and 2 g. of 30% palladium-carbon were heated under reflux in 12 ml. of *p*-cymene under carbon dioxide atmosphere for 2 hr., during which time 70 ml. of gases evolved. After cooling, the precipitate was collected by filtration, washed with benzene, and extracted with methanol in a continuous extractor. After evaporation of the methanol and addition of water, the mixture was acidified with dilute hydrochloric acid to *p*H 4.8 and extracted with chloroform to remove the unchanged starting material. The aqueous layer was treated with decolorizing charcoal, and concentrated to dryness to give a brown material (580 mg.) which was crystallized from methanol-acetone and then from methanol to give 60 mg. of *Py*-tetradehydroyohimbine hydrochloride (Vb), yellow prisms, m.p. 234–234.5° (dec.), $[\alpha]_D^{17}$ +216.3° (C, 0.36, AcOH). Ultraviolet: $\lambda_{max}^{alc}$ 255, 306, 361 mμ (log ε 4.45, 4.35, 3.71); $\lambda_{min}^{alc}$ 226, 280, 325 mμ (log ε 4.13, 3.78, 3.25).

*Anal.* Calcd. for $C_{21}H_{23}ClN_2O \cdot {}^3/_5CH_3OH$: C, 63.88; H, 6.30; N, 6.89; ${}^3/_5CH_3O$, 12.23. Found: C, 63.47; H, 6.34; N, 6.70; $CH_3O$, 12.22.

(*b*) In a second run, 1.0 g. of yohimbine was dehydrogenated as above and the precipitate was extracted with benzene and then with methanol. The methanol extract was evaporated to give a brown oil (780 mg.) which was washed with chloroform and then crystallized from methanol to give 80 mg. of needles. Recrystallization from methanol gave *Py*-tetradehydroyohimbic acid (Va), pale yellow needles m.p. 330–332° (dec.), $[\alpha]_D^{16}$ +241.4° (C, 0.319, AcOH). Ultraviolet: $\lambda_{max}^{alc}$ 225, 306, 364 mμ (log ε 4.37, 4.26, 3.62); $\lambda_{min}^{alc}$ 226, 280, 325 mμ (log ε 4.03, 3.70, 3.16).

*Anal.* Calcd. for $C_{20}H_{20}N_2O_3$: C, 71.39: H, 5.99; N, 8.33. Found: C, 71.91; H, 5.97; N, 8.35.

The above benzene extract was shaken with dilute hydrochloric acid. The aqueous layer was made alkaline with ammonium hydroxide and extracted with chloroform. The chloroform extract was chromatographed over alumina to furnish 10 mg. of unchanged yohimbine.

*Esterification of* (Va) [*formation of Py-tetradehydroyohimbine* (Vb)]. Eight mg. of *Py*-tetradehydroyohimbic acid (Va) was heated under reflux in 5 ml. of 5% methanolic hydrochloric acid for 2 hr. After removal of the solvent under reduced pressure, the residue was triturated with methanol to yield pale brownish crystals, m.p. 227–230° (dec.), after recrystallization from methanol, the infrared spectrum of which was identical with that of the hydrochloride of (Vb).

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# Amino Acids. IX.[1] 1,3-Di(ω-carbamylalkyl)-ureas and -thioureas and Their Chemistry

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1,3-Di(ω-carbamylalkyl)-ureas and -thioureas were prepared by the ammonolysis and aminolysis of 1,3-di(ω-carbalkoxyalkyl)-ureas and -thioureas. The nitrosation of these amides and the properties of the resulting nitrosamide derivatives are described.

In conjunction with studies on 1,3-di(ω-carboxyalkyl)-thioureas and -ureas,[2] a series of diamides of these dicarboxylic acids have been synthesized. These derivatives (Table I) were prepared by two general methods: A, aminolysis or ammonolysis of the dicarboxylic acid dimethyl esters and B, the reaction of amines with the mixed dianhydrides from 1,3-di(ω-carboxyalkyl)ureas and ethyl hydrogen carbonate.

