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SYNTHESIS OF 5-(ARYLAMINO)-1-BENZYLURACILS

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The synthesis of novel 5-(phenylamino)-, 5-(benzylamino)-, and 5-(phenethylamino) derivatives of 1-benzyluracil-containing different substituents in the aromatic nucleus has been carried out. Using the Hilbert–Johnson reaction it was found that $N_{(1)}$-monosubstitution can be achieved via alkylation of trimethylsilyl derivatives of 5-(arylamino)uracils using benzyl bromide.

Keywords: 5-(arylamino)-1-benzyluracil, 2,4-bis(trimethylsilyloxy)pyrimidine, 5-bromouracil, $N_{(1)}$-alkylation, $C_{(5)}$-amination.

5-(Arylamino)-substituted uracils are a promising compound class in the search for novel biologically active materials. The aim of this work was the synthesis of novel 5-(arylamino)-1-benzyluracils in Hilbert–Johnson reaction conditions.

At this time a silyl modification of the Hilbert-Johnson reaction is widely used in the synthesis of pyrimidine nucleosides and their acyclic analogs [1]. The method is based on treatment of 2,4-bis(trimethylsilyloxy)pyrimidines with highly reactive alkylating agents [2-5]. The use of alkylating agents with modest or low reactivity has been little studied in these method conditions [6-8].

Previously, the introduction of a benzyl type substituent at the nitrogen atom of a pyrimidine system has been brought about by alkylation of the corresponding potassium salts [9] and this has led to a mixture of $N_{(1)}$-mono- and $N_{(1)}$,$N_{(3)}$-disubstitution products which were separated chromatographically. With the aim of broadening the preparative potential of the Hilbert–Johnson reaction we have determined the conditions for the selective introduction of a benzyl substituent at position 1 of the pyrimidine ring and obtained a series of $N_{(1)}$-benzyluracil derivatives with phenylamino-, benzylamino-, and phenethylamino groups as the substituent at the position 5.

The synthesis of the target 5-(arylamino)-1-benzyluracils was carried out by two methods. In the first of these the 5-bromouracil (**1**) was converted to the 5-bromo-2,4-bis(trimethylsilyloxy)pyrimidine and alkylated using benzyl bromides to give the corresponding 5-bromo-1-benzyluracils **2-5**. Subsequent amination with benzylamine or phenethylamine gave the 5-(arylamino)-1-benzyluracils **6-13** (method A). In the second, amination of the bromouracil **1** with aniline or 4-chloro-, 4-methyl-, or 4-methoxyaniline as in the method reported before [10, 11] preceded the $N_{(1)}$-alkylation and gave 5-(phenylamino)- (**14**), 5-[(4-methylphenyl)amino]- (**15**), 5-[(4-methoxyphenyl)amino]- (**16**), and 5-[(4-chlorophenyl)amino]uracil (**17**). The 5-(arylamino)uracils obtained were then converted to the 5-(arylamino)-2,4-bis(trimethylsilyloxy)-pyrimidines and alkylated with the corresponding benzyl bromides (method B), which also gave the target 5-(arylamino)-1-benzyluracils **18-22**.

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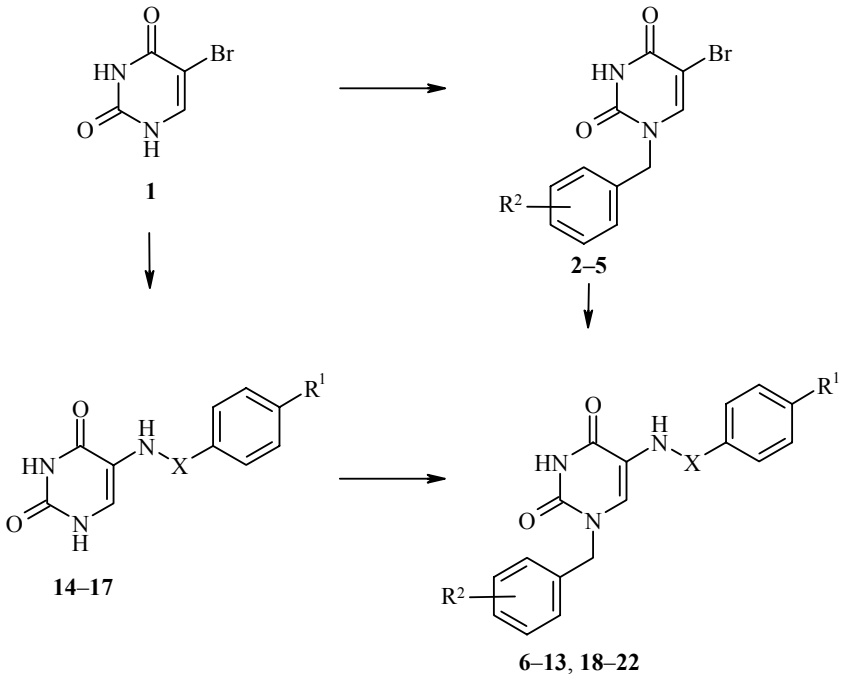

