# N-(ω-CARBALKOXYALKYL)-UREAS AND THEIR CYCLIC DERIVATIVES

## COMMUNICATION 1

O. Yu. Magidson and I. B. Toperman

UDC 615.761.6

In recent years, ω-amino acids, the first of which is glycine, have been acquiring more and more biological significance. An important biological factor is β-alanine, a constituent of pantothenic acid. It has been found that γ-aminobutyric acid (GABA) also participates in the regulation of the activity of the central nervous system [1] and is finding practical application in therapy. Quite recently, ε-aminocaproic acid has found wide use as an antifibrinolytic agent, which stops and prevents hemorrhage [2].

Considering the fact that amino acids can be readily carbamylated in the organism, being converted to ureido acids [3], we undertook a study of the synthesis and properties of ω-ureido acids and their derivatives, beginning with compounds with a small number of methylene units, for example, ω-ureidopropionic and ω-ureidobutyric acids, where the influence of the ureide group is especially great, and ending with ureides of acids with a chain length of more than 10 $CH_2$-units, where the influence of the ureide group is weakened by the predominant importance of the aliphatic acid residue.

In connection with this, the need also arises for studying the simplest conversion of ω-ureido acids to derivatives of pyrimidine, since under biological conditions ureido acids are converted to dihydropyrimidine acids. Orotic acid [4] is synthesized from α-ureidosuccinic acid in the organism in this way.

Our investigations of ω-ureido acids may open up the way not only to N-substituted oxopyrimidines (uracils, cytosines, etc.), but also to other bases contained in the nucleic acids, such as adenine, guanine, etc., in which the carboxyalkyl residue may be at the nitrogen of the pyrimidine ring, as is the case in natural nucleosides, and consequently, we can count on biological activity of the new synthetic compounds.

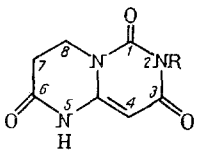
The starting materials in our work were ω-amino acids or their hydrochlorides, which we produced according to the methods described in the literature [6-9]. In most cases the ω-amino acid was converted to the hydrochloride of the methyl or ethyl ester. We used the reaction of hydrochlorides of esters of the α-aminoalkylcarboxylic acid with potassium cyanide to produce the ureido acids or their esters; this reaction proceeds smoothly and gives good yields (Table 1). For 1,3-bis-(ω-carbalkoxyalkyl)ureas, it proved more convenient to use a toluene solution of phosgene. The lower members of the homologous series of methyl esters of ureido acids are characterized by some solubility in water, but the solubility decreases rapidly with increasing length of the aliphatic chain.

Cyanoacetylation of the ureido esters was carried out with cyanoacetic acid and acetic anhydride. In this case we obtained 1-cyanoacetyl-3-(ω-carbalkoxyl)ureas (Table 2) and 1,3-bis-(β-carbomethoxyethyl)-1-cyanoacetylurea. Treatment of these substances with concentrated alkali yielded a series of 1-(N-carboxyalkyl)-6-amino-2,4-dioxotetrahydropyrimidines [1-(ω-carboxyalkyl)-6-aminouracils] (Table 3).

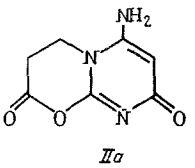
In the case of β-ureidopropionic acid (I) [5], cyclization was conducted by the interaction of cyanoacetic acid with ethyl ether in a methanol solution of sodium methylate. In this case a compound was obtained, the analysis and properties of which did not correspond to the proposed formula of $N_1$-carboxyethyl-6-aminouracil, but exactly corresponded to some sort of anhydrided form of it, i.e., either the lactam (II) or the lactone (IIa) is formed (see following page).

The probability of closing of the lactam ring is substantially greater, which was also confirmed in an investigation of the IR spectrum. The presence of an extremely intense absorption band in the spectrum at 1700 $cm^{-1}$, just like the absence of absorption bands in the interval 1700-1800 $cm^{-1}$, where the characteristic frequencies of the carbonyl group of lactones and esters, including vinyl esters, are usually localized,

S. Ordzhonikidze All-Union Pharmaceutical Chemistry Scientific Research Institute, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, No. 8, pp. 9-13, August, 1967. Original article submitted October 25, 1966.



II - R=H
III - R=$CH_2CH_2COOH$



IIa

is evidence of the presence of lactam structure. Thus, the compound obtained is 1,3,6-trioxo-$\Delta^4$-octahydropyrimido(1,2-c)pyrimidine (II) [cf. 12].

