

On Symmetrically Di-substituted Urea¹

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It was known¹⁾²⁾³⁾ that when dry carbon dioxide passed into the liquid, or the ethereal solution, of primary amines RNH_2 , such as methylamine, ethylamine and benzylamine, white crystalline substances were yielded with evolving of heat, and these compounds melted under decomposition. From the composition $(\text{RNH}_2)_2 \cdot \text{CO}_2$, it was assumed²⁾ that these compounds be the mono-substituted ammonium salt of N-substituted carbamic acid, $\text{RNHCO}_2 \cdot \text{NH}_3\text{R}$. These writers recognized⁴⁾ that the addition of amine and carbon dioxide took place generally as to the primary amines, except aromatic amines, and found that when primary amine-carbon dioxide compounds were heated under the atmospheric pressure, they easily decomposed into their two components, carbon dioxide and primary amine, at constant temperature which was more or less different in each case of the amines, from about 70° to 120° . The following are the amines which were studied by the writers.

n-propylamine ($72^\circ \sim 73^\circ$), *tertiary*-butylamine ($68^\circ \sim 69^\circ$), *n*-amylamine ($79^\circ \sim 80^\circ$), *n*-hexylamine ($91^\circ \sim 92^\circ$), *n*-octylamine ($84^\circ \sim 86^\circ$), *p*-tolu-benzylamine ($107^\circ \sim 108^\circ$), α -phenylethylamine ($96^\circ \sim 97^\circ$), β -phenylethylamine ($103^\circ \sim 104^\circ$), benzhydrylamine ($102^\circ \sim 104^\circ$), α -naphthomethylamine ($118^\circ \sim 119^\circ$), α -naphthylethylamine ($103^\circ \sim 105^\circ$), furylamine ($72^\circ \sim 74^\circ$), cyclohexylamine ($100^\circ \sim 101^\circ$), *ac*-tetrahydro-naphthylamine ($111^\circ \sim 112^\circ$), 1-menthylamine ($98^\circ \sim 99^\circ$), *d*-dihydrocarvylamine ($102^\circ \sim 103^\circ$), camphylamine ($109^\circ \sim 110^\circ$), bornylamine ($87^\circ \sim 88^\circ$).

Each temperature in the above parentheses is the decomposition temperature which was determined in a small tube used for determination of melting point. The decomposition temperature determined by this method showed a narrow range. However, when the decomposition temperature was determined by a thermometer inserted in 1 to 2 g sample in a tube which was heated in a bath, the decomposition temperature was constant, as indicated in Fig. 1.

The process of the decomposition of carbon dioxide compound was investigated by the experiment of decomposition which was made in a glass tube connecting with a burette containing carbon dioxide. As an

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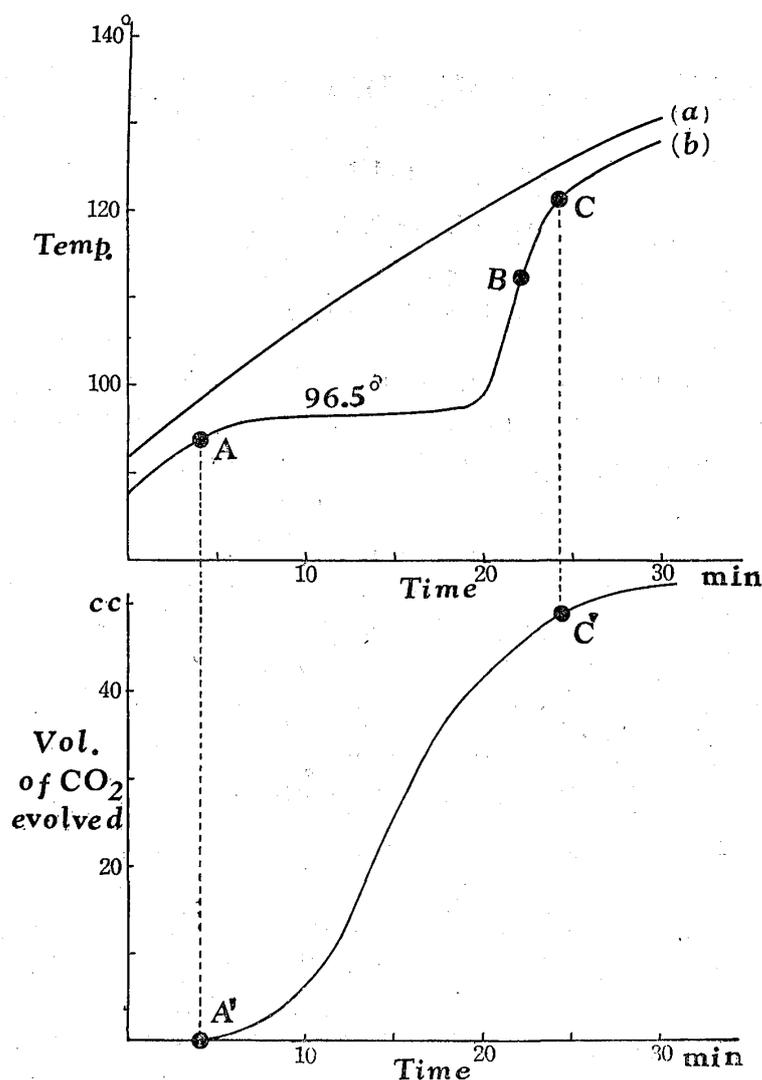


