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SYNTHESIS OF N^2-ALKYL(ARYL, DIALKYL, CYCLOALKYL)GUANINES

P. M. Kochergin, L. V. Persanova, E. V. Aleksandrova, L. A. Gutorov,* and V. S. Korsunskii*

Novel N^2-alkyl(aryl, dialkyl, cycloalkyl)guanines have been synthesized by treating 2-chloro-7-benzylhypoxanthine with amines and debenzylation of the N^2-substituted 7-benzylguanine products by means of palladium catalyzed hydrogenation.

N^2-Alkyl(dialkyl, aryl, cycloalkyl) substituted guanines are used in the synthesis of biologically active materials, including N^2-substituted thioguanines [1-4], guanine analogs of kinetin [5-8], and guanylhistamine [9]. The simplest members of this series (N^2-methyl- and N^2-dimethylguanines) are separated from naturally derived products, e.g., human urea [10, 11] and nucleic acid hydrolysates [12, 13].

Synthetic methods are known for preparing N^2-substituted guanines from pyrimidines and purines. Hence, 2-methyl(dimethyl)guanine has been synthesized from the corresponding 2-substituted 4,5-diaminopyrimidines and formamide [14, 15]. Besides being a multistage process, this method can lead to undesired results in the final stage. It has been reported [16] that heating 2,4,5-triamino-6-hydroxypyrimidine with formamide gave not guanine but other products whose structure has not been established. In similar conditions, 2-methylamino-4,5-diamino-pyrimidine gave 2-aminopurine and not the expected 2-methylamino-purine [17]. More reliable is the method of synthesis of N^2-guanines from purines by the nucleophilic substitution of 2-methylmercaptohypoxanthines [1-3, 5, 6] or 2-chlorohypoxanthines [8, 9, 18] with amines at 130-160°C. The reaction of 2-chloro-hypoxanthine with histamine occurs in refluxing butanol [9] but low basicity amines (e.g., 4-nitroaniline) do not react with 2-chlorohypoxanthine [8].

Drawbacks of the indicated method for synthesizing N^2-substituted guanines are the multistage process for preparing the starting materials and the inconvenience of working with methyl mercaptan.

There are reports of the preparation of certain N^2-alkyl-guanines from guanosine [19] and guanine [20], but these methods do not have preparative potential due to the complexity of the reaction and the low compound yields.

In the course of our work [21] we have studied the nucleophilic substitution of the available 2-chloro-7-benzyl-hypoxanthine (I) [21, 22] with primary and secondary aliphatic, aromatic, and alicyclic amines, including p-aminobenzene-sulfonamide. Sulfanilamide derivatives of 2,6- and 8-aminopurines are known [23] but not reported for guanines and 7-substituted analogs.

Replacement of the chlorine atom by the amine residue occurs at high temperature (140-185°C). Water, alcohol, or DMF can be used as solvent. For high boiling amines the process can be performed by heating in an excess of the same solvent or in DMF. As HCl acceptor, an excess of the same amine can be used (minimum 1 mole) or potassium carbonate in the case of sulfanilic acid. The yield of the N^2-substituted 7-benzylguanines II-XIII was 63-86%.

Reaction of I with p-aminobenzenesulfonamide can occur at the N^1 or N^4 nitrogen atoms of the starting sulfonamide. Refluxing the components in DMF gives the N^2-p-sulfonamido-phenyl-7-benzylguanine (VII). Under the same conditions, the use of the sulfonamide potassium salt gives N^2-sulfanylamido-7-benzylguanine (VIII).

*Deceased.

Center for the Chemistry of Medicinal Compounds. All Russian Chemico-Pharmaceutical Science Research Institute, Moscow 119815. State Institute for Blood Substitutes and Medicinal Preparations, Moscow 109044. Zaporozh'e State Medicinal Institute, Zaporozhe'e 330074. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 391-394, March, 1996. Original article submitted January 6, 1996.