6-14, **19** R^1 = H; **15**, **20** R^1 = Me; **16**, **21** R^1 = OMe; **17**, **18**, **22** R^1 = Cl; **2**, **6**, **7** R^2 = 4-Me; **3**, **8**, **9** R^2 = 3,5-Me_2; **4**, **10**, **11**, **18** R^2 = 3-Cl; **5**, **12**, **13**, **19–22** R^2 = 2,4-Cl_2; **14–22** X = direct bond; **6**, **8**, **10**, **12** X = CH_2; **7**, **9**, **11**, **13** X = $(CH_2)_2$

It was found that the 1-benzyluracils that contain benzylamino- or phenethylamino group at position 5 could be prepared *via* both methods. By amination of 1-benzyl-5-bromouracils **2-5** using method A we have synthesized the 5-(benzylamino)- **6,8,10,** and **12** and 5-(phenethylamino) derivatives **7,9,11,** and **13** in 63-80 and 69-85% yields respectively. However, 1-benzyl-5-(phenylamino)uracils were not formed under the conditions of method A. The synthesis of the 1-benzyl-5-(phenylamino)uracils **18-22** could only be achieved *via* method B using substituted benzyl bromides and 5-(phenylamino)-2,4-bis(trimethylsilyloxy)pyrimidines (prepared from the corresponding 5-(phenylamino)uracils **14-17**) in 1,2-dichloroethane at 85°C. The yields of the target 1-benzyl-5-(phenylamino)uracils **18-22** were 55-67% using method B conditions.

When contrasting both methods one should note their advantages and disadvantages. Hence the presence of electron-donor substituents in the pyrimidine ring generally leads to a decrease in the reactivity of the 5-bromopyrimidines towards nucleophilic substitution [10, 12]. Apparently this explains the fact that 1-benzyl-5-bromouracils **18-22** do not react with anilines having a low nucleophilicity but are aminated by benzylamine or phenethylamine which are primary amines with a higher nucleophilicity. Hence method A compared with method B has specific limits related to the chemical nature of the aminating agent but it provides a higher yield of the final products.

The physicochemical characteristics of the synthesized compounds are presented in Table 1. The structure of compounds **2-13** and **18-22** was confirmed by ^{1}H NMR spectroscopy. The protons of the heterocyclic nucleus, the 1-benzyl substituent, and the aromatic fragment at position 5 appear in the expected regions. The singlet signals for the H-6 protons of the pyrimidine ring in the 5-(benzylamino) and 5-(phenethylamino) derivatives **6-13** are shifted to high field when compared with the starting bromides **2-5** by an average of 1.7 ppm while the high field shift in the 5-(phenylamino) derivatives is less at an average of 0.6 ppm. The chemical shifts, multiplicities, and proton signal integrated intensities for the compounds synthesized agreed with calculated values. The purity and homogeneity of the compounds prepared were proved by TLC and their composition by elemental analysis.