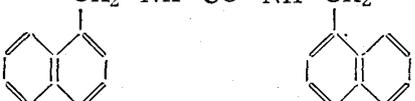
Fig. 1 The thermal decomposition of α -phenylethylamine-carbon dioxide compound.
 (a) Temperature of the bath. (b) Heating curve.

example of the results, that of α -phenylethylamine, which is similar to the case of other amines, is shown in Fig. 1. *A*, *B*, *C*, *A'* and *C'* of Fig. 1 stand for states of the decomposition: *A* for the appearance of liquid of amine (the beginning of the decomposition), *B* for the disappearance of solid, *C* for the end of the decomposition, *A'* for the beginning of the evolving of carbon dioxide gas, and *C'* for the end of the evolving of carbon dioxide gas. When the hot sealed tube, containing the decomposition products, carbon dioxide and amine, was gradually cooled, crystals of $(RNH_2)_2 \cdot CO_2$ were yielded at about 82° , which is lower than the decomposition temperature 96.5° in the case of heating.

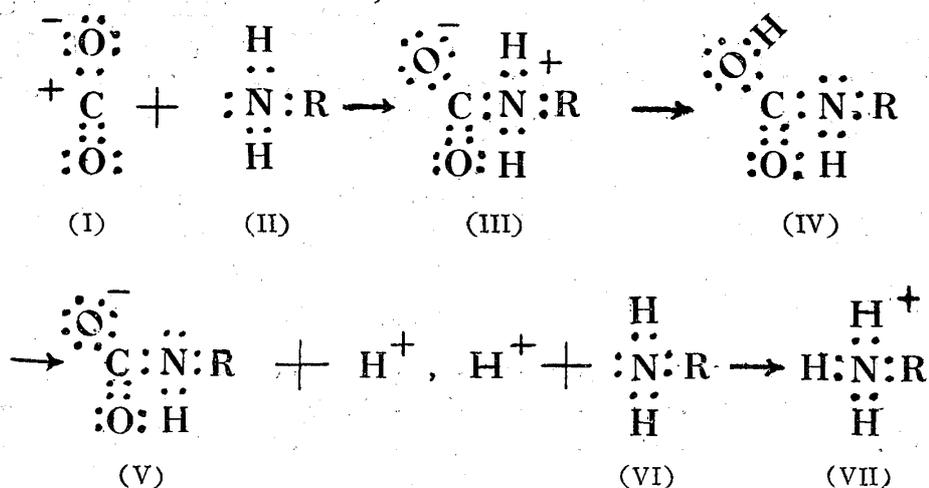
When primary amine-carbon dioxide compound was heated in a sealed tube at $180^\circ \sim 200^\circ$ for ten or more hours with or without alumina as a catalyst, dehydration partially occurred, *N*, *N'*-symmetrically di-substituted urea, $RNH-CO-NHR$, being yielded. The formation of di-substituted urea has been already known²⁾ in the cases of methylamine, ethylamine

and benzylamine. The present study showed that the formation of di-substituted urea from primary amine-carbon dioxide compound took place generally. N, N'-symmetrically di-substituted ureas which were obtained in the present study are shown in Table 1.

