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SYNTHESIS OF N^2-GUANYLCARBOXYLIC ACIDS

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A novel method has been developed for synthesizing N^2-guanylcarboxylic acids by reaction of 2-chloro-7-benzyl-hypoxanthine with amino acids and debenzylation of the 7-benzyl-N^2-guanylcarboxylic acid products by means of palladium catalyzed hydrogenation.

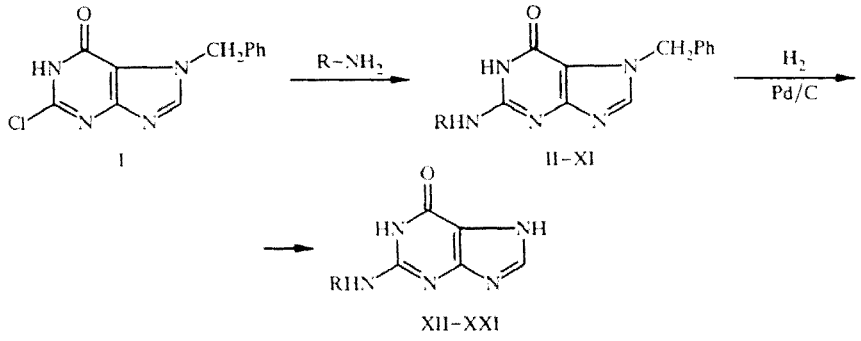
Amino acids containing a guanine residue at the amino group are interesting for biological investigation because compounds of this series are contained in naturally derived products. Hence N^2-(1-carboxyethyl)guanine was separated as the riboside from the *Fusarium* species [1-4]. The authors propose that this amino acid plays a part in the biosynthesis of flavine and pteridine.

The synthesis of this amino acid [1, 2, 5] and a series of other N^2-guanylcarboxylic acids [1, 2] has been reported using 2-chlorohypoxanthine and the sodium salts of amino acids at 125°C. Parameters and analyses were not reported for the amino acids obtained. The drawbacks of this method for preparing guanylcarboxylic acids are the multistage synthesis of 2-chlorohypoxanthine, the low yields (40-50%), and the complex chromatographic purification of the compounds.

It should also be mentioned that amino acid esters do not react with 2-chlorohypoxanthine when heated at 130-150°C [6].

Having available a simple preparative method for 2-chloro-7-benzylhypoxanthine (I) [7, 8] as an intermediate in the synthesis of hypoxanthine [7], guanine [8], and its N^2-alkyl analogs [9], we investigated the reaction of this compound with amino acids. The latter were α-, β-, γ, and ω-amino acids and included the dibasic sparagine and glutamine.

As for 2-chlorohypoxanthine, the indicated reaction occurs only at increased temperature, i.e., heating I with the potassium salts of the amino acids in aqueous solution at 120-140°C for 18-24 h. As a result, a series of previously unreported 7-benzyl-N^2-guanylcarboxylic acids (II-XI, Table 1) has been prepared in 70-98% yields.



II, XII R = $HOOCCH_2$; III R = $HOOCCHCH_3$; IV, XIV R = $HOOCC(CH_3)_2$;
VI, XVI R = $HOOCCHCH_2Ph$; VII, XVII R = $HOOC(CH_2)_2$; VIII, XVIII R = $HOOC(CH_2)_3$;
IX, XIX R = $HOOC(CH_2)_5$; X, XX R = $HOOCCH_2CHCOOH$; XI, XXI R = $HOOC(CH_2)_2CHCOOH$

As is the case for other 7-benzyl purine [7-9], the benzyl group of II-XI is readily removed by catalytic hydrogenation in the presence of a palladium catalyst on carbon. The yield of the N^2-guanylcarboxylic acids (XII-XXI, Table 1) was 60-90%.

