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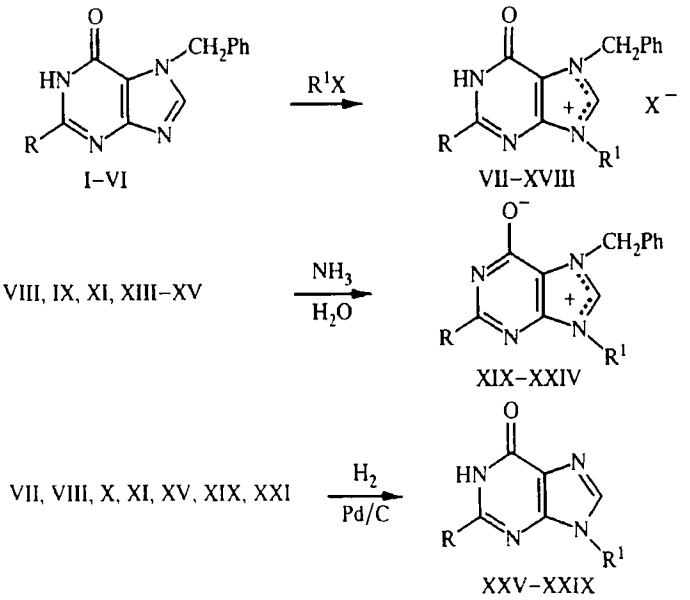
NEW SYNTHESIS OF 9-ALKYLGUANINES AND THEIR N^2-SUBSTITUTED DERIVATIVES

P. M. Kochergin, L. V. Persanova, and E. V. Aleksandrova

A new method of synthesizing 9-alkyl guanines and their N^2-substituted derivatives from 7-benzylguanine and its N^2-substituted derivatives has been developed by quaternization with alkyl halides, dialkyl sulfates, or arenesulfonic acid esters, and subsequent removal of the benzyl protection by hydrogenation of the intermediate quaternary salts or of the betaines obtained from them.

The majority of the known methods of obtaining 9-substituted guanines from guanine [1], including acyclic analogs of guanosine [2, 3], possess the significant drawback of forming a mixture of 7- and 9-isomers, the separation of which requires complex preparative chromatography.

With the aim of searching for a method of obtaining 9-alkylguanines and their N^2-substituted derivatives avoiding the formation of 7-alkylguanines, we have extended the studies of [4, 5] and have investigated the quaternization reaction of 7-benzylguanine and of some of its derivatives substituted by nitrogen at position 2 (II-VI).



I, VII, VIII, XIX, XXV, XXVI R = NH_2; II, IX, X, XX, XXVII R = NHPh; III, XI—XIII, XXI, XXII, XXVIII R = NMe_2; IV, XIV, XXIII R = $N(CH_2)_5$; V, XV, XVI, XXIV, XXIX R = $N(CH_2)_7$; VI, XVII, XVIII R = $N(CH_2CH_2)_2O$.

VII, IX, XI, XIV, XV, XVII, XX, XXI, XXIII—XXV, XXVIII, XXIX R^1 = Me; VIII, X, XIX, XXVI, XXVII R^1 = Et; XII, XIII, XVI, XVIII R^1 = CH_2COOMe; XXII R^1 = CH_2CONH_2.

VII, IX, XIV, XV, XVII X = *p*-$MeC_6H_4SO_3$; VIII, X X = $PhSO_3$; XI, XIII, XVI, XVIII X = ClO_4; XII X = Br. R^1X = $R^1Br(I)$, $(R^1)_2SO_4$, $ArSO_3R^1$

Center for Drug Chemistry, All-Russian Scientific Research Institute for Pharmaceutical Chemistry, Moscow 119815. State Institute for Blood Substitutes and Medicinal Preparations, Moscow 109044, Russia. Zaporozhe State Medical Institute, Zaporozhe 330074, Ukraine. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 542-546, April, 1998. Original article submitted June 28, 1997.