The aminolysis and ammonolysis reactions were performed in methanolic solution in the presence of sodium methoxide[3,4] as catalyst. Under similar reaction conditions, ammonia, benzylamine, and most primary straight chain amines reacted with 1,3-di-(ε-carbomethoxypentyl)urea (Ia) to give good yields of the corresponding diamides (II). With dodecylamine, hexadecylamine, and octadecylamine, the intermediate monoamide-monoesters (Table II) separated from solution readily and hence prevented complete aminolysis. These latter products were identified by their analyses and infrared spectra which showed the presence of carbonyl bands due to the ester group (1729 cm.$^{-1}$) together with those of the amide (1634–1637 cm.$^{-1}$) and urea (1610–1618 cm.$^{-1}$) functions.

Of the branched chain primary amines, those with branching on the carbon alpha to the nitrogen atom (isopropylamine, *t*-butylamine, cyclohexylamine) failed to react under the same experimental conditions. However, with the branching farther along the chain (2-*N*,*N*-dimethylaminoethylamine, 2-*N*,*N*-diethylaminoethylamine, 3-*N*,*N*-dimethylaminopropylamine) the aminolysis proceeded normally. With secondary amines (dimethylamine, diethylamine, di-*n*-butylamine), only dimethylamine reacted to give a diamide (II), while the remaining reaction mixtures yielded starting material. These

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TABLE I

$R_2R_1NC(=O)(CH_2)_nNHC(=O)NH(CH_2)_nC(=O)NR_1R_2$

| $R_1$ | $R_2$ | $n$ | Yield, % | M.P., °C. | Formula | C Calcd. | C Found | H Calcd. | H Found | N Calcd. | N Found |
|---|---|---|---|---|---|---|---|---|---|---|---|
| H | H | 3 | 81.0[a] | 209–210[c] | $C_9H_{18}N_4O_3$ | 46.94 | 46.93 | 7.88 | 7.71 | 24.33 | 24.31 |
| H | H | 5 | 87.0[a] | 201–202[d] | $C_{13}H_{26}N_4O_3$ | 54.52 | 54.43 | 9.15 | 9.30 | 19.56 | 19.41 |
| $CH_3$ | H | 5 | 95.0[a] | 171.5–172[c] | $C_{15}H_{30}N_4O_3$ | 57.30 | 57.47 | 9.62 | 9.67 | 17.82 | 17.52 |
| $C_2H_5$ | H | 5 | 71.2[a] | 179–180[e] | $C_{17}H_{34}N_4O_3$ | 59.62 | 59.68 | 10.01 | 9.87 | 16.36 | 16.63 |
| $n$-$C_3H_7$ | H | 5 | 41.6[a] | 186–187[f] | $C_{19}H_{38}N_4O_3$ | 61.58 | 61.71 | 10.34 | 10.11 | 15.12 | 15.28 |
| $n$-$C_4H_9$ | H | 5 | 61.2[a] | 179–180[g] | $C_{21}H_{42}N_4O_3$ | 63.28 | 63.15 | 10.62 | 10.65 | 14.06 | 13.76 |
| $n$-$C_8H_{17}$ | H | 5 | 65.3[a] | 174–175[h] | $C_{29}H_{58}N_4O_3$ | 68.19 | 67.84 | 11.45 | 11.26 | 10.97 | 10.95 |
| $CH_2{=}CHCH_2$ | H | 5 | 83.5[a] | 182–183[h] | $C_{19}H_{34}N_4O_3$ | 62.26 | 62.23 | 9.35 | 9.47 | 15.29 | 15.69 |
| $CH_3OCH_2CH_2CH_2$ | H | 5 | 47.9[a] | 160–161[h] | $C_{21}H_{42}N_4O_5$ | 58.57 | 58.42 | 9.83 | 9.72 | 13.01 | 12.98 |
| Cyclohexyl | H | 5 | 88.0[b] | 215–216[c] | $C_{25}H_{46}N_4O_3$ | 66.63 | 66.88 | 10.29 | 10.37 | 12.43 | 12.38 |
| $C_6H_5CH_2$ | H | 5 | 38.8[a] | 196–197[i] | $C_{27}H_{38}N_4O_3$ | 69.49 | 69.82 | 8.20 | 8.20 | 12.00 | 11.96 |
| $(CH_3)_2NCH_2CH_2$ | H | 5 | 27.4[a] | 155–156[j] | $C_{21}H_{44}N_6O_3$ | 58.84 | 58.96 | 10.34 | 10.25 | 19.61 | 19.52 |
| $(C_2H_5)_2NCH_2CH_2$ | H | 5 | 16.8[a] | 122–123[k] | $C_{25}H_{52}N_6O_3$ | 61.94 | 61.69 | 10.81 | 10.64 | 17.34 | 16.97 |
| $(CH_3)_2N(CH_2)_2CH_2$ | H | 5 | 73.4[a] | 142–143[l] | $C_{23}H_{48}N_6O_3$ | 60.49 | 60.10 | 10.59 | 10.35 | 18.40 | 18.48 |
| $CH_3$ | $CH_3$ | 5 | 81.9[a] | 101.5–102.5[m] | $C_{17}H_{34}N_4O_3$ | 59.62 | 59.62 | 10.01 | 9.90 | 16.36 | 16.76 |
| $n$-$C_4H_9$ | $n$-$C_4H_9$ | 5 | 64.1[b] | Liquid[n] | $C_{29}H_{58}N_4O_3$ | 68.19 | 67.85 | 11.45 | 11.51 | 10.97 | 11.17 |
| $CH_3(CH_2)_3CH(C_2H_5)CH_2$ | $CH_3(CH_2)_3CH(C_2H_5)CH_2$ | 5 | 71.6[b] | Liquid[o] | $C_{45}H_{90}N_4O_3$ | 73.51 | 73.42 | 12.34 | 12.33 | 7.62 | 7.90 |