Table 1

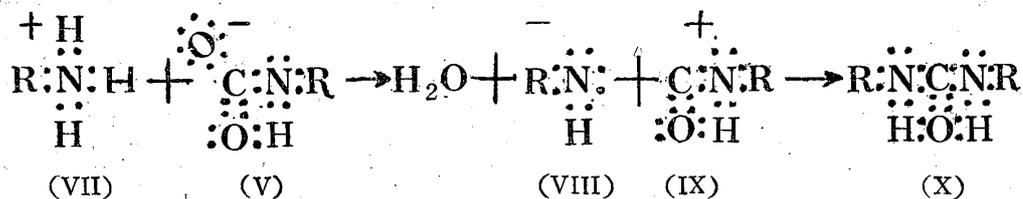
Amine	N, N'-Disubstituted Urea	
	Constitution	mp
<i>n</i> -propylamine	$\text{CH}_3 \cdot (\text{CH}_2)_2 \cdot \text{NH} \cdot \text{CO} \cdot \text{NH} \cdot (\text{CH}_2)_2 \cdot \text{CH}_3$	103°~104°
<i>n</i> -amylamine	$\text{CH}_3 \cdot (\text{CH}_2)_4 \cdot \text{NH} \cdot \text{CO} \cdot \text{NH} \cdot (\text{CH}_2)_4 \cdot \text{CH}_3$	86°~87°
<i>n</i> -octylamine	$\text{CH}_3 \cdot (\text{CH}_2)_7 \cdot \text{NH} \cdot \text{CO} \cdot \text{NH} \cdot (\text{CH}_2)_7 \cdot \text{CH}_3$	88°~89°
<i>p</i> -tolubenzylamine	$\text{CH}_3 \text{---} \langle \text{---} \rangle \text{---} \text{CH}_2 \cdot \text{NH} \cdot \text{CO} \cdot \text{NH} \cdot \text{CH}_2 \text{---} \langle \text{---} \rangle \text{---} \text{CH}_3$	215°~216°
cyclohexylamine	$\begin{array}{c} \text{H}_2 \quad \text{H}_2 \\ \quad \\ \text{C} \text{---} \text{C} \\ \quad \\ \text{H}_2 \quad \text{H}_2 \end{array} \text{CH} \cdot \text{NH} \cdot \text{CO} \cdot \text{NH} \cdot \text{HC} \begin{array}{c} \text{H}_2 \quad \text{H}_2 \\ \quad \\ \text{C} \text{---} \text{C} \\ \quad \\ \text{H}_2 \quad \text{H}_2 \end{array} \text{CH}_2$	228°~229°
α -phenylethylamine	$\text{C}_6\text{H}_5 \cdot \text{CH}(\text{CH}_3) \cdot \text{NH} \cdot \text{CO} \cdot \text{NH} \cdot \text{CH}(\text{CH}_3) \cdot \text{C}_6\text{H}_5$	158°~159°
β -phenylethylamine	$\text{C}_6\text{H}_5 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{NH} \cdot \text{CO} \cdot \text{NH} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{C}_6\text{H}_5$	137°~138°
α -naphthomethylamine	$\text{CH}_2 \cdot \text{NH} \cdot \text{CO} \cdot \text{NH} \cdot \text{CH}_2$ 	233°~234°

Although there was neither evidence nor investigation about the constitution, primary amine-carbon dioxide compound was assumed to be substituted carbamate, $\text{RNHCO}_2 \cdot \text{NH}_3\text{R}$.²⁾ The writers considered about the mechanism of the formation and the constitution of this compound, and also about the mechanism of the formation of di-substituted urea, which follows:—From the facts that the primary amine-carbon dioxide compound was produced very easily from its two components, that it possessed a little of an amine odour even at ordinary temperature, and that, when it was heated, the decomposition into its two components took place with ease, it was thought that white crystalline amine-carbon dioxide compound, $(\text{RNH}_2)_2 \cdot \text{CO}_2$, was either a coördination complex compound or a compound of the type of ammonium salt. The latter constitution is more probable from the following consideration. Oxygen atom has an electron affinity higher than carbon atom. Therefore the constitution (I), in which carbon atom acquires a positive charge, is considered to make some contribution to the resonance state of carbon dioxide. Primary amine, RNH_2 (II), forms an intermediate addition compound (III) by donating the unshared electron pair of nitrogen atom to the positively charged carbon atom of (I). At the same time there occurs an attraction between hydrogen of NH_2 and oxygen of CO_2 , which attraction is favourable for the formation of the addition compound (III). The