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TABLE 1. Data of Elemental Analysis and Yields of Quaternary Salts (VII)-(XVIII)

Compound	Empirical formula	Found, % / Calculated, %					mp, °C (with decomposition)	Yield, %
		C	H	N	S	Hal		
VII	$C_{20}H_{21}N_5O_4$	56,64 / 56,19	5,16 / 4,95	16,39 / 16,38	7,37 / 7,50		272...273	89
VIII	$C_{20}H_{21}N_5O_4$	56,37 / 56,19	4,94 / 4,95	16,53 / 16,38	7,49 / 7,50		265...267	90
IX	$C_{26}H_{25}N_5O_4$	62,69 / 62,01	5,35 / 5,00	14,05 / 13,91	6,0 / 6,37		257...259	89
X	$C_{26}H_{25}N_5O_4$	62,11 / 62,01	5,08 / 5,00	13,71 / 13,91	6,41 / 6,37		258...261	98
XI	$C_{15}H_{18}ClN_5O_5$	47,11 / 46,94	4,67 / 4,73	18,29 / 18,25		9,35 / 9,24	225...227	80...84
XII	$C_{17}H_{20}BrN_5O_3$	48,52 / 48,35	5,18 / 4,77	16,69 / 16,58		18,80 / 18,92	174...176	14
XIII	$C_{16}H_{20}ClN_5O_7$	46,34 / 46,21	4,65 / 4,56	15,77 / 15,85		8,32 / 8,02	176...178	67
XIV	$C_{25}H_{29}N_5O_4$	60,41 / 60,59	5,72 / 5,89	13,84 / 14,13	6,55 / 6,47		139...141	92
XV	$C_{26}H_{31}N_5O_4$	60,64 / 61,28	6,02 / 6,13	13,64 / 13,74	6,20 / 6,29		122...124	92
XVI	$C_{21}H_{26}ClN_5O_7$	51,13 / 50,86	5,37 / 5,28	14,31 / 14,12		6,98 / 7,15	108...110	64
XVII	$C_{24}H_{27}N_5O_5$	57,37 / 57,04	5,92 / 5,47	14,02 / 14,08	6,36 / 6,44		182...183	88
XVIII	$C_{19}H_{22}ClN_5O_8$	47,04 / 47,16	4,99 / 4,58	14,42 / 14,47		7,38 / 7,33	118...120	37

Alkyl halides and esters of halocarboxylic acids, dialkyl sulfates, and esters of arenesulfonic acids were used as alkylating agents.

It was established that quaternization of 7-benzylguanines (I)-(VI) at position 9 of the purine ring occurred readily in organic solvents (such as DMF). In certain cases the reaction also proceeds without solvent (in an excess of arenesulfonic acid ester). A series of 9-alkyl (or alkoxycarbonylalkyl)-7-benzylguanine quaternary salts (VII)-(XVIII) was obtained.

Quaternary salts of certain purine bases, particularly halides and mesylates, are readily soluble in water, the lower alcohols, and in DMF. Consequently we used the exchange reaction with sodium perchlorate to isolate such compounds [the less soluble perchlorates (XI), (XIII), (XVI), and (XVIII) were obtained by this method].

Treatment of the quaternary salts (VIII), (IX), (XI), and (XIII)-(XV) with ammonia in aqueous solution in the cold gave the corresponding zwitter-ionic compounds, viz., 2-amino(arylamino, dialkylamino, cycloalkylamino)-6-hydroxy-7-benzyl-9-alkyl(carbamoylmethyl)purinium betaines (XIX)-(XXIV). These are synthetic analogs of the naturally occurring betaine 2-amino-6-hydroxy-7,9-dimethylpurinium betaine (herbipoline) [6, 7]. On reacting perchlorate (XIII) with aqueous ammonia replacement of the ester group by amide occurs as a result of which the betaine (XXII) is formed.

Certain betaines (XX) and (XXI) were moderately soluble in water, consequently the direct yields of these compounds (without evaporating the mother liquors) were only 40-50%.

Fission of the benzyl protection is the final step in the synthesis of 9-alkylguanines. This was achieved by hydrogenation of the quaternary salts or betaines in the presence of palladium catalyst. The reaction was carried out using the quaternary salts (VII), (VIII), (X), (XI), and (XV), and betaines (XIX) and (XXI) as examples. As a result the 9-alkylguanines and their N^2-substituted derivatives (XXV)-(XXIX) were obtained.

The homogeneity of compounds (XXV)-(XXIX) was confirmed by TLC, and their composition and structure by data of IR spectra, elemental analysis and also by the identity of 9-methyl- and N^2-dimethyl-9-methylguanines (XXV), (XXVIII) obtained by us with authentic known specimens of these compounds [8].