[a] Prepared by Method A. [b] Prepared by Method B. [c] Recrystallized from methanol-water. [d] Ethanol-water. [e] Methanol-acetone. [f] Methanol-ether. [g] Acetone-water. [h] Methanol. [i] Chloroform-methanol. [j] Chloroform-benzene. [k] Acetone. [l] Methanol-benzene. [m] Acetone-hexane. [n] B.p. 215–240°/0.8 mm. [o] B.p. 260–267°/0.1 mm., $n_D^{25}$ 1.48233, $d_4^{25}$ 0.934.

TABLE II

$RNHC(=O)(CH_2)_5NHC(=O)NH(CH_2)_5C(=O)OCH_3$

| R | Yield,[a] % | M.P., °C.[b] | Formula | C Calcd. | C Found | H Calcd. | H Found | N Calcd. | N Found |
|---|---|---|---|---|---|---|---|---|---|
| $n$-$C_{12}H_{25}$ | 84.2 | 134–135 | $C_{26}H_{51}N_3O_4$ | 66.48 | 66.65 | 10.95 | 10.89 | 8.95 | 8.85 |
| $n$-$C_{16}H_{33}$ | 33.1 | 135–136 | $C_{30}H_{59}N_3O_4$ | 68.53 | 68.80 | 11.31 | 11.30 | 7.99 | 7.92 |
| $n$-$C_{18}H_{37}$ | 29.7 | 135–136 | $C_{32}H_{63}N_3O_4$ | 69.39 | 69.18 | 11.47 | 11.54 | 7.59 | 7.83 |

[a] Prepared by Method A. [b] Recrystallized from methanol.

TABLE III

$$RNHC(CH_2)_5NHCNH(CH_2)_5CNHR$$

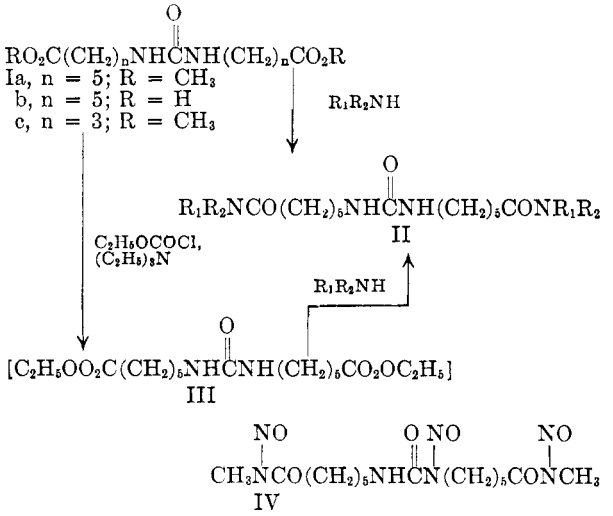
| R | Yield,[a] % | M.P., °C. | Formula | C Calcd. | C Found | H Calcd. | H Found | N Calcd. | N Found | S Calcd. | S Found |
|---|---|---|---|---|---|---|---|---|---|---|---|
| H | 47.5 | 177.5–179[b] | $C_{13}H_{26}N_4O_2S$ | 51.62 | 51.58 | 8.67 | 8.59 | 18.53 | 18.68 | 10.60 | 10.38 |
| $CH_3$ | 23.1 | 135–135.5[c] | $C_{15}H_{30}N_4O_2S$ | 54.51 | 54.70 | 9.15 | 8.99 | 16.95 | 17.09 | 9.70 | 9.55 |