intermediate addition compound (III) gets stabilized by the rearrangement to carbamic acid (IV), which involves an O:H linking formed by the migration of proton from N:H. This OH group dissociates into carbamate ion (V) and proton. The liberated proton coordinates with nitrogen atom of primary amine (VI), a positively charged N-substituted ammonium ion (VII) being formed. These negatively and positively charged ions, (V) and (VII), combine by ionic bond, forming crystalline carbamate $\text{RNHCO}_2 \cdot \text{NH}_3\text{R}^+$. (In the case of aromatic primary amine the electron density of an unshared electron pair of nitrogen atom diminishes by the resonance effect, so coordination of nitrogen with oxygen of carbon dioxide does not occur, and hence carbamate is not produced.)

When this ionic carbamate is heated in the atmosphere, it decomposes into two original components by the fission of C:N bond of carbamate ion (V) and by the transfer of proton of ammonium ion (VII). When the carbamate $\text{RNHCO}_2 \cdot \text{NH}_3\text{R}$ is heated in a sealed tube, two protons of substituted ammonium ion (VII) and a negatively charged ionic oxygen atom in (V) combine and give water molecule, as shown in the following



scheme. The remaining part of an ammonium ion, $\text{R}:\text{N}:$ (VIII), combines to that of a carbamate ion $\text{C}^+\text{-NHR}$ (IX), then N, N'-symmetrically di-substituted urea $\text{RNH}-\text{C}-\text{NHR}$ (X), being given. That the formation

of water from carbamate compound occurs is probable also from the point of the spatial configuration of the substituted carbamate $\text{RNHCO}_2^- \cdot \text{NH}_3\text{R}^+$, in which two protons are supposed to exist near the negatively charged oxygen atom.

Experimental

1. N, N'-Di-*n*-propyl-urea. $\text{CH}_3 \cdot \text{CH}_2 \cdot \text{CH}_2\text{-NHCONH-CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_3$

The carbon dioxide compound of *n*-propylamine was obtained by passing dry carbon dioxide in *n*-propylamine cooled in a freezing mixture. It decomposed at $69^\circ \sim 70^\circ$. This compound (0.2~0.5 g) was heated in a small sealed tube with or without equal quantity of alumina in an oil bath at 200° for about 15 hours. In the case in which alumina was not added, the reaction product was heated with water, and the undissolved di-*n*-propyl-urea was filtered. In the case in which alumina was added, the filtered residual solid, which was a mixture of di-*n*-propyl-urea and alumina, was heated with ethyl alcohol, and the alcoholic solution, separated from alumina, was evaporated, di-*n*-propyl-urea being obtained. The percentage of yield was not high, about 20%, nearly equal to that of other cases. The yield was generally better in the case in which alumina was added. Di-*n*-propyl-urea was recrystallized from water, melting at $103^\circ \sim 104^\circ$.

Substance	3.125 mg
Found	N 19.55%, Calc. for $\text{C}_7\text{H}_{16}\text{N}_2\text{O}$ N 19.43%

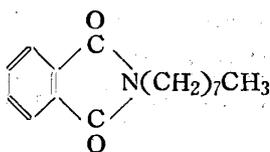
2. N, N'-Di-*n*-amyl-urea. $\text{CH}_3(\text{CH}_2)_4\text{-NHCONH-(CH}_2)_4\text{CH}_3$

n-Amylamine $\text{CH}_3(\text{CH}_2)_4\text{NH}_2$ was prepared by the reduction of *n*-valeronitrile with sodium and boiling ethyl alcohol. *n*-Amylamine-carbon dioxide compound was obtained by passing dry carbon dioxide in a concentrated ethereal solution of amine, and decomposed at $79^\circ \sim 80^\circ$. When the carbon dioxide compound was heated in a sealed tube, as in the case of propylamine, N, N'-di-*n*-amyl-urea was obtained by the treatment similar to that of di-propyl-urea. It was recrystallized from ethylalcohol, melting at $86^\circ \sim 87^\circ$.