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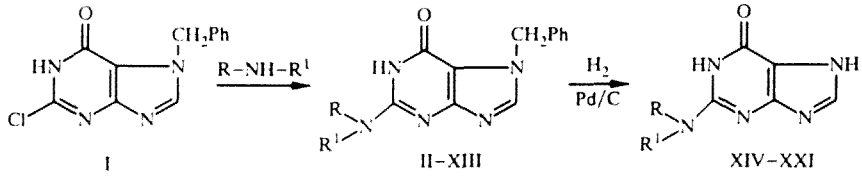
The reaction of I with hydrazines occurs similarly. Hence, heating I with phenylhydrazines at 170-180°C gives 2-phenyl-hydrazino-7-benzylhypoxanthine (XIII).

To prepare N^2-substituted guanines we looked at the debenzylation of most of the N^2-substituted 7-benzylguanines (II, III, V, VII, IX-XII). Hydrogenolysis of the N^7-benzyl group occurs readily at 85-90°C under hydrogen at atmospheric pressure with palladium catalyst on carbon. The yield of N^2-substituted guanines XIV-XXI was 60-95%.



I II–XIII XIV–XXI

VI—VIII, XIII—XVII R^1 = H; IX, XVIII R^1 = CH_3; II, IX, XIV, XVIII R = CH_3 ;
III, XV R = CH_2CH_2OH; IV R = $(CH_3)_2NCH_2CH_2$; V, XVI R = C_6H_5;
VI R = $C_6H_4SO_3H$-*p*; VII, XVII R = $C_6H_4SO_2NH_2$-*p*; VIII R = $SO_2C_6H_4NH_2$-*p* ;
XIII R = C_6H_5NH; X, XIX R, R^1 = $(CH_2)_5$; XI, XX R, R^1 = $(CH_2)_6$;
XII, XXI R, R^1 = $O(CH_2CH_2)_2$

The structure of II-XXI was confirmed from elemental analytical data and from IR spectroscopy which identified the stretching bands of the CO and NH groups.

The given method of synthesizing N^2-substituted guanines also has preparative potential [24]. It differs advantageously from other methods reported in the literature both in the availability of starting materials and in the yield of final products.

EXPERIMENTAL

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

Elemental analytical data for II-V, IX-XIII, XV, and XX (for C, H, and N) and VI, VII, VIII, and XVII (C, H, N, and S) agreed with those calculated. Melting points of high melting compounds were measured on a PTP (m) TU-92-89-1011-90 instrument.

2-Chloro-7-benzylhypoxanthine (I) was obtained as [21, 22].

N^2-Methyl-7-benzylguanine (II, $C_{13}H_{13}N_5O$). A mixture of I (4 g) in aqueous methylamine solution (25%, 20 ml) was heated in an autoclave for 5 h at 140-150°C and the product evaporated to small volume and cooled. The precipitate was separated and washed with water and acetone to give II (2.8 g, 71%) with mp 299-301°C (decomp.). The pure sample has mp 305-306°C (decomp., from 60% acetic acid).

N^2-β-Hydroxyethyl-7-benzylguanine (III, $C_{14}H_{15}N_5O_2$). A mixture of I (4.45 g) and aminoethanol (25 ml) was refluxed for 4 h, cooled, poured into water (125 ml), neutralized with HCl to pH 6, and the precipitate was filtered, washed with water, acetone and ether to give III (3.85 g, 86%) with mp 248-251°C (decomp.). For analysis of III, recrystallization from DMF gave mp 255-257°C (decomp.).

N^2-β-Dimethylaminoethyl-7-benzylguanine (IV, $C_{18}H_{24}N_6O$). A mixture of I (5 g) and dimethylaminoethylamine (25 ml) was refluxed for 4 h, cooled, poured into water (125 ml), neutralized with HCl to pH 6, and the precipitate filtered, washed with water, acetone, and ether to give IV (4.02 g, 67%) with mp 218-220°C (decomp., from ethanol).

N^2-Phenyl-7-benzylguanine (V, $C_{18}H_{15}N_5O$). A mixture of I (11 g) and aniline (60 ml) was refluxed for 1 h 40 min and cooled. Ether was added and the precipitate was filtered, washed with water, acetone, and ether to give V (11.7 g, 88%) with mp 319-322°C (decomp.). A pure sample has mp 324-325°C (decomp., from acetic acid).