[a] Prepared by Method A. [b] Recrystallized from ethanol. [c] Ethanol-benzene.

results are in accord with kinetic data on the aminolysis of esters with primary and secondary amines provided by Day and collaborators,[5] who attributed these rate differences of amines with similar basicity to a steric effect.[6]

Ammonolysis of 1,3-di(γ-carbomethoxypropyl)urea (Ic) proceeded normally (Table I). Similarly, the reaction of ammonia and methylamine with 1,3-di(ε-carbomethoxypentyl) thiourea gave the corresponding thiourea diamides (Table III), although in lower yields.

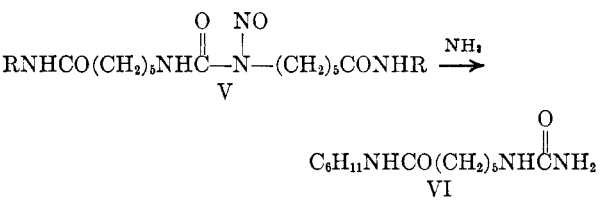
The second method of preparation (B) of amides involved the reaction of ethyl chloroformate and the bistriethylamine salt of 1,3-di(ε-carboxypentyl)-urea (Ib) to give an intermediate mixed dianhydride (III) which on treatment with an amine afforded the diamide (II). This method was first utilized by Boissonnas[7] in peptide syntheses. Primary and secondary amines (cyclohexylamine, di-*n*-butylamine, di-2-ethylhexylamine) which failed to react under aminolysis conditions, all gave excellent yields by this technique.




(5) E. McC. Arnett, J. G. Miller, and A. R. Day, *J. Am. Chem. Soc.*, **72**, 5635 (1950); *J. Am. Chem. Soc.*, **73**, 5393 (1951).

(6) M. S. Newman has proposed an empirical "Rule of Six" to aid in the evaluation of such steric effects. For a complete discussion, see *Steric Effects in Organic Chemistry*, John Wiley and Sons, Inc., New York, N. Y., 1956, Chap. 4.

(7) R. A. Boissonnas, *Helv. Chim. Acta*, **34**, 874 (1951). *Cf.* J. D. Roberts, W. T. Moreland, and W. Frazer, *J. Am. Chem. Soc.*, **75**, 637 (1953); T. Wieland, W. Schafer, and E. Bokelmann, *Ann.*, **573**, 99 (1951).




Investigation of the nitrosation of some of these diamides has revealed that only 1,3-di(ε-*N*-methylcarbamylpentyl)urea (II, $R_1$ = $CH_3$; $R_2$ = H) gave a trinitroso compound, identified as 1-nitroso-1,3-di(ε-*N*-nitroso-*N*-methylcarbamylpentyl)urea (IV). Other diamides (from ethylamine, *n*-propylamine, *n*-butylamine, cyclohexylamine, and benzylamine) afforded 1-nitroso-1,3-di(ε-*N*-alkylcarbamylpentyl)ureas (V) (Table IV), even in the presence of excess nitrous acid. The position of the nitroso group has been established by ammonolysis experiments. The action of ammonia on 1-nitroso-1,3-di(ε-*N*-cyclohexylcarbamylpentyl)urea (V, R = $C_6H_{11}$) gave 1-(ε-*N*-cyclohexylcarbamylpentyl)urea (VI), a cleavage reaction characteristic of nitrosoureas.[2] The identity of this monosubstituted urea (VI) was confirmed by its synthesis from 1-(ε-carboxypentyl)urea and cyclohexylamine by the mixed anhydride method.

