Chemistry of Heterocyclic Compounds, Vol. 31, No. 5, 1995

SYNTHESIS OF N-(ω-TRIMETHYLSILYLALKYL)PURINES UNDER CONDITIONS OF INTERFACIAL CATALYSIS

É. Alksnis, M. Lidak, and É. Kyjevits

A method of synthesis of N-(ω-trimethylsilylalkyl)purines, by alkylation of potassium salts of purine bases by 3-chloropropyltrimethylsilane and chloromethyltrimethylsilanes under conditions of interfacial catalysis, has been developed. Hydroxylation of the N-allyl group by dimethylphenylsilane, which is an alternative pathway of synthesis of silicon-containing purine derivatives, has been accomplished for the first time in the purine series. The structure of the compounds obtained was established by methods of PMR and UV spectroscopy.

Continuing investigations of the N-alkylation of purine bases [1-3], we carried out the alkylation of potassium salts of theophylline (I), theobromine (II), adenine (III), 6-benzyladenine (IV), and 2-amino-6-methylmercaptopurine (V) by 3-chloropropyltrimethylsilane and that of 6-benzyladenine (IV) by chloromethyltrimethylsilane.

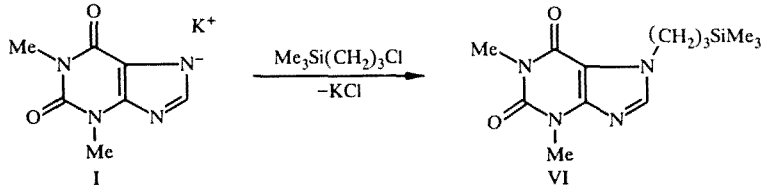
The interest in silicon-containing purine derivatives is due to the increased lipophilicity of the trimethylsilylalkyl group, the presence of which may promote transport of the compound through biological membranes and binding to the lipophilic portion of the active site of the enzyme to be inhibited.

Alkylation of potassium salts of purine bases (I-IV) by 3-chloropropyltrimethylsilane proceeds smoothly and regioselectively under conditions of interfacial catalysis (IFC) without a solvent (160°C, catalyst crown ether 18-K-6); 7-(3-trimethylsilylpropyl)theophylline (VI), 1-(3-trimethylsilylpropyl)theobromine (VII), 9-(3-trimethylsilylpropyl)adenine (VIII), and 6-benzyl-9-(3-trimethylsilylpropyl)adenine (IX) are formed, respectively, with yields of 42-79%.

Alkylation of the potassium salt of 6-benzyladenine (IV) by chloromethyltrimethylsilane, as well as alkylation of the potassium salt of 2-amino-6-methylthiopurine (V) by 3-chloropropyltrimethylsilane, proceeds at 80°C, using an equimolar amount of the catalyst triethylbenzylammonium chloride in the first case of IFC (5 h, yield of 6-benzyl-9-(trimethylsilylmethyl)adenine (XI) 82%), and 0.1 equivalent of the catalyst Aliquat 336 in the second (2 h, yield of 2-amino-6-methylthio-9-(3-trimethylsilylpropyl)purine (X) 68%). The direction of alkylation of the purine bases (I-V) corresponded on the whole to the literature data [4]. In the case of alkylation of potassium salts of adenine (III) and 2-amino-6-methylmercaptopurine (V), other alkylation products were present in the reaction mixtures in small amounts (data of thin-layer chromatography) but were not isolated.

Hydrolysis of a derivative of 2-amino-6-methylmercaptopurine (X) with 3 N hydrochloric acid was used to synthesize 9-(3-trimethylsilylpropyl)guanidine (XII).

As an alternative pathway for the synthesis of silicon-containing purine derivatives we tested the hydroxylation of the N-allyl group. The object of investigation was N^6,N^6-diethyl-9-allyladenine (XIV), which we synthesized with a yield of 51% from N^6,N^6-diethyladenine (XIII) and allyl bromide under IFC conditions.



I VI

Latvian Institute of Organic Synthesis, Riga LV-1006. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 654-658, May, 1995. Original article submitted October 25, 1994.

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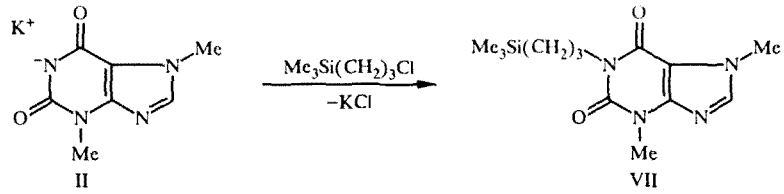
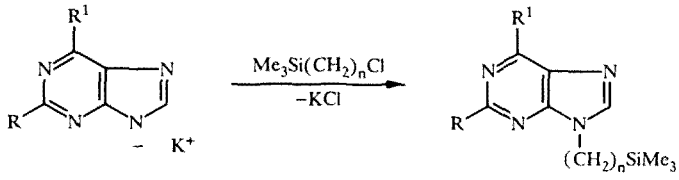
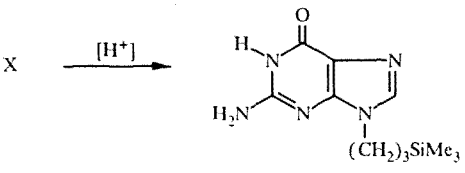