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TABLE 1. Yields and Parameters for II-XXI

Compound	Empirical formula	Mp, °C (with decomp.)	Yield, %
II	$C_{14}H_{13}N_5O_3 \cdot 1/2\ H_2O$	342...344	95
III	$C_{15}H_{15}N_5O_3$	215...217	73
IV	$C_{16}H_{17}N_5O_3 \cdot H_2O$	163...164	71
V	$C_{17}H_{19}N_5O_3 \cdot 1/4H_2O$	163...165	88
VI	$C_{21}H_{19}N_5O_3$	147...149	72
VII	$C_{15}H_{15}N_5O_3$	258...260	70
VIII	$C_{16}H_{17}N_5O_3 \cdot H_2O$	234...235	96
IX	$C_{18}H_{21}N_5O_3 \cdot H_2O$	193...194	98
X	$C_{16}H_{15}N_5O_5 \cdot H_2O$	187...188	78
XI	$C_{17}H_{17}N_5O_5$	181...182	70
XII	$C_7H_7N_5O_3 \cdot H_2O$	> 330	90
XIII	$C_8H_9N_5O_3 \cdot 1/2\ H_2O$	242...244	70
XIV	$C_9H_{11}N_5O_3 \cdot 1/2\ H_2O$	253...254	68
XV	$C_{10}H_{13}N_5O_3 \cdot 1/2\ H_2O$	202...203	60
XVI	$C_{14}H_{13}N_5O_3$	257...258	60
XVII	$C_8H_9N_5O_3 \cdot 1/4\ H_2O$	> 300	85
XVIII	$C_9H_{11}N_5O_3$	> 350	76
XIX	$C_{11}H_{15}N_5O_3$	284...285	72
XX	$C_9H_9N_5O_5$	260...261	83
XXI	$C_{10}H_{11}N_5O_5$	195...197	61

TABLE 2. Microanalytical Results for II-XI

Compound	Empirical formula	Found, %			Found, %		
		C	H	N	C	H	N
II	$C_{14}H_{13}N_5O_3 \cdot 1/2\ H_2O$ [a]	54,81	4,60	22,61	54,54	4,58	22,72
III	$C_{15}H_{15}N_5O_3$	57,26	5,10	21,66	57,50	4,83	22,35
IV	$C_{16}H_{17}N_5O_3 \cdot H_2O$ [b]	55,81	5,88	20,50	55,65	5,55	20,28
V	$C_{17}H_{19}N_5O_3 \cdot 1/4H_2O$ [c]	58,89	5,81	20,45	59,04	5,68	20,25
VI	$C_{21}H_{19}N_5O_3$	64,45	4,95	18,00	64,77	4,95	17,98
VII	$C_{15}H_{15}N_5O_3$	57,90	4,89	21,96	57,50	4,83	22,35
VIII	$C_{16}H_{17}N_5O_3 \cdot H_2O_3$ [d]	55,73	5,66	20,49	55,65	5,55	20,28
IX	$C_{18}H_{21}N_5O_3 \cdot H_2O_3$ [e]	58,25	6,26	18,85	57,90	6,21	18,75
X	$C_{16}H_{15}N_5O_5 \cdot H_2O_3$ [f]	51,01	4,67	18,72	51,20	4,57	18,66
XI	$C_{17}H_{17}N_5O_5$	54,71	4,82	19,01	54,98	4,61	18,86

a) H_2O, Found, %: 3.07. Calculated, % 2.92.
b) H_2O, Found, %: 4.98. Calculated, % 5.22.
c) H_2O, Found, %: 1.53. Calculated, % 1.30.
d) H_2O, Found, %: 5.37. Calculated, % 5.22.
e) H_2O, Found, %: 4.69. Calculated, % 4.82.
f) H_2O, Found, %: 4.97. Calculated, % 4.80.

The purities of II-XXI were confirmed by TLC, and their structure by IR spectroscopy and from elemental analytical data (Tables 2 and 3).

EXPERIMENTAL

IR spectra of II-XXI were recorded on a UR-10 instrument for Vaseline oils. TLC was carried out on Silufol UV-254 plates with iodine visualization.

