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SYNTHESIS OF N^6-SUBSTITUTED ADENINES FROM 3-METHYLXANTHINE

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A series of 6-arylalkyl(hetarylalkyl, cycloalkyl, carboxyalkyl)amino-7-benzyl-2-chloropurines have been synthesized from 3-methylxanthine via the reaction of the intermediate 7-benzyl-2,6-dichloropurine with amines and aminoacids. N^6-benzyladenine, N^6-(α-furfuryl)adenine (kinetin), and N-(purinyl)glycine have been obtained via the catalytic hydrogenation of 7-benzyl-6-benzyl(furfuryl, carboxymethyl)amino-2-chloropurines.

Keywords: benzyladenine, dichlorobenzylpurine, substituted adenines, kinetin, methylxanthine.

Methods for the preparation of N^6-substituted derivatives of adenine starting from adenine, 6-chloropurine, and 6-methylmercaptopurine have been reviewed in a monograph [1]. N^6-Benzyladenine has also been synthesized from 2,6,8-trichloropurine [2] and 2,6-dichloropurine [3]. Some N^6-substituted adenines, N^6-α-furfurylaminopurine (kinetin) and N^6-benzyladenine in particular, have high activity and are of practical interest in plant growing [4-8]. A preparative method for adenine, hypoxanthine, guanine, its N^2- and N^9-derivatives, purine, and the pharmaceutical etadene has been developed from the readily available 3-methylxanthine (an industrial by-product derived from caffeine and theobromine) *via* the intermediate 7-benzyl-2,6-dichloropurine (**1**).

It seemed of interest to synthesize some N^6-substituted adenines according to modified scheme. With this in mind, the reaction of the dichloropurine **1** with primary and secondary amines, and α-, β-, and ω-amino acids has been studied, using KOH and NaOH as acceptor for the HCl displaced by the nucleophilic substitution of the chlorine atom by the amino group.

When 2 moles of amine were used per mole of compound **1** in boiling *n*-butanol substitution of two chlorine atoms occurred. 7-Benzyl-2,6-di(benzylamino)purine (**2**) was obtained in this way. However at the lower temperature in boiling acetonitrile and with equimolar amounts of compound **1** and amines or amino acids the more reactive chlorine atom at position 6 of the purine bicycle was substituted to give the corresponding N^6-amino-substituted 7-benzyl-2-chloropurines (**3-12**) in high yields (70-91%).

The previously undescribed monochloro compounds **3-12** open new possibilities for the synthesis of various 2,6-di- and 2,6,7-trisubstituted purines, and by catalytic dechlorination with simultaneous debenzylation they permit the synthesis of N^6-substituted adenines, including cytokinins and purinyl-6-amino acids. For example, N^6-benzyladenine, N^6-α-furfuryladenine (kinetin), and N-(purinyl-6)glycine (**13-15**) were obtained by hydrogenation of 7-benzyl-6-benzyl(furfuryl, carboxymethyl)amino-2-chloropurines (**3**, **4**, **8**) in ethanol at 70-75°C in atmospheric pressure of hydrogen in the presence of palladium on charcoal. Under these conditions, hydrogenation of di(benzylamino) compound **3** led to the elimination of the benzyl group (as toluene) attached to the nitrogen atom at position 7, while the benzyl group on the nitrogen atom at position 6 was unaffected.

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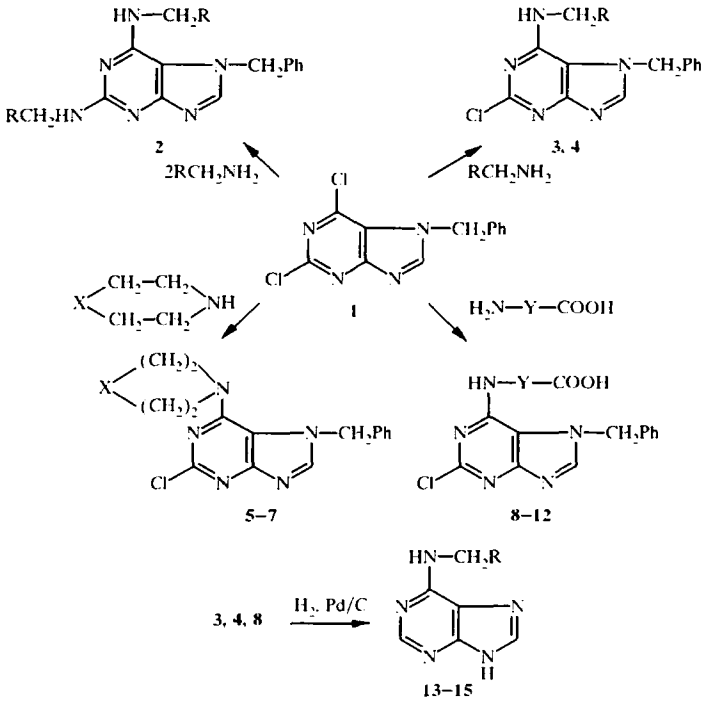

2, 3, 13 R = Ph; 4, 14 R = α-furfuryl; 15 R = COOH; 5 X = CH_2; 6 X = $-CH_2CH_2-$; 7 X = O; 8 Y = CH_2; 9 Y = CHMe; 10 Y = $CH(CHMe_2)_2$; 11 Y = $(CH_2)_5$; 12 Y = $(CH_2)_8$

Purity of the compounds prepared was confirmed by TLC, and their structures – by elemental analysis, conversion into compounds **13-15** (described in the literature), and IR spectra, which contained stretching vibrations of the functional groups (NH, CO).