EXPERIMENTAL

The IR spectra of compounds were taken on a Perkin-Elmer model 682 instrument as suspensions in Nujol or in KBr disks. The purity of compounds was determined by TLC on Silufol UV-254 plates, visualizing with iodine vapor or in UV

TABLE 2. Data of Elemental Analysis and Yields of Purinium Betaines (XIX)-(XXIV) and 9-Alkylpurines (XXV)-(XXIX)

Compound	Empirical formula	Found, % / Calculated, %				mp, °C (with decomposition)	Yield, %
		C	H	N	H_2O		
XIX	$C_{14}H_{15}N_5O \cdot 1/2H_2O$	60,85 / 60,42	6,21 / 5,79	24,84 / 25,16	3,49 / 3,24	249...251	87
XX	$C_{19}H_{17}N_5O$	68,49 / 68,95	5,62 / 5,51	20,85 / 21,15		266...269	40
XXI	$C_{15}H_{17}N_5O \cdot H_2O$	60,38 / 59,79	6,67 / 6,35	23,03 / 23,24	6,20 / 6,00	197...199	55
XXII	$C_{16}H_{18}N_6O_2$	59,30 / 58,89	5,80 / 5,56	25,48 / 25,75		281...283	92
XXIII	$C_{18}H_{21}N_5O$			21,15 / 21,70		254...256	91
XXIV	$C_{19}H_{23}N_5O \cdot 1/2H_2O$	65,42 / 65,87	7,21 / 6,98	20,41 / 20,21	3,15 / 2,67	140...142	93
XXV	$C_6H_9N_5O$			42,31 / 42,47		>350*	61
XXVI	$C_7H_9N_5O$	46,34 / 46,92	5,04 / 5,06	39,16 / 39,09		>350†	53...70
XXVII	$C_{13}H_{13}N_5O \cdot 1/4H_2O$	60,34 / 60,10	5,08 / 5,24	27,01 / 26,96	1,96 / 1,74	>360	76
XXVIII	$C_8H_{11}N_5O$	49,59 / 49,73	5,91 / 5,74	35,84 / 36,25		331...333‡	62...70
XXIX	$C_{12}H_{17}N_5O$	57,97 / 58,28	7,14 / 6,93	28,00 / 28,32		304...305	50

*According to [8], mp >350°C; according to [9], mp >300°C.

†From [9], the mp of this compound was not determined.

‡From [8], mp 331-333°C.

light. The melting points of the high melting compounds were determined on a PTP (M) instrument, technical specification 92-89-1011-90.

The initial 7-benzyl substituted guanine (I), N^2-phenylguanine (II), N^2-dimethylguanine (III), 2-piperidinohypoxanthine (IV), 2-(1-azacyclo-1-octyl)hypoxanthine (V), and 2-morpholinohypoxanthine (VI) were obtained by the method suggested in [4, 5].

2-Amino-7-benzyl-9-methyl-6-oxo-1,6-dihydropurinium Tosylate (VII). A mixture of compound (I) (7.0 g, 29 mmole) and methyl tosylate (21.0 g, 113 mmole) was stirred for 2 h at 135-145°C (in a bath), cooled, the precipitate was washed with ether (5 × 20 ml), then with acetone, and dried. The yield of compound (VII) was 11.0 g (89%), of mp 240-261°C.

Tosylates (IX), (XIV), (XV), and (XVII), and benzenesulfates (VIII) and (X) were obtained analogously. Compounds (XIV) and (XV) were obtained similarly with the only difference that the reaction mixtures were heated at 75-80°C.

7-Benzyl-2-dimethylamino-9-methyl-6-oxo-1,6-dihydropurinium Perchlorate (XI). A. A mixture of compound (II) (0.7 g, 2.6 mmole) and dimethyl sulfate (1.9 g, 15 mmole) in DMF (7 ml) was stirred at 80-90°C for 5 h. The solution was poured into water (35 ml), warmed with carbon, and filtered. An excess of aqueous 12% sodium perchlorate was added to the filtrate, the solid compound (XI) which precipitated was filtered off, washed with water, with alcohol, and dried. Yield was 0.8 g (80%), mp 223-225°C.

B. A mixture of compound (II) (0.7 g, 2.6 mmole) and methyl iodide (1.07 g, 7.5 mmole) in DMF (7 ml) was heated at 85-95°C (in a bath) for 6 h, then treated as described in experiment A. The yield of compound (XI) was 0.84 g (84%), mp 220-224°C. A mixing test with the substance obtained by method A gave no depression of melting point.

