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# NOVEL SYNTHESIS OF 5-HALOURACILS FROM 5-MERCURI-2,4-DIMETHOXYPYRIMIDINES

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UDC 547.854.04

Direct C-mercuration of 2,4-dimethoxypyrimidine with mercury (II) acetate has been shown to give the 5-mercuri-derivative, which is readily converted, either directly or via 5,5'-mercuribis (2,4-dimethoxypyrimidine), into the 5-halo derivatives. Hydrolysis of the latter with hydrochloric acid affords the 5-halouracils.

Conversion of 5-halouracils into their mercuri-derivatives is hindered by the formation, on treatment of uracil with solutions of mercury(II) salts, of difficultly soluble 1:1 mercury complexes, which do not undergo further rections [1]. It has, however, recently been reported that micro-amounts of radioactive 5-halouracils may be obtained without isolation of the intermediate 5-chloromercuriuracil [2]*. Unlike uracil itself, 1-methyluracil [3], 1,3-dimethyluracil [3-5], uridine [6], and 2-desoxyuridine [7] are readily C-mercurated in high yields with mercury(II) acetate solution.

We have previously reported [8] the direct C-mercuration of 1-acetyluracil with mercury (II) trifluoroacetate in anhydrous acetonitrile. Symmetrization of the resulting 5-trifluoroacetozymercuriuracil with potassium iodide, and hydrolytic removal of the acyl protection affords 5,5'-mercuribisuracil, which is readily converted into 5-iodo- and 5-chlorouracil [8].

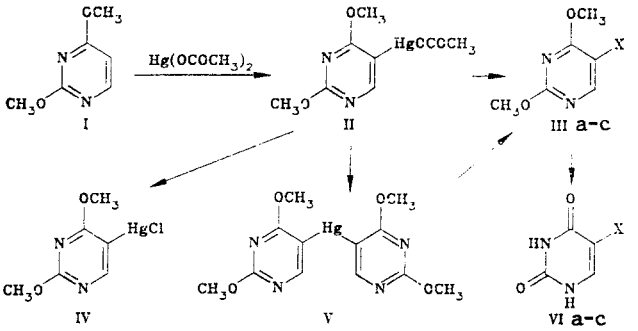
We here report the use of this method for the preparation in high yields of 5-bromouracil (VIb), by treatment of 1-acetyl-5-trifluoroacetoxy-mercuriuracil or 5,5'-mercuribisuracil with $KBr_3$ solution. A drawback of this method, which has also been used for the preparation of 8-halotheophyllins and theobromines [9], is the great ease of hydrolysis of the N-acyl protection and the consequent reduction of the electron density at the 5-position in the uracil, requiring the use of a more powerful mercurating agent such as the expensive trifluoromercuriacetate, the use of the more readily available mercury(II) and chloride being unsatisfactory in this instance [8, 9].

In the present investigation, we therefore developed a novel, general approach to 5-halouracils (VI) via the intermediate 5-mercuri-2,4-dimethoxy-pyrimidines:

*The use of this method for large quantities will form the subject of a further communication.

Faculty of Pharmacy, Polish Academy of Medicine, Warsaw 02-097. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 249-252, February, 1989. Original article submitted May 13, 1987; revision submitted, March 31, 1988.

0009-3122/89/2502-0205$12.50  



III, IV a X=I, b X=Br, c X=Cl

2,4-Dimethoxypyrimidine (I) is obtained from uracil by treatment with $POCl_3$ [10], followed by sodium methoxide in methanol [11]. 5-Acetoxymercuri-2,4-dimethoxypyrimidine (II), obtained by treatment of (I) with a hot solution of mercuric acetate in the presence of acetic acid, is converted without isolation by treatment with iodine or $KBr_3$ with heating into 5-iodo- (IIIa) or 5-bromo-2,4-dimethoxypyrimidine (IIIb). Treatment of a hot solution of (II) with sodium chloride results in precipitation of 5-chloro-mercuri-2,4-dimethoxypyrimidine (IV). On boiling a solution of (II) with KI, symmetrization takes place to give 5,5'-mercuribis(2,4-dimethoxypyrimidine) (V), which may readily be converted into 5-iodo- (IIIa), 5-bromo- (IIIb), or 5-chloro-2,4-dimethoxypyrimidine (IIIc) by treatment with hot aqueous solutions of $KI_3$ or $KBr_3$, or with $S_2Cl_2$ respectively. The resulting 5-halopyrimidines (III) are converted into the 5-halouracils (VI) by hydrolysis with hot, dilute hydrochloric acid [11].