TABLE 3. Microanalytical Results for XII-XXI

Compound	Empirical formula	Found, %			Found, %		
		C	H	N	C	H	N
XII	$C_7H_7N_5O_3 \cdot H_2O$[a]	37.27	4.36	30.51	37.01	3.99	30.82
XIII	$C_8H_9N_5O_3 \cdot 1/2\ H_2O$[b]	42.26	4.48	30.51	42.20	4.21	30.76
XIV	$C_9H_{11}N_5O_3 \cdot 1/2\ H_2O$[c]	43.94	5.29	28.73	43.90	4.91	28.47
XV	$C_{10}H_{13}N_5O_3 \cdot 1/2\ H_2O$[d]	46.22	5.80	26.75	46.15	5.42	26.91
XVI	$C_{14}H_{13}N_5O_3$	56.26	4.85	23.33	56.18	4.38	23.40
XVII	$C_8H_9N_5O_3 \cdot 1/4\ H_2O$[e]	42.19	4.58	30.73	42.20	4.21	30.76
XVIII	$C_9H_{11}N_5O_3$	45.26	4.85	29.48	45.57	4.67	29.52
XIX	$C_{11}H_{15}N_5O_3$	49.93	5.90	26.43	49.81	5.69	26.40
XX	$C_9H_9N_5O_5$	40.31	3.61	26.28	40.46	3.39	26.21
XXI	$C_{10}H_{11}N_5O_5$	42.64	3.83	24.81	42.71	3.94	24.90

a) H_2O, Found, %: 7.60. Calculated, % 7.93.
b) H_2O, Found, %: 1.83. Calculated, % 1.98.
c) H_2O, Found, %: 3.28. Calculated, % 3.66.
d) H_2O, Found, %: 3.18. Calculated, % 3.46.
e) H_2O, Found, %: 1.72. Calculated, % 1.98.

Elemental analytical data for C, H, and N in II-XXI agreed with that calculated (Tables 2, 3). The melting points of high melting compounds were measured on a PTP (m) TU-92-89-1011-90 instrument.

All α-amino acids except L-glutamine were used as the racemate.

2-Chloro-7-benzylguanine (I) was prepared as in [7, 8].

7-Benzyl-N^2-guanylcarboxylic Acids (II-XI, Tables 1, 2). A stainless steel autoclave of capacity 100 ml was filled with 40 ml of a solution prepared by careful mixing of the amino acid (41 mmole) and potassium carbonate (24 mmole) in water (in the case of the dibasic amino acids, potassium carbonate was used in twice the amount). Compound I (20 mmole) was added and the mixture was heated for 24 h at 120-130°C or 18 h at 135-140°C (for III, V, and VII) with agitation of the autoclave. After cooling, the autoclave was emptied (care, foaming) and the solution transferred to a beaker, neutalized with hydrochloric acid to pH 4-5, and the separated precipitate of the guanylamino acids II-XI filtered, washed with water and acetone, and dried. II-XI are colorless, crystalline materials, soluble in hydrochloric and aqueous base solutions, difficultly soluble in the cold in the majority of organic solvents, and insoluble in water. For analysis, they were purified by crystallization from 20-40% aqueous DMF (II, VI, VII, X, XI) or 25-50% ethanol (III-V, VIII, IX).

N^2-Guanylcarboxylic Acids (XII-XXI, Tables 1, 3). A mixture of II-XI (5 mmole), an equal amount by weight of palladium on carbon (5%), and HCl (36%, 1 ml) in water (20-25 ml) was hydrogenated at 85-90°C and stirred until absorption of hydrogen ceased (3-5 h). HCl (1 N, 10 ml) was added to the product and it was heated to boiling, filtered, and the catalyst washed with hot water (6-7 ml). The combined filtrates were neutralized with aqueous ammonia to pH 4-5 and the precipitate was filtered and washed with water and acetone to give amino acids XII-XV and XVII-XXI. For preparation of amino acid XVI the reaction mixture at the end of hydrogenation of VI was basified with sodium hydroxide and the solution heated and filtered. The filtrate was neutralized with hydrochloric acid to pH 4-5.

For analysis, compounds were purified by reprecipitation with aqueous ammonia from hydrochloric acid solution (XII, XIV, XVI, XVII), crystallization from water (XIII, XV, XX, XXI), or from aqueous DMF (XVIII, XIX).

Compounds XII-XXI are colorless, high melting, crystalline materials, difficultly soluble in cold water and the majority of organic solvents. A number of the products (see Table 3) crystallized with 0.25-1.0 moles of water.

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