In the cyclization of 1,3-bis($\beta$-carbomethoxyethyl)-1-cyanoacetylurea, instead of the expected 1,3-di($\beta$-carboxyethyl)-6-aminouracil, we obtained a compound, which, on the basis of analogous considerations, should be assigned the structure of 1,3,6-trioxo-2($\beta$-carboxyethyl)$\Delta^4$-octahydropyrimido(1,2-c)-pyrimidine (III). The formation of a lactam structure in this case is also confirmed by the data of the IR spectrum; in particular, the intense absorption band at 1688 $cm^{-1}$ can evidently be assigned to the carbonyl of the unsubstituted lactam group. The absorption band in the region of 1610-1640 $cm^{-1}$ may probably be ascribed to the vibrations of the carbonyl of the substituted lactam groups of the uracil ring, while the absorption band in the region of 1730 $cm^{-1}$ should be assigned to the characteristic frequencies of the carbonyl of the carboxyl group.

TABLE 1. N-($\omega$-Carbalkoxyalkyl)ureas $NH_2CONH(CH_2)_nCOOR$

| n | R | Yield (in %) | Mp (in degrees) | Formula of substance | Found (in %) | | | Calc. (in %) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | C | H | N | C | H | N |
| 3 | $CH_3$ | 78,7 | 106—108 | $C_6H_{12}N_2O_3$ | 45,18 | 7,31 | 17,35 | 44,99 | 7,55 | 17,49 |
| 4 | $CH_3$ | 72,4 | 94—96 | $C_7H_{14}N_2O_3$ | 48,00 | 7,90 | 16,04 | 48,26 | 8,10 | 16,08 |
| 5 | $C_2H_5$ | 86,6 | 75—76 | $C_8H_{16}N_2O_3$ | 53,58 | 8,90 | 13,80 | 53,45 | 8,97 | 13,85 |
| 6 | $CH_3$ | 85,1 | 97—98 | $C_8H_{16}N_2O_3$ | 53,33 | 9,00 | 14,08 | 53,45 | 8,97 | 13,85 |
| 10 | $CH_3$ | 94,2 | 113—114 | $C_{13}H_{26}N_2O_3$ | 60,40 | 10,00 | 10,71 | 60,43 | 10,14 | 10,84 |

TABLE 2. 1-($\omega$-Carboxyalkyl)-6-aminouracils
$CNCH_2CONH - CO - NH(CH_2)_nCOOR$

| n | R | Yield (in %) | Mp (in degrees) | Formula of substance | Found (in %) | | | Calc. (in %) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | C | H | N | C | H | N |
| 3 | $CH_3$ | 65,4 | 137—138 | $C_9H_{13}N_3O_4$ | 47,54 | 5,88 | 18,74 | 47,57 | 5,76 | 18,49 |
| 4 | $CH_3$ | 90,5 | 122—123 | $C_{10}H_{15}N_3O_4$ | 49,56 | 6,21 | 17,01 | 49,79 | 6,27 | 17,42 |
| 5 | $C_2H_5$ | 90,7 | 106—107 | $C_{12}H_{19}N_3O_4$ | 53,70 | 7,04 | 15,58 | 53,52 | 7,11 | 15,60 |
| 6 | $CH_3$ | 81,4 | 123—124 | $C_{12}H_{19}N_3O_4$ | — | — | 15,53 | — | — | 15,60 |
| 10 | $CH_3$ | 82,1 | 118—119 | $C_{16}H_{27}N_3O_4$ | 59,33 | 8,26 | 12,92 | 59,06 | 8,33 | 12,91 |

TABLE 3. 1-($\omega$-Carboxyalkyl)-6-aminouracils

| n | Yield (in %) | Mp (in degrees) | Found (in %) | | | Calc. (in %) | | | Formula of substance | $\lambda_{max}$ (in m$\mu$) ($E_{(max)}$) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | C | H | N | C | H | N | | |
| 3 | 87,2 | 252—254 | 44,78 | 4,96 | 19,76 | 45,09 | 5,20 | 19,72 | $C_8H_{11}N_3O_4$ | 269 (23 700)[1]<br>268 (17 500)[2] |
| 4 | 85,4 | 241—242 | 47,40 | 5,50 | 18,03 | 47,57 | 5,77 | 18,49 | $C_9H_{13}N_3O_4$ | |
| 5 | 85,1 | 236—237 | 49,90 | 6,11 | 17,29 | 49,79 | 76,27 | 17,42 | $C_{10}H_{15}N_3O_4$ | 268 (15 600)[2] |

[1] In alcohol solution.
[2] In 0.1 N NaOH solution.

