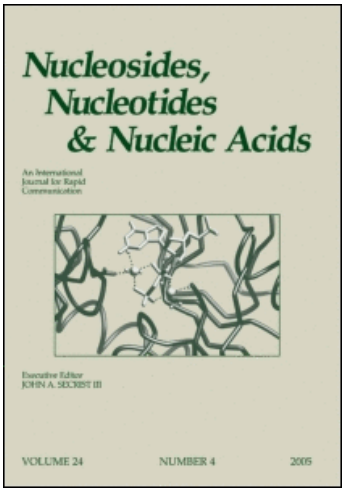

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SYNTHESIS OF 5-CHLORO-1-(2,3-O-ISOPROPYLIDENE-4-KETO RHAMNOPYRANOSYL)-URACIL

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Abstract: Syntheses of 5-chloro-1-(2,3,4-tri-O-acetyl-α-L-rhamnopyranosyl)-uracil (1), 5-chloro-1-(α-L-rhamnopyranosyl)-uracil (2), 5-chloro-1-(2,3-O-isopropylidene-α-L-rhamnopyranosyl)-uracil (3), and 5-chloro-1-(2,3-O-isopropylidene-4-keto-rhamnopyranosyl)-uracil (4) are reported. Oxidation of 3 to 4 was effected using pyridinium chlorochromate.

A decade ago Antonakis and his associates[1-3] observed that the four ketonucleosides, 7-(2-ketofucopyranosyl) and 7-(4-ketorhamnopyranosyl) theophylline as well as 6-chloro-9-(2-fucopyranosyl) and 6-chloro-9-(4-ketorhamnopyranosyl) purines showed growth inhibitory activity against KB cells. To investigate the biological activity of the ketonucleosides of the above deoxy sugars viz. α-L-fucopyranose and α-L-rhamnopyranose with uracil and C-5 substituted uracils, we have attempted to synthesize 1-(4-keto-α-L-rhamnopyranosyl)-uracil and other C-5 substituted ketonucleosides. Efforts to oxidize 5-chloro-1-(2,3-O-isopropylidene-α-L-rhamnopyranosyl)-uracil, 3, to the keto compound 4, according to Pfitzner-Moffatt method[4] and chromium trioxide-pyridine complex in the presence of acetic anhydride[5] were unsuccessful. The first method showed the formation of a small amount of ketonucleoside (TLC), but cumbersome purification procedures to get rid of dicyclohexylurea did not give a satisfactory yield. The second method showed hardly any formation of the ketonucleoside. However, very