N^2-p-Sulfophenyl-7-benzylguanine (VI, $C_{18}H_{14}N_5SO_4$). A mixture of I (5.2 g, 0.02 mole), sulfanilic acid (8.6 g, 0.04 mole) and potassium carbonate (3.3 g, 24 mmole) in water (30 ml) was heated for 24 h in an autoclave at 175-180°C. After cooling, the precipitate was filtered, transferred to a beaker, washed with dilute HCl, and the precipitate was filtered and washed with water and acetone to give VI in a mixture with sulfanilic acid (TLC data). For removal of the latter the precipitate was dissolved by heating in aqueous ammonia (15%, 170 ml), stirring with carbon, filtering, and cooling to 5-10°C. The ammonium salt of acid VI precipitate was separated and washed with acetone to give VI (4.1 g, mp 279-283°C). The filtrate was acidified and the precipitated acid VI filtered and purified as described above to give an additional 1 g of ammonium salt

TABLE 1. Elemental Analysis for II-XX

Compound	Empirical formula	Found, %				Calculated, %			
		C	H	N	S	C	H	N	S
II	$C_{13}H_{13}N_5O$	61.08	5.63	27.48		61.17	5.13	27.43	
III	$C_{14}H_{15}N_5O_2$	59.54	5.41	24.44		58.94	5.30	24.55	
IV	$C_{18}H_{24}N_6O$	63.20	7.18	24.55		63.51	7.10	24.68	
V	$C_{18}H_{15}N_5O$	68.16	5.09	21.87		68.13	4.76	22.07	
VI	$C_{18}H_{14}N_5SO_4$	54.64	4.02	17.20	8.04	54.40	3.80	17.62	8.07
VII	$C_{18}H_{16}N_6SO_3$	55.08	4.24	21.49	7.43	54.54	4.07	21.20	8.09
VIII	$C_{18}H_{16}N_6SO_3$	54.95	4.01	21.14	7.65	54.54	4.07	21.20	8.09
IX	$C_{14}H_{15}N_5O$	62.42	5.96	26.25		62.44	5.61	26.01	
X	$C_{17}H_{19}N_5O$	66.06	6.28	22.46		66.00	6.19	22.04	
XI	$C_{18}H_{21}N_5O$	67.27	6.88	21.38		66.85	6.55	21.65	
XII	$C_{16}H_{17}N_5O_2$	61.62	5.79	22.15		61.72	5.50	22.49	
XIII	$C_{18}H_{16}N_6O$	64.65	5.24	25.15		65.04	4.85	25.28	
XV	$C_7H_9N_5O_2 \cdot 1/2\ H_2O$*	41.37	4.84	34.89		41.09	4.91	34.32	
XVII	$C_{11}H_{10}N_6SO_3$	43.10	3.51	27.56	10.80	43.13	3.29	27.44	10.47
XX	$C_{11}H_{15}N_5O \cdot 1/4\ H_2O$†	55.41	6.79	28.92		55.56	6.57	29.45	

*Found, %: H_2O 4.65. Calculated, %: H_2O 4.41.

†Found, %: H_2O 1.95. Calculated, %: H_2O 1.89.

of VI. The precipitates were combined, dissolved by heating in water, and acidified using HCl to pH 6. The precipitate was filtered and washed with water and acetone to give acid VI (5 g, 63%) with mp above 300°C.

N^2-p-Sulfonamidophenyl-7-benzylguanine (VII, $C_{18}H_{16}N_6SO_3$). A mixture of I (2.6 g, 0.01 mole) and p-aminobenzenesulfonamide (5.2 g, 0.03 mole) in DMF (20 ml) was refluxed for 3 h, carbon was added, and the hot solution was filtered, poured into water (100 ml), and the precipitate filtered washed with water and acetone to give VII (3.4 g, 85%) with mp 277-280°C (decomp.,). Mp of purified sample 304-306° (decomp., from DMF).

N^2-Sulfanilamido-7-benzylguanine (VIII, $C_{18}H_{16}N_6SO_3$). A mixture of p-aminobenzenesulfonamide (10.3 g, 0.06 mole) and anhydrous potash (8.3 g, 0.06 mole) in DMF (30 ml) was refluxed for 30 min. I (7.8 g, 0.03 mole) was added to the obtained potassium salt of the sulfonamide and the mixture was refluxed for 3 h, cooled, poured into water (100 ml), and carbon added. The solution was stirred, filtered, acidified with 1 N HCl to pH 6, and the precipitate filtered, washed with water, acetone, and ether to give VIII (8.6 g, 72%) with mp 248-250°C (decomp.). Mp of pure sample 258-260°C (decomp., from 60% aqueous DMF).