In the presence of acetic anhydride, substituted 1,3-bis-(ω-carbomethoxyalkyl)ureas are capable of condensing with malonic acid, forming the corresponding 1,3-di(ω-carbomethoxyalkyl)-barbituric acids [13].

## EXPERIMENTAL SECTION

Hydrochloride of the Methyl Ester of ω-Aminoenanthic Acid. Dry HCl was passed for 12 h at 5° through a suspension of 86 g $NH_2(CH_2)_6COOH$ in 400 ml methanol. After the methanol was distilled off, the dry residue was recrystallized from acetone. Yield of the hydrochloride of the methyl ester of ω-aminoenanthic acid quantitative, mp 119-121°. Found, %: N 7.07, 7.12; Cl 18.59, 18.66. $C_8H_{18}ClNO_2$. Calculated, %: N 7.15; Cl 18.12.

N-(ω-carbalkoxyalkyl)ureas with the general formula $NH_2CONH \cdot CH_2COOR$ are synthesized by the reaction of hydrochlorides of esters of ω-aminoalkylcarboxylic acids with the general formula $HCl\ NH_2(CH_2)_nCOOR$ with KOCN, which was preliminarily purified according to Erdmann's method [14]. In the case of n=3, an aqueous solution of equivalent amounts of $HCl \cdot NH_2 \cdot (CH_2)_3COOCH_3$ and KOCN was evaporated to dryness on a water bath, after which $NH_2CONH(CH_2)_3COOCH_3$ was extracted from the reaction mixture with hot absolute alcohol. In all the remaining cases, an aqueous solution of an equivalent amount of KOCN was added to an aqueous solution of the hydrochloride of the amino ester, the mixture was mixed at 70-80° from 20 min to 1 h, and cooled. The urea precipitated was removed, and after drying under vacuum the product was recrystallized from alcohol (n=3, 10) or from water (n=4, 5, 6).

All the N-(ω-carboxyalkyl)ureas form colorless prismatic needles; at room temperature they are poorly soluble in the usual organic solvents.

1,3-Bis(γ-carbomethoxypropyl)urea, mp 111-112° (water), was synthesized according to the method of Gränacher and Landolt [15]. Colorless needles. Found, %: C 50.96; H 7.88; N 10.70. $C_{11}H_{20}N_2O_5$. Calculated, %: C 50.75; H 7.74; N 10.76.

1,3-Bis-(β-carbomethoxyethyl)-1-cyanoacetylurea. Portions of 6.96 g (0.03 mole) 1,3-bis(β-carbomethoxyethyl)-urea [10] and 2.55 g (0.03 mole) cyanoacetic acid were dissolved in 10 ml of acetic anhydride at 30-40°, mixed for 5 h at 60-70°, the acetic anhydride and acetic acid distilled off under vacuum at 60-70°, the residue washed with cold water and dried under vacuum. Yield 5.6 g (62.4%); the substance forms colorless prisms with mp 92-93° (methanol). Found, %: C 48.23; H 6.00; N 14.31. $C_{12}H_{17}N_3O_6$. Calculated, %: C 48.21; H 5.73; N 14.04.

1-(ω-Carbalkoxyalkyl)-3-cyanoacetylureas were synthesized according to the procedure cited above. They crystallize from methanol in the form of colorless prismatic needles, insoluble in water and the usual organic solvents at room temperature.

1-(1-Carboxyalkyl)-6-aminouracils were produced in the following way. The corresponding 1-(ω-carbalkoxyalkyl)-3-cyanoacetylurea was dissolved in three equivalents of a 25-40% sodium hydroxide solution. Dissolution, as a rule, was accompanied by an appreciable thermal effect. When the solution was acidified with concentrated hydrochloric acid to pH 1.0-2.0, 1-(ω-carboxyalkyl)-6-aminouracil was isolated, washed with distilled water, and dried under vacuum.

1,3-Bis-(β-carbomethoxyethyl)-1-cyanoacetylurea, after dissolving in three equivalents of a 30% NaOH solution, and acidification to pH 1.0-2.0, formed 1,3,6-trioxo-2-(β-carboxyethyl)-$\Delta^4$-octahydropyrimido-(1,2-c)-pyrimidine (III), yield 86.2%, mp 264-265°. Found, %: C 47.32; H 4.44; N 16.65. $C_{10}H_{11}N_3O_5$. Calculated, %: C 47.43; H 4.38; N 16.59.

UV spectrum: $\lambda_{max}$ (in alcohol) 279 mμ (E 19,500); $\lambda_{max}$ (in 0.1 N NaOH solution) 233, 274, 300 mμ (E 9450, 12,300, 23,250).