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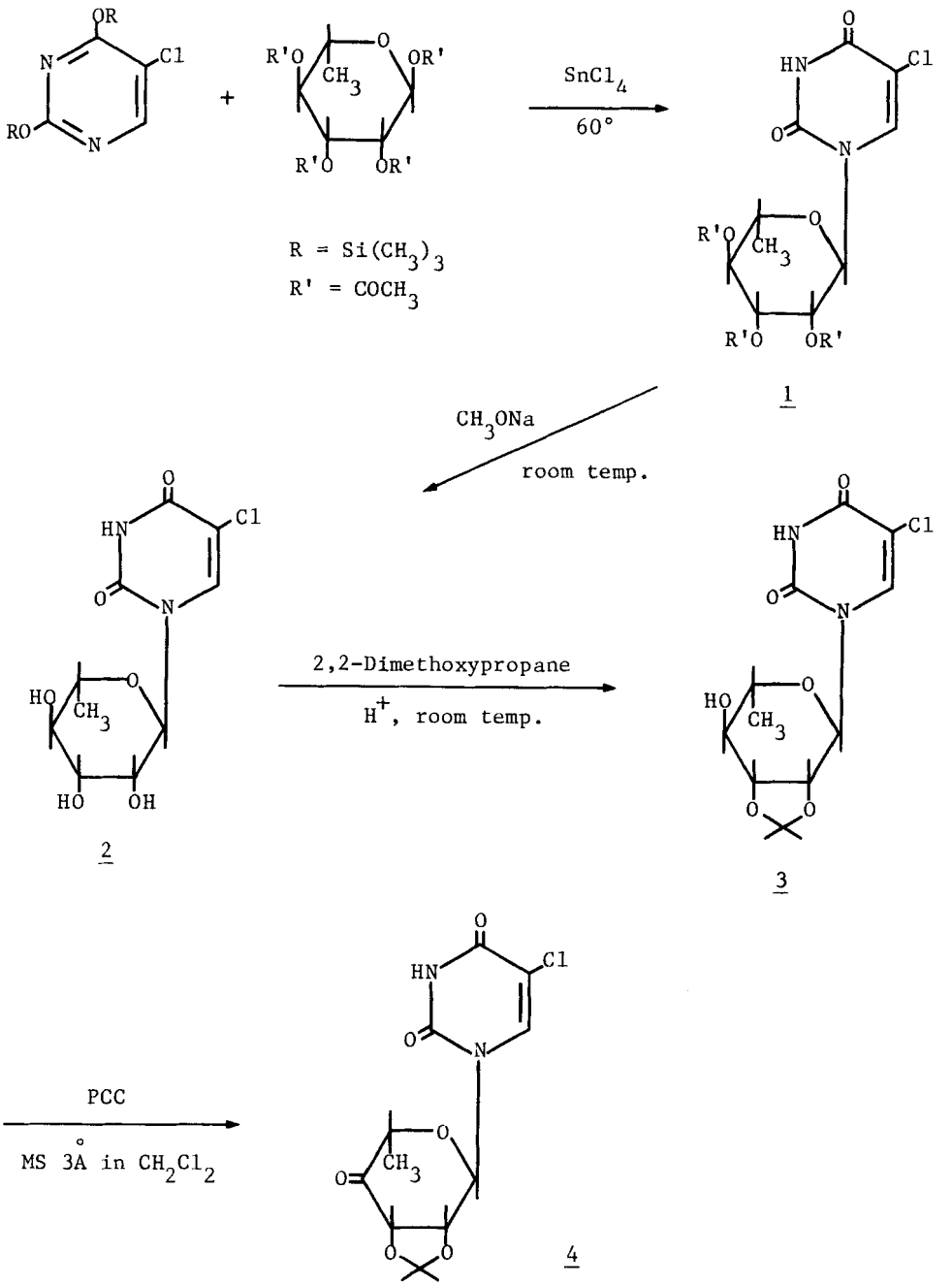
encouraging results were obtained when pyridinium chlorochromate (PCC) in the presence of molecular sieve (MS) 3Å was used as per the Herscovici-Antonakis method[6]. Biological studies on the title compound are under way. Results will be reported in due course. The NMR spectrum of the compound (4) has shown a doublet corresponding to H_1, having a coupling constant $J_{1',2'}$, equal to 7Hz. This indicates that H_1, and H_2, are trans diaxial due to the sugar moiety, assuming a $4C_1$ configuration.

EXPERIMENTAL SECTION

Melting points (uncorrected) were determined using Mel-Temp apparatus. Thin layer chromatography (TLC) was done on precoated silica gel plastic sheets 60 F_{254} (0.2mm) EM Reagents. Compounds were detected under short UV light. Sugar was detected by spraying with 3% concd. sulfuric acid in ethanol (w/v) and heating the TLC plastic strips. Four solvent systems were used for TLC, (A) chloroform/methanol 92:8 (v/v); (B) chloroform/methanol 75:25 (v/v); (C) chloroform/acetone 85:15 (v/v), and (D) ethyl acetate. Optical rotations were determined using a "Quick" polarimeter and Model SR6 polarimeter from PolyScience Corporation. Nuclear magnetic resonance (NMR) spectrum was recorded using a Bruker/IBM-SY200. Ethyl acetate and dichloromethane used in the oxidation step were first distilled and stored in glass containers over molecular sieve (MS) 4Å, at least for a week before use. Molecular sieve 3Å, used for oxidation, was finely powdered, and was heated to about 375°C, just before the experiment in a vacuum in the vicinity of P_2O_5 in the sleeve of a specially designed tube. MS was cooled to ambient temperature before adding to the reaction mixture.

5-Chloro-1-(2,3,4-tri-O-acetyl-α-L-rhamnopyranosyl)-uracil(1)

Compound 1 was synthesized following essentially the method by Niedballa and Vorbrüggen[7]. 5-Chlorouracil (0.34 mole) was silylated in hexamethyldisilazane (HMDS) in the presence of a catalytic amount of chlorotrimethylsilane. After removing the excess of HMDS by vacuum distillation, the silylated base was coupled with peracetylated rhamnose (0.33 mole) in the presence of stannic chloride (0.28 mole) at 60° in



300 ml of absolute 1,2-dichloroethane. Completion of coupling was determined by TLC in solvent systems (A) and (B). The reaction mixture was diluted with about 200 ml of ethyl acetate and 150 ml of distilled water, and neutralized with saturated sodium bicarbonate solution. The precipitated stannic oxide was filtered off under vacuum. The organic layer was separated from the aqueous layer, washed once with water, dried over anhydrous Na_2SO_4, and evaporated to dryness in vacuo. Crystallization from absolute ethanol gave a 67% yield of 1, m.p. 143-144°, $(\alpha)_D^{20}$ - 17.5° (c 0.1, $CHCl_3$) R_f 0.91 (Solvent B).