## EXPERIMENTAL[8]

*Preparation of amides. Method A.* A solution of 1,3-di(ε-carbomethoxypentyl)urea[2] (5.0 g., 0.0158 mole) in anhydrous methanol (60 ml.) containing a small amount of sodium methoxide (from 0.10 g. of sodium metal) was treated with an amine (15.0 g., 0.06 to 0.38 mole) and allowed to stand at room temperature in a stoppered flask for 48 hr. followed by an equal time interval at 10°. The cooling period increased the yields of diamides which precipitated at room temperature and caused the separation of those from benzylamine and 3-methoxypropylamine. The products were collected, washed, and dried to give the crude yields reported in Table I. The precipitates obtained by this method from *n*-dodecyl-, *n*-hexadecyl-, and *n*-octadecyl-amines proved to be monoamide-monoesters and are reported in Table II. Concentration of the mother liquors gave mixtures from which pure amides were difficult to separate. The diamides from 2-*N*,*N*-dimethylaminoethylamine, 2-*N*,*N*-diethylaminoethylamine, and 3-*N*,*N*-dimethylaminopropylamine failed to precipitate from solution. The solutions were evaporated to dryness *in vacuo* and the products were separated from inorganic material by trituration of the residue with chloroform. These products were very soluble in cold water.

Ammonolysis experiments were performed by saturation

(8) All melting points are uncorrected. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill.

TABLE IV

$$RNHC(CH_2)_5NHCN(CH_2)_5CNHR$$

| R | Yield, % | M.P., °C. (dec.) | Formula | C Calcd. | C Found | H Calcd. | H Found | N Calcd. | N Found |
|---|---|---|---|---|---|---|---|---|---|
| $C_2H_5$ | 86.6 | 116–117[a] | $C_{17}H_{33}N_5O_4$ | 54.95 | 55.30 | 8.95 | 8.97 | 18.85 | 19.11 |
| $n$-$C_3H_7$ | 92.4 | 115–116[b] | $C_{19}H_{37}N_5O_4$ | 57.11 | 56.86 | 9.34 | 9.03 | 17.53 | 17.74 |
| $n$-$C_4H_9$ | 83.7 | 116–117[c] | $C_{21}H_{41}N_5O_4$ | 58.93 | 58.49 | 9.66 | 9.77 | 16.38 | 16.06 |
| Cyclohexyl | 87.5 | 133.5–134[c] | $C_{25}H_{45}N_5O_4$ | 62.61 | 62.88 | 9.46 | 9.32 | 14.61 | 14.91 |
| $C_6H_5CH_2$ | 87.6 | 120–121[c] | $C_{27}H_{37}N_5O_4$ | 65.43 | 65.30 | 7.53 | 7.62 | 14.14 | 14.55 |

[a] Recrystallized from acetone–petroleum ether. [b] Acetone. [c] Acetone-water.

of the methanolic solution with ammonia (76 g. ammonia/l. of methanol). Best yields were obtained by allowing the reaction to proceed at room temperature for 7 days.

The diamides (Table III) from 1,3-di(ε-carbomethoxypentyl)thiourea[2] were prepared in the same manner as described above with the exception that less methanol (2 ml./g. of thiourea diester) was used as solvent.

*Method B.* The preparation of 1,3-di(ε-*N*-cyclohexylcarbamylpentyl)urea demonstrates the general procedure. A solution of 1,3-di(ε-carboxypentyl)urea (2.0 g., 0.0069 mole) in dimethylformamide (40 ml.) was treated with triethylamine (1.40 g., 0.0139 mole) and cooled to 0°. Rapid addition of ethyl chloroformate (1.51 g., 0.0139 mole) caused precipitation of triethylamine hydrochloride. After 10 min. at 0°, the mixture was treated with cyclohexylamine (1.37 g., 0.0139 mole). Within 5 min., a heavy precipitate began to separate. The mixture was diluted with dimethylformamide (20 ml.) and allowed to stand at room temperature overnight. The paste was poured into 300 ml. of water and the precipitate was collected and dried to yield 2.76 g. (88.0%) of diamide, m.p. 214–216°. Recrystallization from ethanol-water (60 ml.) gave pure product (m.p. 215–216°, 84% recovery).

Substitution of di-*n*-butylamine and di-2-ethylhexylamine for cyclohexylamine in the above procedure gave the liquid diamides (Table I). These were isolated by chloroform extraction, after the reaction mixture had been diluted with water, and were purified by rapid distillation. Prolonged contact with heat caused some decomposition to occur.