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %				mp, °C (dec.)	Yield, %
		C	H	Cl	N		
2	$C_{26}H_{24}N_6 \cdot 1/2H_2O$*	70.77 69.78	6.45 6.08		18.81 18.77	213-215	49
3	$C_{19}H_{16}ClN_5$	65.64 65.24	4.74 4.61	10.99 10.14	20.10 20.02	216-217	84
4	$C_{17}H_{14}ClN_5O$				20.31 20.60	>200	71
5	$C_{17}H_{18}ClN_5$	62.46 62.29	5.67 5.53	11.45 18.81	21.17 21.36	181-183	82
6	$C_{18}H_{20}ClN_5$	63.05 63.24	5.87 5.90	11.44 10.37	20.47 20.49	170-172	88
7	$C_{16}H_{16}ClN_5O$	58.46 58.27	4.93 4.89	11.54 10.75	21.45 21.24	173-174	85
8	$C_{14}H_{12}ClN_5O_2$	53.68 52.92	3.74 3.81	11.78 11.16	22.65 22.04	233-234	73
9	$C_{15}H_{14}ClN_5O_2$	54.33 54.31	4.38 4.25		22.05 21.11	234-235	71
10	$C_{17}H_{18}ClN_5O_2$				19.60 19.46	210-211	87
11	$C_{15}H_{14}ClN_5O_2$	54.29 54.31	4.51 4.25		22.01 21.11	225-226	70
12	$C_{18}H_{20}ClN_5O_2$				18.90 18.73	172-173	91

* H_2O. Found, %: 5.73. Calculated, %: 6.04.

EXPERIMENTAL

Purity of compounds was determined by TLC on Silufol UV-254 strips with detection by iodine vapor or UV light. IR spectra of nujol mulls or KBr disks were recorded with a Perkin-Elmer 682 machine.

7-Benzyl-2,6-dichloropurine **1** was prepared by a method [10].

7-Benzyl-2,6-di(benzylamino)purine (2). A mixture of compound **1** (5.6 g, 0.02 mol), freshly distilled benzylamine (4.8 g, 0.045 mol), and NaOH (1.8 g, 0.045 mol) in *n*-butanol (25 ml) was boiled for 3 h. NaCl was filtered from the hot solution. The precipitate which formed on cooling was filtered off, washed with water and dried to give compound **2** (4.0 g); mp 209-210°C. After recrystallization from acetone–water (4:1), mp 213-215°C.

7-Benzyl-6-benzylamino-2-chloropurine (3). A mixture of compound **1** (56.0 g, 0.2 mol), benzylamine (23.5 g, 0.22 mol), and KOH (11.2 g, 0.2 mol) in acetonitrile (250 ml) was boiled for 2.5-3 h, cooled, the precipitate was filtered off, washed with water and cold acetonitrile, and dried. Yield of the technical product 57.0 g; mp 207-208°C.

Compounds **4-7** were prepared analogously from furfurylamine, piperidine, hexamethyleneimine, and morpholine but using 40% aqueous NaOH instead of solid KOH. For analysis the compounds were recrystallized from 70-80% aqueous acetonitrile (**3**, **4**, **6**) or 65-70% ethanol (**5**, **7**).

7-Benzyl-6-carboxymethylamino-2-chloropurine (8). A mixture of compound **1** (5.6 g, 0.02 mol), glycine (1.67 g, 0.025 mol), NaOH (2.0 g, 0.05 mol) and water (2 ml) in acetonitrile (20 ml) was boiled for 2.5 h, cooled, and the precipitate filtered off, dissolved in water, and the solution acidified to pH 3 with dilute HCl. The precipitate formed was filtered off, washed with water, and dried. Yield of technical product 4.6 g; mp 219-224°C (dec.). Compounds **9-12** were prepared from d,l-alanine, d,l-valine, β-alanine, and ω-aminocaproic acid. For analysis compounds were purified by recrystallization from DMSO–water, 2:3 (**10**, **12**) or by precipitation with water (**8**, **9**) or 70% ethanol from hot DMSO solution.

N^6-Benzyladenine (13). A mixture of compound **3** (52.5 g, 0.15 mol), KOH (18.0 g, 0.32 mol), and 5% palladium on charcoal (22 g) in ethanol (450 ml), was hydrogenated at atmospheric pressure until absorption of hydrogen ceased (about 15 h). The hot solution was filtered and the residue washed three times with hot ethanol. The filtrate was evaporated almost to dryness, the residue was dissolved in water with heating, the solution was neutralized with dilute HCl, cooled to 4-6°C, the precipitate was filtered off, washed with water, and dried to give compound **13** (23.2 g, 69%); mp 226-228°C. After recrystallization from ethanol, mp 230-231°C (mp 230°C [2]).

Hydrogenation of compounds **4** and **8** under the same conditions gave N^6-(α-furfuryl)adenine (kinetin, **14**), yield 65%; mp 266-267°C (ethanol) (mp 266-267°C [4]), and N-(purinyl-6)glycine (**15**), yield 66%; mp >325°C (water) (mp >325°C [15]).

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