Substance	2.628 mg
Found	N 14.03%, Calc. for $\text{C}_{11}\text{H}_{24}\text{N}_2\text{O}$ N 13.99%

3. N, N'-Di-*n*-octyl-urea. $\text{CH}_3(\text{CH}_2)_7\text{-NHCONH-(CH}_2)_7\text{CH}_3$

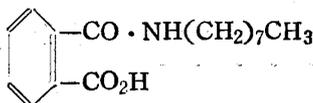
n-Octylamine was prepared by the Gabriel reaction as follows: *n*-octyliodide which was obtained from *n*-octylalcohol by the reaction with iodine and yellow phosphorus, and boiled at $222^\circ \sim 223^\circ$, was heated with potassium phthalimide in a salt bath at $240^\circ \sim 250^\circ$ for 5~10 hours. After heating was done, water was added to the cooled reaction product. N-*n*-Octyl-phthalimide



separated, was filtered. From 5 g of potassium phthalimide and 10 g of octyl iodide, was obtained 7 g of octylphthalimide. This compound was recrystallized from ethyl alcohol in colorless thin plate crystal, melting at $47.5^{\circ}\sim 48.5^{\circ}$.

Substance	4.257 mg		
Found	N 5.55%	Calc. for $C_{16}H_{21}NO_2$	N 5.41%

Octyl-phthalimide was heated with 10% potassium hydroxide solution in water bath, until the mixture became clear. When the clear solution was acidified with hydrochloric acid, *N*-*n*-octyl-phthalaminoacid



appeared in oily state and crystallized when cooled in ice water. This crystal was recrystallized from benzene in colorless fine thin plate crystal, melting at $88^{\circ}\sim 89.5^{\circ}$.

Substance	4.118 mg		
Found	N 5.17%	Calc. for $C_{16}H_{23}NO_3$	N 5.05%

The solution of *n*-octyl-phthalaminoacid in sodium hydroxide solution showed a forthy property. The surface tension of 2.5% solution in 0.1 N NaOH solution was about 5/9 of that of water, when measured by a stalagmometer.

Octyl-phthalaminoacid was heated with concentrated hydrochloric acid by direct heating for about 10 hours. After the reaction product was cooled, concentrated potassium hydroxide solution was added. *n*-Octyl amine separated was extracted with ether, boiling at $171^{\circ}\sim 173^{\circ}$. Silky white crystals of *n*-octyl amine-carbon dioxide compound were obtained by passing dry carbon dioxide in an ethereal solution of amine. It decomposed at $84^{\circ}\sim 86^{\circ}$. The carbon dioxide compound was heated in a sealed tube and treated by the method similar to that of *n*-propylamine, and di-*n*-octyl-urea was obtained. It was recrystallized in plate crystal from ethyl alcohol, melting at $88^{\circ}\sim 89^{\circ}$.

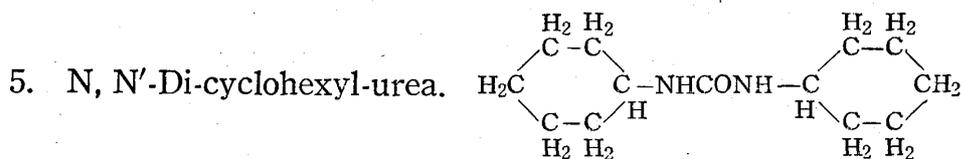
Substance	3.205 mg		
Found	N 9.99%	Calc. for $C_{17}H_{36}N_2O$	N 9.85%

4. *N,N'*-Di-*p*-tolubenzyl-urea. $CH_3-\langle \text{C}_6\text{H}_4 \rangle-\text{CH}_2-\text{NHCONH}-\text{CH}_2-\langle \text{C}_6\text{H}_4 \rangle-\text{CH}_3$

p-Tolubenzylamine was prepared from *p*-tolualdehyde oxime by the reduction with aluminium amalgam in a boiling ethyl alcoholic solution

containing water. The carbon dioxide compound of amine, obtained by the method similar to that of other cases, decomposed at $107^{\circ}\sim 108^{\circ}$. It was heated in a sealed tube, and di-*p*-tolubenzyl-urea, melting at $215^{\circ}\sim 216^{\circ}$, was obtained.