N^2-Dimethyl-7-benzylguanine (IX, $C_{14}H_{15}N_5O$) was obtained similarly to II in 80% yield with mp 277-280°C (decomp., from acetic acid).

N^2-Pentamethylene-7-benzylguanine (X, $C_{17}H_{19}N_5O$). A mixture of I (10 g) and piperidine (50 ml) was refluxed for 1 h and treated as described above for III to give product (10.2 g, 85%) with mp 246-248°C (decomp., from EtOH).

N^2-Hexamethylene-7-benzylguanine (XI, $C_{18}H_{21}N_5O$). A mixture of I (20 g) and hexamethylenimine (100 ml) was refluxed for 2 h, cooled, and the precipitate filtered, washed with acetone, water, and again acetone to give product (20.3 g, 82%) with mp 253-255°C (decomp., from EtOH).

N-Morpholino-7-benzylhypoxanthine (XII, $C_{16}H_{17}N_5O_2$) was obtained similarly to XI in 83% yield with mp 295-297°C (decomp., from EtOH).

N^2-Phenylhydrazino-7-benzylhypoxanthine (XIII, $C_{18}H_{16}N_6O$) was obtained similarly to III in 44% yield with mp 265-268°C (decomp., from DMF).

N^2-Methylguanine (XIV). A mixture of II (2 g), 5% palladium catalyst on carbon (2 g), concentrated HCl (2 ml), and water (40 ml) was hydrogenated at 85-90°C and atmospheric pressure until absorption of hydrogen ceased. The hot product was filtered and the catalyst precipitate heated with HCl (1 N, 20 ml) to boiling, filtered, and the precipitate washed on the filter with hot water. The combined filtrates were neutralized with aqueous ammonia, and the separated precipitate was filtered and washed with water and acetone to give product (0.94 g 73%) with mp above 360°C (decomp.). According to [15], the melting point is above 300°C.

N^2-β-Hydroxyethylguanine (XV, $C_7H_9N_5O_2$) was obtained similarly to XIV. The yield was 95% and the mp 285-287°C (from water). It crystallized with $^1/_2$ molecule of water.

N^2-Phenylguanine (XVI) was obtained similarly to XIV with the difference that, at the completion of hydrogenation of amine V, the product was poured into HCl (1 N, 150 ml), heated to reflux, filtered, and the base HCl of XVI precipitated on cooling the filtrate. For separation of the base the product was heated to dissolve the precipitate, neutralized with aqueous ammonia, and the precipitate was washed with water and acetone to give product (92%) with mp 227-229°C (decomp.). In [1], compound XVI is reported as the hydrochloride. In patent [3], the mp of the XVI base is not given.

N^2-p-Sulfonamidophenylguanine (XVII, $C_{11}H_{10}N_6SO_3$) was obtained similarly to amine XIV in 71% yield with mp above 350°C (decomp., from DMF).

N^2-Dimethylguanine (XVIII) was obtained by hydrogenation of IX similarly to amine XIV with the difference that, at the end of the reaction, the hot product was filtered from catalyst and the filtrate neutralized with aqueous ammonia to give product (72%) with mp above 360°C (decomp.). According to [15] mp is above 300°C.

N^2-Pentamethyleneguanine (XIX) was obtained similarly to XVIII in 79% yield with mp above 360°C (decomp.). In the patent [3], parameters for XIX are not given.

N^2-Hexamethyleneguanine (XX, $C_{11}H_{15}N_5O$) was obtained similarly to XVI in 60% yield with mp above 360°C (decomp., precipitated from HCl solution using aqueous ammonia). The product crystallized with $^1/_4$ molecule of water.

N^2-Morpholinohypoxanthine (XXI) was obtained similarly to XVIII in 77% yield with mp 328-330°C (decomp.). According to [8], mp is 325-326°.

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