II VII



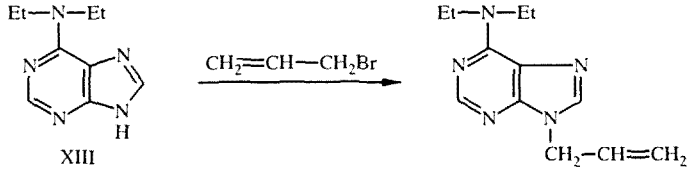
III–V VIII–XI



XII

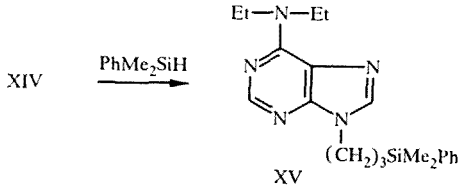
III R = H, R^1 = NH_2; IV R = H, R^1 = $HNCH_2Ph$; V R = NH_2, R^1 = SCH_3;
VIII R = H, R^1 = NH_2, n = 3; IX R = H, R^1 = $HNCH_2Ph$, n = 3; X R = NH_2, R^1 = SCH_3, n = 3;
XI R = H, R^1 = $HNCH_2Ph$, n = 1

Hydroxylation of the adenine derivative XIV with a 10% excess of dimethylphenylsilane proceeds to an extent of 90% in 2 h at 150°C in the presence of 0.01 equivalent of $(Bu_4N)_2PtCl_6$ (thin-layer chromatography, system A).



XIII XIV

The reaction product N^6,N^6-diethyl-9-(3-phenyldimethylsilylpropyl)adenine (XV), could not be obtained in analytically pure form. The signals of the allyl group at 4.62 (m, 2H), 4.87-5.20 (m, 2H), 5.64-6.13 ppm (m, 1H) are absent in the PMR spectrum of compound XV in $CDCl_3$, and the signals of three methylene groups at 0.73 (m, 2H), 1.82 (m, 2H), and 3.93 (overlaps with the N^6—CH_2 signals), as well as the protons of the phenyldimethylsilane group at 0.33 (m, 6H) and 7.27 ppm (m, 5H), are observed. The structure of the purine derivatives synthesized (VI-XII, XIV) was confirmed by a comparison of their NMR and UV spectra (Tables 1 and 2) with the literature data [1-3].



XV

EXPERIMENTAL

The ^1H NMR spectra were recorded on a Bruker WH-90 spectrometer; the chemical shifts were measured relative to an internal standard TMS. The UV spectra were taken on a Specord spectrophotometer. Analytical thin-layer chromatography was conducted on Silufol UV-254 plates in the systems chloroform—ethyl acetate, 1:1 (A), chloroform—ethanol, 9:1 (B), and chloroform—ethanol, 3:1 (C) (volume ratios); column chromatography was conducted on a column (2 × 30 cm) with Silasorb 600 (LC) silica gel, 30 μ in the same systems.

General Method of Alkylation of Purine Bases (I-V) by 3-Chloropropyltrimethylsilane. A suspension containing 10mmolesof purine (I-V), 0.62 g (11 mmoles) finely pulverized KOH, 10 ml of benzene, and 0.264 g (1 mmole) 18-K-6 was

TABLE 1. Physicochemical Characteristics of Purine Derivatives (VI-XII, XIV)

Compound	Gross formula	mp, °C	Molecular weight	UV spectrum, λ_{max}, nm	Found, %			Calculated, %		
					C	H	N	C	H	N
VI	$C_{13}H_{22}N_4O_2Si$	100...101	294,5	272	53,21	7,70	18,96	52,97	7,55	19,03
VII	$C_{13}H_{22}N_4O_2Si$	88...89	294,5	276	53,12	7,69	18,99	52,97	7,55	19,03
VIII	$C_{11}H_{19}N_5Si$	186...187	249,5	263	53,21	7,90	28,51	52,96	7,69	28,08
IX	$C_{18}H_{25}N_5Si$	97...98	339,4	273	63,96	7,55	20,72	63,70	7,36	20,62
X	$C_{12}H_{21}N_5SSi$	154...155	295,5	248, 313	48.94	7,15	23,68	48,72	7,18	23,70
XI	$C_{16}H_{21}N_5Si$	98...99	311,3	273	61,53	6,84	22,52	61,69	6,81	22,47
XII	$C_{11}H_{19}N_5OSi \cdot 0{,}75\ H_2O$	*	279,7	256 (268)	47,17	7,31	24,97	47,31	7,34	25,08
XIV	$C_{12}H_{17}N_5$	Oil	231,3	280	62,40	7,44	30,14	62,31	7,41	30,28

*Does not melt at temperatures below 250°C.

