ANALOGS OF PYRIMIDINE NUCLEOSIDES

XI.* SYNTHESIS OF 1-(2-TETRAHYDROFURYL) DERIVATIVES OF PYRIMIDINE BASES WITH THE AID OF 2-ACETOXYTETRAHYDROFURAN

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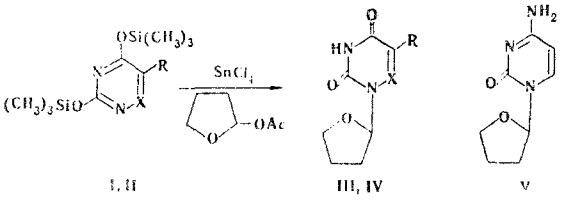
A new method was developed for the synthesis of 1-(2-tetrahydrofuryl) derivatives of uracil, 5-substituted uracils, 6-azauracil, and cytosine by alkylation of 2,4-bis(trimethylsilyl) derivatives of pyrimidine bases with 2-acetoxytetrahydrofuran in the presence of Lewis acids. In contrast to 2-chlorotetrahydrofuran, which is used in a previously described method, 2-acetoxytetrahydrofuran is stable at room temperature and reacts under these conditions with silyl derivatives of uracils in the presence of $SnCl_4$ to give 1-(2-tetrahydrofuryl) derivatives of pyrimidine bases in 80-85% yields.

We have previously described a method for the preparation of 1-(2-tetrahydrofuryl)uracils [2], 5-substituted uracils, and 6-azauracils [3] by alkylation of 2,4-bis(trimethylsilyl) derivatives of the corresponding bases with 2-chlorotetrahydrofuran (CTF). In connection with the instability of CTF, the reaction was carried out at −20°C to −10°C. It is desirable to use an excess amount of the alkylating agent, but excess CTF decomposes to give HCl, which leads to hydrolysis of the final products. We therefore developed a method for alkylation with 2-acetoxytetrahydrofuran in the presence of Lewis acids [4].

2-Acetoxytetrahydrofuran is stable and alkylates bis(trimethylsilyl) derivatives of pyrimidine bases (I, II) at room temperature in the presence of $SnCl_4$ to give 1-(2-tetrahydrofuryl)uracils in 80-90% yields. Silicon tetrachloride is less effective (the reaction takes place at 30-40°C, and the yields are lower).



I, II III, IV V

I-III X = CH; a R = H; b R = CH_3; c R = F; d R = Cl; e R = Br; f R = CF_3; II, IV X = N; a R = H; b R = CH_3; c R = Br

The synthesis of derivatives of 6-azauracil and 5-substituted 6-azauracils presented special difficulties. Thus 1-(2-tetrahydrofuryl)-6-azauracil was obtained in only 27% yield in the reaction of 2-chlorotetrahydrofuran with 2,4-bis(trimethylsilyl)-6-azauracil; this is possibly associated with its rapid hydrolysis under the reaction conditions. The use of 2-acetoxytetrahydrofuran in the presence of $SnCl_4$ made it possible to raise the yield to 80%.

Nidballa and Vorbrüggen [5] synthesized the similarly constructed 1-(2-tetrahydrofuryl)-6-azauracil by reaction of II (R = H) with 2-chloro-, 2-acetoxy-, or 2-methoxytetrahydrofuran in the presence of $SnCl_4$ in acetonitrile.

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We obtained 1-(2-tetrahydrofuryl)cytosine (V) by reaction of O,N-bis(trimethylsilyl)cytosine with 2-chlorotetrahydrofuran or 2-acetoxytetrahydrofuran in the presence of $SnCl_4$.

Thus the new method for the preparation of 1-(2-tetrahydrofuryl) derivatives of uracil, 6-azauracil, and cytosine has a number of advantages and may serve as a basis for improvement of the technology for the preparation of 1-(2-tetrahydrofuryl)-5-fluorouracil (ftorafur), which is used as an antitumorigenic preparation.

EXPERIMENTAL

The melting points were determined with a Boetius microscope stage. The purity of the compounds was monitored by chromatography on FN-1 paper in a n-butanol–acetic acid–water system (4:1:5).

2-Acetoxytetrahydrofuran. A total of 54 g [51.5 ml (0.9 mole)] of glacial acetic acid was added gradually to 70 g [76.5 ml (1 mole)] of 2,3-dihydrofuran, and the mixture was heated at 65-70°C for 1 h. It was then cooled and treated with 35 g of anhydrous potassium carbonate and 30 ml of methylene chloride. The mixture was stirred at room temperature for 2 h, after which it was filtered, and the filtrate was evaporated. The residue was vacuum distilled with collection of the fraction with bp 67-72°C (12 mm) (bp 69°C (13 mm) and n_D^{20} 1.431 [6]) to give 92.3 g (70%) of 2-acetoxytetrahydrofuran. A sample of the product is suitable for subsequent reaction without vacuum distillation.

1-(2-Tetrahydrofuryl)-5-fluorouracil (III, R = F). A 19.5-g [17.8 ml (0.15 mole)] sample of 2-acetoxytetrahydrofuran was added to a solution of 27.2 g (0.1 mole) of I (R = F) in 30 ml of dry methylene chloride, and a solution of 14.3 g [6.4 ml (0.055 mole)] of stannic chloride in 20 ml of methylene chloride was added dropwise in such a way that the temperature of the mixture did not exceed 25°C. The mixture was allowed to stand at room temperature for 2 h, after which 40 ml of ethanol was added in such a way that the temperature did not rise above 20°C. The mixture was then stirred at room temperature for 1 h, and the precipitate was removed by filtration. Evaporation of the filtrate gave an additional amount of product. The product was recrystallized from chloroform to give 16.5 g (82%) of III (R = F), which was identical to the compound described in [7].

1-(2-Tetrahydrofuryl)-6-azauracil (IV, R = H). The reaction was carried out as described for III. The addition of ethanol precipitated the 6-azauracil (8%), which was removed by filtration. The filtrate was evaporated to one-fourth of its original volume, and the concentrate was cooled. The resulting precipitate was recrystallized for chloroform to give azauracil IV (R = H) (80%), which was identical to the compound described in [3].

1-(2-Tetrahydrofuryl)cytosine (V). A solution of 5.6 g [5,2 ml (0.045 mole)] of 2-acetoxytetrahydrofuran in 50 ml of dry dichloroethane was added to O,N-bis(trimethylsilyl)cytosine, obtained from 3.4 g (0.03 mole) of cytosine, and the mixture was cooled to 0°C. A solution of 6.25 g [2.8 ml (0.024 mole)] of stannic chloride in 10 ml of dichloroethane was added dropwise to the mixture, and the new mixture was maintained at room temperature for 3 h. It was then cooled to 0°C and treated with 10 ml of ethanol. The precipitated cytosine (1 g) was removed by filtration, and the filtrate was evaporated. Ethanol (5 ml) was added to the oily residue, and the mixture was cooled and worked up to give 2 g (33%) of 1-(2-tetrahydrofuryl)cytosine hydrochloride with mp 179-181°C [chloroform–ethanol (1:1)] and R_f 0.83. The salt was suspended in 300 ml of chloroform, 20 g (0.02 mole) of triethylamine was added, and the mixture was stirred at room temperature for 20 h. The resulting precipitate was removed by filtration, washed with chloroform, and recrystallized from ethanol and ethyl acetate to give 1.5 g (27%) of cytosine V with mp 192-194°C (mp 193-194°C [8]).

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