TABLE 1. Characteristics for the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	R_f*	Yield, %
		C	H	N			
2	$C_{12}H_{11}BrN_2O_2$	49.07 / 48.84	3.89 / 3.76	9.16 / 9.49	201-203	0.49	74
3	$C_{13}H_{13}BrN_2O_2$	50.66 / 50.51	4.19 / 4.24	8.98 / 9.06	163-165	0.58	48
4	$C_{11}H_8BrClN_2O_2$	41.93 / 41.87	2.87 / 2.56	8.71 / 8.88	202-205	0.34	65
5	$C_{11}H_7BrCl_2N_2O_2$	37.20 / 37.75	2.34 / 2.02	8.13 / 8.00	214-216	0.32	63
6	$C_{19}H_{19}N_3O_2$	71.62 / 71.01	5.77 / 5.96	12.81 / 13.08	216-218	0.71	63
7	$C_{20}H_{21}N_3O_2$	72.00 / 71.62	6.18 / 6.31	12.14 / 12.53	130-132	0.75	71
8	$C_{20}H_{21}N_3O_2$	71.71 / 71.62	6.19 / 6.31	12.66 / 12.53	148-150	0.68	71
9	$C_{21}H_{23}N_3O_2$	72.33 / 72.18	6.72 / 6.63	11.86 / 12.03	150-153	0.73	85
10	$C_{18}H_{16}ClN_3O_2$	63.63 / 63.25	4.97 / 4.72	12.04 / 12.29	187-189	0.47	80
11	$C_{19}H_{18}ClN_3O_2$	64.26 / 64.14	5.16 / 5.10	11.48 / 11.81	113-116	0.50	69
12	$C_{18}H_{15}Cl_2N_3O_2$	57.68 / 57.46	3.83 / 4.02	11.22 / 11.17	176-178	0.78	75
13	$C_{19}H_{17}Cl_2N_3O_2$	58.14 / 58.48	4.15 / 4.39	10.64 / 10.77	167-168	0.79	70
18	$C_{17}H_{13}Cl_2N_3O_2$	56.68 / 56.37	3.74 / 3.62	11.75 / 11.60	220-223	0.51	59
19	$C_{17}H_{13}Cl_2N_3O_2$	56.05 / 56.37	3.28 / 3.62	11.82 / 11.60	178-180	0.61	67
20	$C_{18}H_{15}Cl_2N_3O_2$	55.26 / 55.12	3.98 / 3.85	10.87 / 10.71	195-197	0.64	60
21	$C_{18}H_{15}Cl_2N_3O_3$	55.42 / 55.12	3.97 / 3.85	10.43 / 10.71	163-165	0.68	66
22	$C_{17}H_{12}Cl_3N_3O_2$	51.54 / 51.48	3.00 / 3.05	10.21 / 10.59	220-223	0.48	55

* Ethyl acetate for compounds **2-9, 12, 13** and ethyl acetate–chloroform (1:1) for compounds **10, 11, 18-22**.

Hence we have developed two variants of the synthesis of 5-(arylamino)-1-benzyluracils which can be used to prepare novel, biologically active pyrimidine ring compounds.

EXPERIMENTAL

^{1}H NMR spectra were recorded on Bruker WP-200 (200 MHz) and Tesla BS-567A (100 MHz) instruments using a mixture of DMSO-d_6 and acetone-d_6 (1:1) and with HMDS as internal standard (δ 0.02 ppm). The licensed product ACD/HNMR Predictor 3.0 Pro from Advanced Chemistry Development Inc. was used for interpretation of the ^{1}H NMR spectra. TLC was performed using Silufol UV-254 plates and revealed using iodine vapour. Kieselgur 60 (Fluka AG) silica gel was used for preparative chromatography. Melting points were measured in glass capillaries using a Mel-Temp 3.0 instrument (Laboratory Devices Inc., USA).

5-Bromo-1-(4-methylbenzyl)uracil (2). A solution of 4-methylbenzyl bromide (5.0 g, 27.02 mmol) in 1,2-dichloroethane (10 ml) was added to a solution of 5-bromo-2,4-bis(trimethylsilyloxy)pyrimidine (prepared by refluxing 5-bromouracil (5.0 g, 26.18 mmol) in HMDS (100 ml) in the presence of NH_4Cl (0.5 g)) in 1,2-dichloroethane (50 ml). The solution obtained was refluxed for 12 h. The product was treated with EtOH (20 ml) and the precipitate formed was filtered off. The filtrate was evaporated to one third volume and diluted with hexane (20 ml). The precipitate formed was combined with the previous precipitate and recrystallized from a mixture of EtOH and DMF (2:1) to give the uracil **2** (5.6 g, 74%) as light-yellow, large flaked crystals. ^{1}H NMR spectrum, δ, ppm: 2.22 (3H, s, CH_3); 4.81 (2H, s, CH_2); 7.00-7.30 (4H, m, aryl); 8.18 (1H, s, H-6 uracil); 11.40 (1H, br. s, NH).

