical results and by comparing its IR spectrum with that of the authentic sample prepared by the reaction of benzamide with acetyl isocyanate: mp 210—212°C (lit,[15] 187°C); IR(KBr disk) 3360, 3230, 1745 and 1690 cm^{-1}. NMR(CF_3COOH)(τ) 2.07(m, 2H), 2.37(m, 3H), 7.49(s, 3H). Mass(70 eV) *m/e* (rel. intensity) 147(40)-($C_6H_5CONCO^+$), 105(100)($C_6H_5CO^+$), 59(62)(CH_2=C-(OH)NH_2^+). Found: C, 58.43; H, 4.85; N, 13.61%. Calcd for $C_{10}H_{10}N_2O_3$: C, 58.24; H, 4.89; N, 13.59%.

The other ureas (**11**) and diacylamines (**9**) were confirmed on the basis of the IR and mass spectra as follows:

N-*benzoyl*-N′-*valerylurea* ***(11b)***: IR(mull) 3320, 3170, 1733, 1683, 1268, and 1190 cm^{-1}. Mass(70 eV) *m/e* (rel. intensity) 248(M^+), 147(30)($C_6H_5CONCO^+$), 105(85)-($C_6H_5CO^+$), 59(100)(CH_2=C(OH)NH_2^+).

N-*Benzoyl*-N′-*caproylurea* ***(11c)***: IR(mull) 3320, 3170, 1735, 1683, 1268, and 1187 cm^{-1}. Mass(70 eV) *m/e* (rel. intensity) 262(M^+), 147(7.5)($C_6H_5CONCO^+$), 105(100)-($C_6H_5CO^+$), 59(25)(CH_2=C(OH)NH_2^+).

Divalerylamine ***(9b)***: mp 96.0—99.0°C(lit,[16] 100°C). IR(mull) 3285, 3195, 1740, 1538, and 1506 cm^{-1}. Mass-(70 eV) *m/e* 185(M^+).

Dicaproylamine ***(9c)***. mp 91.0—93.0°C (lit,[17] 92.5°C). IR(mull) 3280, 3200, 1740, 1538, 1505, and 1170 cm^{-1}. Mass (70 eV) *m/e* 213(M^+).

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13) J. A. Hendry and R. F. Homer, *J. Chem. Soc.*, **1952**, 328.
14) M. Robba and R. Moreau, *Bull. Soc. Chim. Fr.*, **1960**, 1648.
15) O. C. Billeter, *Ber.*, **36**, 3213 (1903).
16) M. J. Tarbouriech and M. A. Haller, *Compt. Rend.*, **137**, 128 (1903).
17) C. Norstedt and H. A. Wahlforss, *Chem. Ber.*, **25**, Ref., 637 (1892).