*Nitrosation experiments.* (*a*) *1-Nitroso-1,3-di(ε-N-nitroso-N-methylcarbamylpentyl)urea* (IV). A solution of 1,3-di)(ε-*N*-methylcarbamylpentyl)urea (II, $R_1 = CH_3$; $R_2 = H$-(0.50 g., 0.0016 mole) in 35% nitric acid (3 ml.) was cooled to 0° and treated with potassium nitrite (0.42 g., 0.049 mole) in water (3 ml.). The yellow oil which separated soon began to crystallize as the mixture was allowed to warm to room temperature. The yellow nitroso compound was collected and dried *in vacuo* over potassium hydroxide pellets to yield 0.34 g. (53.3%), m.p. 58–61°. Recrystallization from ethanol-water (5 ml.) gave pale yellow crystals, m.p. 63–64° dec. (68% recovery).

*Anal.* Calcd. for $C_{15}H_{27}N_7O_6$: C, 44.88, H, 6.78; N, 24.43. Found: C, 45.03; H, 6.51; N, 23.97.

(*b*) *1-Nitroso-1,3-di(ε-N-alkylcarbamylpentyl)ureas* (V) (Table IV). These compounds were all prepared by the same general method, which is described below in the preparation of 1-nitroso-1,3-di(ε-*N*-cyclohexylcarbamylpentyl)urea. To a cold (0°) solution of the diamide (10.0 g., 0.021 mole) in a minimum volume of 80% acetic acid (220 ml.) was added a solution of potassium nitrite (6.82 g., 0.080 mole) in water (12 ml.). After 10 min. at 0–5°, the solution was allowed to stand at room temperature overnight. It was poured into water (1500 ml.) and the resulting precipitate was collected and dried to give the mononitroso diamide, m.p. 133–134° dec. (9.31 g., 87.5%). The product was recrystallized from acetone-water (100 ml.) to yield 8.48 g., m.p. 133.5–134° dec.

Nitrosation of 1,3-di(ε-*N*-cyclohexylcarbamylpentyl)urea by procedure (*a*) with 35% nitric acid as solvent gave the same product (m.p. 132–133° dec.) in 65% yield. A mixture melting point determination of samples of the products from these two procedures gave no depression.

*Ammonolysis of 1-nitroso-1,3-di(ε-N-cyclohexylcarbamylpentyl)urea.* A solution of the nitroso compound (1.0 g., 0.00209 mole) in ethanol (10 ml.) and 28% ammonium hydroxide (5 ml.) was heated on a steam bath for 5 min., in which time, the original pale yellow color was discharged to give a colorless solution. The solution was diluted with water (15 ml.) and cooled to give a small amount (80 mg.) of 1-(ε-*N*-cyclohexylcarbamylpentyl)urea (VI), m.p. 199–200°. The filtrate was evaporated to dryness *in vacuo* and the solid residue was triturated with hot acetone (30 ml.). The insoluble product was collected and dried to give a second crop, m.p. 190.5–193° (490 mg.). Recrystallization of the total crude product from methanol-water (10 ml.) gave 500 mg. (93.9%), m.p. 194–195.5°. Further recrystallization from the same solvent pair raised the melting point of the analytical sample to 199–200°.

*Anal.* Calcd. for $C_{13}H_{25}N_3O_2$: C, 61.14; H, 9.87; N, 16.46. Found: C, 61.11; H, 9.79; N, 16.19.

A comparison sample of 1-(ε-*N*-cyclohexylcarbamylpentyl)urea (VI) was prepared from the corresponding acid. Ethyl chloroformate (0.62 g., 0.0058 mole) was added to a solution of 1-(ε-carboxypentyl)urea[2] (1.00 g., 0.0058 mole), triethylamine (0.58 g., 0.0058 mole), and dimethylformamide (20 ml.) at 0°. After 10 min. at this temperature, cyclohexylamine (0.60 g., 0.0058 mole) was introduced and the reaction was allowed to proceed at room temperature for 3 hr. The mixture was diluted with water (125 ml.) and the precipitate was collected and recrystallized from methanol-water (15 ml.) to yield 1-(ε-*N*-cyclohexylcarbamylpentyl)-urea, m.p. 197–198.5° (0.93 g., 63.4%). Two recrystallizations from methanol-water raised the melting point to 199–200°, yield 0.70 g. This sample of 1-(ε-*N*-cyclohexylcarbamylpentyl)urea on admixture with the above analytical sample did not depress its melting point.

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