7-Benzyl-2-dimethylamino-9-methoxycarbonylmethyl-6-oxo-1,6-dihydropurinium Bromide (XII) and Perchlorate (XIII). A mixture of compound (II) (3.7 g, 13.75 mmole) and methyl bromoacetate (6.4 g, 41.5 mmole) in anhydrous DMF (20 ml) was stirred at 85-90°C for 5 h. The solution was cooled, the solid bromide (XII) was filtered off, washed with acetone, and dried. Yield was 0.8 g (14%), mp 168-170°C. An aqueous 12% solution (190 ml) of sodium perchlorate was added to the filtrate, the precipitated solid perchlorate (XIII) was filtered off, washed with water, and dried. Yield was 4.1 g (67%), mp 165-171°C.

The perchlorates (XVI) and (XVIII) were prepared analogously from compounds (V) and (VI) without isolating the intermediate bromides.

The quaternary salts (VII)-(XVIII) were colorless or cream crystalline substances, soluble in water, the lower alcohols, and DMF. Compounds were purified for analysis by crystallization from ethanol (VII), (VIII), aqueous ethanol (XIV), (XVII), methanol (IX), (X), isopropanol (XII), and water (XI), (XIII), (XV), (XVI), and (XVIII).

9-Alkyl(carbamoylmethyl)-2-amino(arylamino, dialkylamino, cycloalkylamino)-7-benzyl-6-hydroxypyridinium Betaines (XIX)-(XXIV). The quaternary salt (VIII), (IX), (XI), (XIII)-(XV) (2-3 g) was added to 12-25% aqueous ammonia solution (20-30 ml) with stirring. A precipitate separated shortly after. The reaction mixture was stored for 1-2 h, the solid filtered off, washed with water, and dried. Betaines (XIX)-(XXIV) were obtained as colorless crystalline substances, soluble in water, and in aqueous solutions of mineral acids, DMF, the lower alcohols, and in water (on heating). Compounds were purified for analysis by crystallization from water (XIX), (XXI), (XXII), a 1:1 mixture of water–DMF (XX), and 50% aqueous methanol (XXIII), (XXIV).

9-Ethylguanine (XXVI). A. A mixture of quaternary salt (VIII) (2.0 g, 4.7 mmole) and 10% palladium on carbon (2.0 g) in ethanol (70 ml) was hydrogenated at atmospheric pressure and 75-80°C (in a bath) until cessation of hydrogen absorption. The reaction mixture was then heated to boiling, filtered, and the catalyst washed with hot ethanol. The combined filtrates were neutralized with aqueous ammonia to a weakly alkaline reaction, cooled, the precipitated solid compound (XXVI) was filtered off, washed with ethanol, with water, with acetone, and dried. The yield of compound (XXVI) was 0.45 g (53%), mp >350°C (from DMF).

Compounds (XXV), (XXVIII), and (XXIX) were obtained analogously from quaternary salts (VII), (XI), and (XV).

Compounds were purified for analysis by crystallization from DMF (XXV), water (XXVIII), and 30% aqueous ethanol (XXIX). The IR spectrum of base (XXV) coincided with the IR spectrum of an authentic sample [8]. There was no depression of the melting points of samples.

B. A mixture of betaine (XIX) (0.67 g, 2.4 mmole) and 10% palladium on carbon (1.0 g) in water (15 ml) was hydrogenated at 25°C and treated as described in experiment A. The yield of compound (XXVI) was 0.3 g (70%), mp >350°C. The IR spectra of the samples of compounds (XXVI) obtained by methods A and B coincided.

Compound (XXVIII) was obtained analogously in 70% yield from betaine (XXI) and gave no depression of melting point with samples of this substance obtained by method A (62% yield) or by the method of [8]. The IR spectra of all three samples coincided.

9-Ethyl-N^2-phenyguanine (XXVII). A mixture of quaternary salt (X) (2.0 g, 4 mmole) and 10% palladium on carbon (1.0 g) in ethanol (50 ml) was hydrogenated at 75-80°C until cessation of hydrogen uptake. A 1 N NaOH solution (50 ml) was added, the mixture heated to boiling, filtered, and the catalyst washed with hot water. The combined filtrates were cooled, neutralized with 1 N HCl, the precipitated solid was filtered off, washed with water, with acetone, and dried. Yield was 0.8 g (76%), mp >350°C (with decomposition, from a mixture of DMF–water, 9:1).

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