Substance 3.583 mg
 Found N 10.57%, Calc. for $C_{17}H_{20}N_2O$ N 10.44%



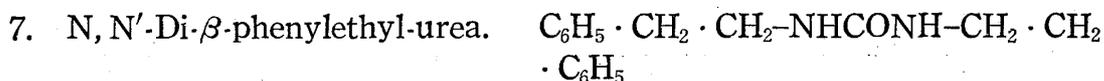
Cyclohexylamine was prepared by the reduction of cyclohexanone-oxime with aluminium amalgam in a boiling ethyl alcoholic solution containing some water. The carbon dioxide compound of amine, obtained by the usual method, decomposed at $100^{\circ}\sim 101^{\circ}$. Di-cyclohexyl-urea obtained by the treatment similar to that of other amines, was recrystallized from ethyl alcohol in colorless fine needle crystal, melting at $228^{\circ}\sim 229^{\circ}$.

Substance 3.275 mg
 Found N 12.61%, Calc. $C_{13}H_{24}N_2O$ N 12.49%



α -Phenylethylamine was prepared by the reduction of acetophenone-oxime with aluminium amalgam in a boiling ethyl alcoholic solution containing water. The carbon dioxide compound of amine, obtained by the method similar to that of other cases, decomposed at $96^{\circ}\sim 97^{\circ}$. The process of decomposition of this carbon dioxide compound was studied as an example. About 1.5 g of this compound, which was placed in a test tube, was heated, and the change of the temperature of the substance during the heating was observed with a thermometer inserted in the substance. The result observed is shown in the upper graph of Fig. 1. The state of the evolving of carbon dioxide during the decomposition was also observed by measuring the volume of carbon dioxide evolved. The observed result is shown in the lower graph of Fig. 1. These results were known to be similar to those of other amine compounds. From carbon dioxide compound of α -phenylethylamine, N, N'-di- α -phenylethyl-urea was obtained by the treatment similar to that of other amines. It was recrystallized from ethyl alcohol in colorless fine needle crystal, melting at $158^{\circ}\sim 159^{\circ}$.

Substance 3.313 mg
 Found N 10.69%, Calc. for $C_{17}H_{20}N_2O$ N 10.44%

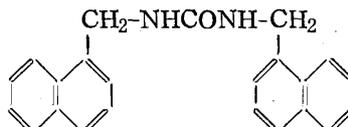


β -Phenylethylamine was prepared by the reduction of benzyl cyanide

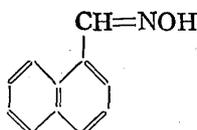
with aluminium amalgam in a boiling ethyl alcoholic solution containing water. From the carbon dioxide compound of this amine, decomposing at $103^{\circ}\sim 104^{\circ}$, di- β -phenylethyl-urea was obtained by the method similar to that of other cases. It was recrystallized from benzene in colorless fine prism crystal, melting at $137^{\circ}\sim 138^{\circ}$.

Substance 3.115 mg
 Found N 10.59%, Calc. for $C_{17}H_{20}N_2O$ N 10.44%

8. N, N'-Di- α -naphtho-methyl-urea.



α -Naphtho-methylamine was obtained by the reduction of α -naphtho-aldoxime



with aluminium amalgam in a boiling ethyl alcoholic solution containing some water. From the carbon dioxide compound of this amine, decomposing at $118^{\circ}\sim 119^{\circ}$, di- α -naphtho-methyl-urea was obtained by the method similar to that of the cases of other amines. It was recrystallized from ethyl alcohol. melting at $263^{\circ}\sim 264^{\circ}$.

Substance 4.125 mg
 Found N 8.19%, Calc. for $C_{23}H_{20}N_2O$ N 8.05%

Summary

The mechanism of the formation of the carbon dioxide compound of primary amine and its constitution and the mechanism of the formation of N, N'-di-substituted urea from primary amine-carbon dioxide compound were discussed. It was concluded that the primary amine-carbon dioxide compound was the substituted ammonium salt of substituted carbamic acid.

Several kinds of N, N'-di-substituted urea R-NHCONH-R (R = *n*-propyl, *n*-amyl, *p*-tolubenzyl, cyclohexyl, α -phenylethyl and α -naphtho-methyl) were prepared.

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