TABLE 2. PMR Spectra of Purine Derivatives (VI-XII, XIV) in DMSO-D_6

Compound	$SiMe_3$	$SiCH_2$	CH_2	$N_{(9)}CH_2$	Purine ring	Other protons
VI	0,04 (s)	0,47 (m)	1,80 (m)	4,18 (t)	8,04 (s)	3,22 (s, 3H, NCH_3), 3,42 (s, 3H, NCH_3)
VII	0,05 (s)	0,53 (m)	1,58 (m)	3,82 (t)	8,00 (s)	3,42 (s, 3H, NCH_3), 3,89 (s, 3H, NCH_3)
VIII*	0,04 (s)	0,53 (m)	1,96 (m)	4,22 (t)	7,80 (s), 8,38 (s)	5,78 (br. s, 2H, NH_2)
IX	0,06 (s)	0,53 (m)	1,80 (m)	4,11 (t)	8,18 (m, 3H, NH)	4,75 (br. s, 2H, N^6CH_2), 7,27 (m, 5H, Ph)
X	0,04 (s)	0,47 (m)	1,78 (m)	4,02 (t)	7,96 (s)	2,60 (s, 3H, SCH_3), 6,44 (s, 2H, NH_2)
XI*	0,04 (s)	—	—	3,64 (s)	7,48 (s), 8,33 (s)	4,76 (d, 2H, N^6CH_2), 6,00 (br. s, 1H, NH), 7,24(m, 5H, Ph)
XII	0,04 (s)	0,49 (m)	1,73 (m)	3,91 (t)	7,69 (s), 10,62 (s)	6,42 (s, 2H, NH_2)
XIV*	—	—	—	4,62 (m)	7,55 (s), 8,18 (c)	1,13 (t, 6H, CH_3), 3,84 (q, 4H, CH_2), 4,87...5,20 (m, 2H, $=CH_2$), 5,64...6,13 (m, 1H, CH)

*The spectrum was taken in $CDCl_3$.

TABLE 3. Results of the Synthesis of Purine Derivatives VI-XII, XIV

Compound	Alkylating agent	Reaction product	Solvents for crystallization	R_f	System	Yield, %
I	Q	VI	Hexane	0,56	A	79
II	Q	VII	Ether/hexane	0,51	A	51
III	Q	VIII	Ether	0,45	B	42
IV	Q	IX	Ether	0,29	A	65
IV	W	XI	Hexane	0,25	A	82
V	Q	X	Ether	0,62	A	68
X	—	XII	Ether	0,45	C	91
XIII	Z	XIV	Oil	0,59	C	51

*Q) 3-Chloropropyltrimethylsilane; W) chloromethyltrimethylsilane; Z) allyl bromide.

heated with mixing for 1 h at 80°C. Then 5 ml of 3-chloropropyltrimethylsilane was added, the temperature was raised to 160°C, benzene was distilled off, and heating was continued at 160°C (80°C for compound V) for 2 h (see Table 3). The reaction mixture was precipitated, diluted with chloroform, and filtered. The filtrate was evaporated; the reaction products (VI-X) were purified by chromatography on silica gel and crystallized (Tables 1 and 3).

Synthesis of 6-Benzyl-9-(trimethylsilylmethyl)adenine (XI). A suspension containing 2.25 g (10 mmole) 6-benzyladenine (IV), 0.62 G (11 mmoles) finely pulverized KOH, 10 ml of benzene, and 0.4 g (1 mmole) trioctylmethylammonium chloride was heated, with mixing, for 1 h at 80°C. Then 2.09 g (9 mmoles) of triethylbenzylammonium chloride and 1.84 g (15 mmoles) of chloromethyltrimethylsilane were added. Heating and mixing were continued for 5 h. The reaction mixture was cooled, diluted with 10 ml of water, and extracted twice with chloroform. The combined extracts were dried over Na_2SO_4, evaporated, and chromatographed in system A. Yield 2.5 g (82%). The physicochemical characteristics of compound XI are presented in Tables 1 and 2.

9-(3-Trimethylsilylpropyl)guanine (XII). We dissolved 0.89 g (3 mmoles) of 2-amino-6-methylthio-9-(3-trimethylsilylpropyl)purine (X) in a mixture of 1 ml of glacial acetic acid and 3 ml of 3 N hydrochloric acid, placed in a 5 ml hermetic Pierce vessel, and heated for 4 h at 100°C. The reaction mixture was cooled, neutralized with a concentrated ammonia

solution, filtered, washed with water and with acetonitrile, and dried. Yield 0.71 g (85%) of analytically pure 9-(3-trimethylsilylpropyl)guanine XII. The physicochemical properties of compound XII are presented in Tables 1 and 2.

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