Compounds 3-5 were prepared similarly.

5-Bromo-1-(3,5-dimethylbenzyl)uracil (3). ^{1}H NMR spectrum, δ, ppm: 2.19 (6H, s, CH_3); 4.81 (2H, s, CH_2); 6.88 (1H, s, H-4 aryl); 6.92 (2H, s, H-2,6 aryl); 8.12 (1H, s, H-6 uracil); 11.61 (1H, br. s, NH).

5-Bromo-1-(3-chlorobenzyl)uracil (4). ^{1}H NMR spectrum, δ, ppm: 4.89 (2H, s, CH_2); 7.14-7.48 (4H, m, aryl); 8.25 (1H, s, H-6 uracil); 11.62 (1H, br. s, NH).

5-Bromo-1-(2,4-dichlorobenzyl)uracil (5). ^{1}H NMR spectrum, δ, ppm: 4.89 (2H, s, CH_2); 7.09-7.46 (3H, m, aryl); 8.06 (1H, s, H-6 uracil); 11.54 (1H, br. s, NH).

5-(Benzylamino)-1-(4-methoxybenzyl)uracil (6). A mixture of compound **2** (1.5 g, 5.08 mmol), benzylamine (2.0 ml, 18.31 mmol) and ethylene glycol (5 ml) was refluxed for 40 min and cooled to room temperature. The reaction product was crystallized by treating with water (100 ml) and the filtered precipitate was dried in air and recrystallized from acetone-DMF (1: 1) to give compound **6** (0.7 g, 63%) as fine, colorless needles. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.19 (3H, s, CH_3); 4.01 (2H, d, J = 6, Ph–CH_2); 4.60 (2H, s, CH_2–N); 4.79 (1H, m, NH); 6.32 (1H, s, H-6 uracil); 6.94 (4H, m, aryl); 7.14 (5H, m, aryl); 11.27 (1H, br. s, NH).

Compounds 7-13 were prepared similarly.

1-(4-Methylbenzyl)-5-(phenethylamino)uracil (7). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.20 (3H, s, CH_3); 2.62-2.85 (2H, m, Ph–CH_2); 2.85-3.10 (2H, m, CH_2–NH); 4.06 (1H, t, J = 6, C–NH); 4.70 (2H, s, CH_2–N); 6.35 (1H, s, H-6 uracil); 6.93-7.23 (9H, m, aryl); 11.27 (1H, br. s, NH).

5-(Benzylamino)-1-(3,5-dimethylbenzyl)uracil (8). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.12 (6H, s, CH_3); 4.05 (2H, d, J = 6, Ph–CH_2); 4.62 (2H, s, CH_2–N); 4.87 (1H, t, J = 6, CH_2–NH); 6.40 (1H, s, H-4 aryl); 6.72 (2H, s, H-2,6 aryl); 6.78 (1H, s, H-6 uracil); 7.06-7.32 (5H, m, aryl); 11.20 (1H, br. s, NH).

1-(3,5-Dimethylbenzyl)-5-(phenethylamino)uracil (9). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.15 (6H, s, CH_3); 2.64-2.87 (2H, m, Ph–CH_2); 2.87-3.09 (2H, m, CH_2–N); 4.23 (1H, t, J = 5.5, CH_2–NH); 4.71 (2H, s, CH_2–N); 6.57 (1H, s, H-4 aryl); 6.82 (1H, s, H-6 uracil); 6.86 (2H, s, H-2,6 aryl); 7.04-7.25 (5H, m, C_6H_5); 11.24 (1H, br. s, NH).

5-(Benzylamino)-1-(3-chlorobenzyl)uracil (10). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.08 (2H, d, J = 6, Ph–CH_2); 4.72 (2H, s, CH_2–N); 4.88 (1H, t, J = 6, CH_2–N<u>H</u>); 6.51 (1H, s, H-6 uracil); 6.96-7.37 (9H, m, aryl); 11.30 (1H, br. s, NH).