The PMR spectra of (III) and (VI) in the aromatic region show only singlet signals for the 6-H protons (8.2-8.7 ppm), instead of the doublets for the 5-H and 6-H protons in the spectra of the starting uracils and 2,4-dimethoxypyrimidines.

The structures of the novel mercury compounds (II) and (IV) were confirmed by their halodemercuration [3, 9, 10, 12] to give initially the known compounds (IIIa-c), and their hydrolysis to the 5-halouracils (VIa-c).

## EXPERIMENTAL

PMR spectra were obtained on a Tesla BS-487C instrument (80MHz) in DMSO-$D_6$ or $CF_3COOD$ (for (VIb)), internal standard HMDS. Compounds (II) and (IV) gave a positive Lassaigne test for nitrogen, and a positive reaction for mercury (formation of HgS on boiling with $Na_2S$ solution).

2,4-Dimethoxypyrimidine (I). Mp 17.5°C, bp 90-92°C (15 mm Hg), obtained as described in [10, 11], yield 65% calculated on uracil reacted. PMR spectrum: 4.0 (6H, s, 2- and 4-$OCH_3$); 6.9 (1H, d, 5-H); 8.7 ppm (1H, d, 6-H).

5-Acetoxymercuri-2,4-dimethoxypyrimidine (II). To a hot solution of 1.0 g (7.14 mmole) of 2,4-dimethoxypyrimidine (I) in 10 ml of water was added with stirring a hot solution of 2.75 g (8.62 mmole) of mercury(II) acetate and 0.6 g (10 mmole) of glacial acetic acid in 40 ml of water. The mixture was boiled for 2 h, filtered, and the hot solution of (II) used directly in the subsequent reactions. Spectral samples were crystallized from ethanol. PMR spectrum: 2.3 (3H, s, $OCOCH_3$); 4.2 (6H, s, 2- and 4-$OCH_3$); 8.5 ppm (1H, s, 6-H).

5-Chloromercuri-2,4-dimethoxypyrimidine (IV)*. To a hot solution of (II) (obtained from 1 g of the pyrimidine (I)) was added with stirring 10 ml of hot (80-90°C) saturated NaCl solution. On cooling, the colorless, gelatinous precipitate of (IV) was filtered off and washed with water until $Cl^-$ ions were no longer present in the washings. There was obtained the chloromercuri-derivative (IV), yield 1.3 g (48%), insoluble in water and most organic solvents, apart from DMSO. Partial decomposition occurred at 200°C, and the sample did not fuse completely at 300°C. PMR spectrum: 4.1 (6H, s, 2- and 4-$OCH_3$); 8.8 ppm (1H, s, 6-H).

*Obtained with the assistance of Ya. Shimanski [13].

5,5-Mercuribis-(2,4)dimethoxypyrimidine (V). To a boiling aqueous solution of (II) (from 2 g of (I)) was added dropwise with stirring a nearly saturated aqueous solution of 4.65 g (28 mmole) of KI, boiled for 30 min, and the colorless precipitate filtered off and recrystallized from water to give 2.7 g (79%) of the mercuribis-derivative (V), mp 89-90°C (decomp.). PMR spectrum: 3.6 (6H, s, 2- and 2'-$OCH_3$); 4.0 (6H, s, 4- and 4'-$OCH_3$); 8.8 ppm (2H, s, 6- and 6'-H).

5-Iodo-2,4-dimethoxypyrimidine (IIIa). A. To a boiling aqueous solution of (II) (from 1 g of (I)) was added in small portions with stirring ~1.8 g (7.1 mmole) of finely crystalline iodine, until the solution acquired a permanent pale yellow color. After cooling, the solid was filtered off, washed with ~10 ml of cold ethanol, and dried to give 1.1 g of (IIIa), yield 58%, mp 70-71°C (from light petroleum). According to [14], mp 71-72°C. PMR spectrum: 3.8 (3H, s, 2-$OCH_3$); 4.0 (3H, s, 4-$OCH_3$); 8.7 ppm (1H, s, 6-H).