Analysis: for $C_{16}H_{19}N_2Cl$: Calculated: C, 45.88; H, 4.57; N, 6.66
Cl, 8.46
Found: C, 45.59; H, 4.57; N, 6.65;
Cl, 8.97

5-Chloro-1-(α-L-rhamnopyranosyl)-uracil(2)

Fifteen grams of 1 (35.8 mmol) were dissolved in 60 ml absolute methanol and to this was added 75 ml N. sodium methoxide. The mixture was kept refrigerated. Deacetylation was followed by TLC in solvent system (B). Within an hour deacetylation was complete. The solution was diluted with a few milliliters of water and then was neutralized with Rexyn 101(H^+). We have observed that stirring with the resin for 4 to 5 hours was necessary to remove all the Na^+ ions. After filtering off the resin, the filtrate was evaporated to dryness. To remove all traces of moisture, the residue was repeatedly (twice) dissolved in absolute ethanol and evaporated to dryness in vacuo. The product appeared fluffy, becoming sticky as soon as it came in contact with moist air. Yield: 93%. $(\alpha)_D^{20}$ + 22.5 (c 0.1, MeOH) R_f 0.49 (Solvent B). Due to the nature of the compound, correct analytical results could not be obtained. This product was directly used for the next step.

5-Chloro-1-(2,3-O-isopropylidene-α-L-rhamnopyranosyl)-uracil(3)

Six grams of 2 (0.02 mole) were dissolved in the minimum quantity of absolute acetone. To this was added 15.2 ml 2,2-dimethoxypropane (0.12 mole) followed by 0.5 ml of concd. sulfuric acid. The reaction

mixture was kept out of moist air with the help of a drying tube. The mixture was mechanically stirred at the ambient temperature. TLC in the solvent systems (B) and (C) showed the reaction was complete in two hours.

The mixture was neutralized with N sodium hydroxide and then was left in the refrigerator for two hours. Precipitated sodium sulfate was filtered off and the filtrate was evaporated to dryness. Crystallization from ab. ethanol gave 6.0 g of 3 (87%), m.p. 192-193°. $(\alpha)_D^{20}$ + 5.0 (c, MeOH) R_f 0.96 (Solvent C).

Analysis: Calculated for $C_{13}H_{17}O_6N_2Cl$: C, 46.92; H, 5.11; N, 8.42; Cl, 10.66

Found: C, 46.88; H, 5.27; N, 8.31; Cl, 10.08

5-Chloro-1-(2,3-O-isopropylidene-4-keto-rhamnopyranosyl)-uracil(4)

5.0 g of 3 (15 mmol), 8.1 g (37 mmol) of pyridinium chlorochromate, 15.0 g of 3Å molecular sieve (1 g/mmol of 3) and 75 ml of dichloromethane were placed in a round bottomed flask. The mixture was stirred at the ambient temperature, the flask being kept free of moisture with a drying tube. Oxidation was completed in three hours as indicated by TLC in solvent (D). A brown spot showed the formation of the ketonucleoside. Generally, other nucleosides gave a yellow color on heating. The reaction mixture was diluted with 75 ml of dry ethyl acetate and mechanically stirred for 30 minutes. The mixture was vacuum filtered through a 3 - 4 cm thick layer of silica gel containing $CaSO_4$ as binder (Silica Gel PF_{254} Merck) to remove as much of the chromium salts as possible. The black residue in the Buchner funnel was washed three times with 50 ml each of ethyl acetate. The filtrate was concentrated under vacuum at 40°C. The residue was dissolved in the minimum quantity of ethyl acetate and purified by column chromatography using silica gel, 60 - 200 mesh (Baker), in a 54 cm x 3.0 cm column. The column was eluted with ethyl acetate until all the compound had passed through as tested by short UV light. The colorless eluate was combined and evaporated to dryness under vacuum (40°C). The residue was dissolved in a minimum quantity of dry diethyl ether and refrigerated. The ketonucleoside 4, which crystallized overnight, was filtered under vacuum. Yield 3.86 g (78%)

M.P. 145°C, $[\alpha]_D^{20}$ - 49.3° (c 0.8, ethyl acetate) R_f 0.80 (Solvent D).

Analysis for $C_{13}H_{15}O_6N_2Cl$. Found: C, 46.81; H, 4.51; N, 8.60; Cl, 11.21; Calculated: C, 47.21; H, 4.57; N, 8.47; Cl, 10.72.

δ(acetone d_6) 4.7 (d,1,$J_{1',2'}$= 7Hz, $H_{1'}$) 5.1 (dd,1,$J_{2',3'}$= 2Hz,$H_{2'}$) 5.5 (d,1,$H_{3'}$)

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