1-(3-Chlorobenzyl)-5-(phenethylamino)uracil (11). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.66-2.90 (2H, m, Ph–CH_2); 2.90-3.18 (2H, m, CH_2–NH); 4.28 (1H, t, J = 6, CH_2–N<u>H</u>); 4.80 (2H, s, CH_2–N); 6.67 (1H, s, H-6 uracil); 6.93-7.43 (9H, m, aryl); 11.36 (1H, br. s, NH).

5-(Benzylamino)-1-(2,4-dichlorobenzyl)uracil (12). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.02 (2H, d, J = 6, Ph–CH_2); 4.72 (2H, s, CH_2–N); 4.85 (1H, t, J = 6, CH_2–N<u>H</u>); 6.16 (1H, s, H-6 uracil); 6.88-7.35 (8H, m, aryl); 11.40 (1H, br. s, NH).

1-(2,4-Dichlorobenzyl)-5-(phenethylamino)uracil (13). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.66-2.88 (2H, m, Ph–CH_2); 2.88-3.14 (2H, m, CH_2–NH); 4.16 (1H, t, J = 6, CH_2–N<u>H</u>); 4.82 (2H, s, CH_2–N); 6.41 (1H, s, H-6 uracil); 6.97-7.42 (8H, m, aryl); 11.40 (1H, br. s, NH).

1-(3-Chlorobenzyl)-5-[(4-chlorophenyl)amino]uracil (18). A solution of 3-chlorobenzyl bromide (1.4 g, 6.81 mmol) was added to a solution of 2,4-bis(trimethylsilyloxy)-5-[(4-chlorophenyl)amino]pyrimidine (2.25 g, 5.89 mmol) in 1,2-dichloroethane (50 ml). The solution obtained was refluxed for 14 h, cooled to room temperature, and treated with EtOH (20 ml). The precipitate formed was filtered off and the filtrate was evaporated to one third volume and cooled to 0°C. The precipitate formed was combined with the previous precipitate and dried in air at room temperature. The unpurified product (1.65 g) was chromatographed on silica gel (25 g, diameter 2.5 cm) using ethyl acetate–methylene chloride as eluent (1:1). The fractions containing the target material were evaporated to dryness and the residue was recrystallized from EtOH (50 ml) to give analytically pure compound **18** (1.25 g, 59%) as pale yellow, flaked crystals. ^{1}H NMR spectrum, δ, ppm: 4.89 (2H, s, CH_2–N); 6.68-7.16 (4H, m, aryl); 7.16-7.47 (4H, m, aryl); 7.69 (1H, s, H-6 uracil); 11.48 (1H, br. s, NH).

Compounds 19-22 were prepared similarly.

1-(2,4-Dichlorobenzyl)-5-(phenylamino)uracil (19). ^{1}H NMR spectrum, δ, ppm: 4.94 (2H, s, CH_2–N); 6.52-7.57 (10H, m, aryl, NH, H-6 uracil); 11.54 (1H, br. s, NH).

1-(2,4-Dichlorobenzyl)-5-[(4-methylphenyl)amino]uracil (20). ^{1}H NMR spectrum, δ, ppm: 2.11 (3H, s, CH_3); 4.92 (2H, s, CH_2–N); 6.60-6.99 (5H, m, aryl, NH); 7.16-7.54 (4H, aryl, H-6 uracil); 11.56 (1H, br. s, NH).

1-(2,4-Dichlorobenzyl)-5-[(4-methoxyphenyl)amino]uracil (21). ^{1}H NMR spectrum, δ, ppm: 3.64 (3H, s, CH_3); 4.89 (2H, s, CH_2–N); 6.48 (1H, br. s, NH); 6.55-6.94 (4H, m, aryl); 7.09-7.45 (4H, m, aryl, H-6 uracil); 11.48 (1H, br. s, NH).

1-(2,4-Dichlorobenzyl)-5-[(4-chlorophenyl)amino]uracil (22). ^{1}H NMR spectrum, δ, ppm: 4.89 (2H, s, CH_2–N); 6.68-7.16 (4H, m, aryl); 7.16-7.47 (4H, m, aryl); 7.69 (1H, s, H-6 uracil); 11.48 (1H, br. s, NH).

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