B. To a suspension of 1.2 g (2.5 mmole) of the finely ground mercuribis-derivative (V) in 50 ml of saturated aqueous KI solution was added with stirring 1.3 q (5 mmole) of finely-crystalline iodine, and the mixture stirred for 45 min at 60°C. After cooling, the precipitate was filtered off, dried, and recrystallized from light petroleum to give 0.7 g (52%) of (IIIa), mp 70-71°C, identical with material obtained by method A.

5-Bromo-2,4-dimethoxypyrimidine (IIIb). A. A mixture of 50 ml of a saturated aqueous solution of KBr and 2.2 g (14 mmole) of bromine was neutralized with sodium bicarbonate (pH 7), and a solution of (II) (from 2 g of (I)) was added. The mixture was stirred for 45 min at 60-80°C, until the solution became pale yellow in color. The cold solution was extracted with chloroform, and the extract dried over $MgSO_4$, evaporated, and the residue sublimed at 98-100°C (15 mm Hg) to give 1.6 g (51%) of (IIIb), mp 51-52°C. According to [15], mp 51-52°C*. PMR spectrum: 3.6 (3H, s, 2-$OCH_3$); 3.9 (3H, s, 4-$OCH_3$); 8.6 ppm (1H, s, 6-H).

B. To a mixture of 50 ml of saturated aqueous KBr solution and 2.7 g (17 mmole) of bromine, neutralized to pH 7, was added with stirring 4 g (8.35 mmole) of the finely ground mercuribis-compound (V). The reaction was then carried out as in method A, to give 2 g (55%) of (IIIb), mp 50-52°C, identical with the material obtained by method A.

5-Chloro-2,4-dimethoxypyrimidine (IIIc). The finely ground, dry mercuri-derivative (V) (2.4 g; 5 mmole) was added slowly with stirring to 10 ml (124 mmole) of freshly distilled sulfur monochloride (bp 135-136°C). The mixture was kept for 8 h at 20°C. On the following day, the solid was filtered off and sublimed at 100°C (10 mm) to give 0.7 g (49%) of the chloropyrimidine (IIIc), mp 72-73°C ([17], mp 72-73°C). PMR spectrum: 3.6 (3H, s, 2-$OCH_3$); 4.0, (3H, s, 4-$OCH_3$); 8.4 ppm (1H, s, 6-H).

5-Bromouracil (VIb). A. A mixture of 20 ml of saturated aqueous KBr and 2.1 g (13 mmole) of bromine, neutralized to pH 7, was mixed with a hot solution of 1-acetyl-5-trifluoroacetoxymercuryuracil in anhydrous acetonitrile (from 2 g of 1-acetyluracil [8]), and the mixture heated for 30 min at 80°C and evaporated to dryness on the water bath. The residue was dissolved in dioxane, filtered, and evaporated under reduced pressure to give 1.9 g (77%) of the bromouracil (VIb) as colorless needles, mp 297-299°C ([18], mp 293°C). PMR spectrum: 8.2 ppm (1H, s, 6-H).

B. To a mixture of 20 ml of saturated aqueous KBr and 3.2 g (20 mmole) of bromine, neutralized to pH 7, was added in small portions with stirring 4.3 g (10 mmole) of finely ground, dry 5,5'-mercuribisuracil [8]. The mixture was stirred for 30 min at 80°C, cooled, and the precipitate filtered off and recrystallized from water to give 3.2 g (84%) of the bromouracil (VIb), mp 295-297°C, identical with material obtained by method A.

General Method of Preparation of 5-Halouracils (VIa-c) from 5-Halo-2,4-dimethoxypyrimidines (IIIa-c). A solution of 5 mmole of (III) and 20 ml of hot 10% hydrochloric acid was evaporated to dryness on the water bath, when vigorous foaming occurred. The dry residue of the 5-halouracil (VI) was recrystallized from a suitable solvent. 5-Iodouracil (VIa), yield 69%, mp 272-273°C (from alcohol, decomp.) ([18], mp 272-273°C (decomp.)); 5-bromouracil (VIb), yield 83%, mp 295-297°C (from water), gave no depression of melting point on admixture with a sample obtained from 1-acetyl-5-trifluoroacetoxymercuriuracil and 5,5'-mercuribisuracil; 5-chlorouracil (VIc), yield 69%, mp 320-321°C (from alcohol) ([8], mp 320-321°C (decomp.).

We thank the Polish Academy of Sciences for financing these studies, which were carried out within the framework of problem SRVR 01.13.3.

*According to [16], mp 63-64°C; subsequent figure reported [15].

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