All the uracils obtained were purified by repeated recrystallization from water. They give a bright rose color with $NaNO_2$ solution in acid medium (formation of an isonitroso-derivative in the 5-position).

1,3,6-Trioxo-$\Delta^4$-octahydropyrimido-(1,2-c)-pyrimidine (II). To a solution of $CH_3ONa$ in methanol (from 5.75 g, 0.25 g-atom of Na and 100 ml of methanol) we added 13.2 g (0.1 mole) I and 11.3 g (0.1 mole) cyanoacetic ester. The suspension was boiled for 3 h with good mixing, condensed under vacuum to half the original volume, cooled with ice water, and 70 ml of cold water added to the residue. The homogeneous solution was acidified to pH 1.0-2.0 with dilute hydrochloric acid; after a day, the precipitate formed was filtered off, washed with cold water, and dried. After recrystallization from a large amount of water, II

was obtained in the form of colorless prisms, insoluble in the usual organic solvents. Yield 4.9 g (24.6%), mp >330° (dec.). Found, %: C 46.34; H 3.80; N 23.11. $C_7H_7N_3O_3$. Calculated, %: C 46.41; H 3.89; N 23.19.

UV spectrum: $\lambda_{max}$ (in 0.1 N NaOH solution) 269, 296 mμ (E 15,900, 10,800).

1,3-Di-(β-carbomethoxyethyl)-barbituric Acid. Portions of 9.3 g 1,3-bis(β-carbomethoxyethyl)urea and 4.6 g malonic acid were dissolved in 15 ml glacial $CH_3COOH$ at 30-40°. To the solution obtained, 25 ml of acetic anhydride was added drop-wise over a period of 30-40 min. The mixture was mixed at 55-60° for 8 h. The acetic anhydride and $CH_3COOH$ were distilled off under vacuum at 55-60°, the residue recrystallized from 15 ml of ethanol, washed with a 50% solution of ethanol, and dried under vacuum. Yield of 1,3-di-(β-carbomethoxyethyl)-barbituric acid 7.6 g (63.3%), mp 74-75° (alcohol). Found, %: C 47.67; H 5.20; N 9.30. $C_{12}H_{16}N_2O$. Calculated, %: C 48.00; H 5.37; N 9.33. UV spectrum: $\lambda_{max}$ 223, 261 mμ (E 4,400, 14,000).

## LITERATURE CITED


1. E. Muriel et al., J. Med. Pharm. Chem., 4, 31 (1961).
2. C. E. Grossi, L M. Rousselot, and W. F. Panke, J. A. M. A., 187, 1005 (1964).
3. J. Liberman and A. Kornberg, J. Biol. Chem., 207, 911 (1954).
4. C. Cooper, R. Wu, and D. W. Wilson, Ibid., 216, 37 (1955).
5. A. Lengfeld and C. Stieglitz, Am. Chem. J., 15, 516 (1893).
6. J Tafel and M. Stern, Ber. Dtsch. Chem., Ges., 33, 2224 (1900).
7. R. M. Joyce, W. E. Hanford, and J. J. Harmon, J. Am. Chem. Soc., 70, 2529 (1948); N. S Vul'fson and V. I. Zaretskii, Zh. Obshch. Khim., 28, 1911 (1958); A. N. Nesmeyanov et al., Chem. Techn , 9, 139 (1957); L. E. Schiepp and C. S. Marvel, J. Am. Chem. Soc., 57, 1557; D. L. Garmaise, R. Schwartz, and F. A. McKay, Ibid., 80, 3332 (1958).
8. C. S. Marvel et al., Ibid., 68, 1681 (1946).
9. Great Britain Patent 658758, October 10, 1951; Great Britain Patent 591027, August 5, 1947.
10. K. Schlögl, Mhft. Chem., 89, 61 (1959).
11. J. H. Speer and A. L. Raymond, J. Am. Chem. Soc., 75, 114 (1953); F. F. Blicke and H. C. Godt, Ibid., 76, 2798 (1954); V. Papesch and E. Schroeder, J. Org. Chem., 16, 1879 (1951)
12. R. B. Angier and W. V. Curren, Ibid., 26, 1891 (1961); F. Ueda and J. J. Fox, Ibid., 29, 1762, 1770 (1964).
13. H. Biltz and H. Wittek, Ber. Dtsch. Chem. Ges., 54, 1036 (1921).
14. H. Erdmann, Ibid., 26, 2442 (1893).
15. Ch. Gränacher and H. Landolt, Helv. Chim. Acta, 10, 806 (1927).