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An Improved Procedure for the Preparation of 5-Allyl-2'-deoxyuridine (1)

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5-Allyl-2'-deoxyuridine has been found to inhibit nucleoside phosphorylase activity due to PPLO contamination of HeLa cells (2). This observation led to the desire for gram quantities of this compound for evaluation in animal test systems, but the preparation of this amount of material by the published procedure (2) appeared to be impractical. Furthermore, attempts to synthesize the material enzymatically were unsuccessful (3). We, therefore, undertook an investigation of the preparation of this material by a recently published procedure for the preparation of pyrimidine nucleosides (4).

5-Allyl-2,4-trimethylsilyloxyuracil was prepared in high yield by the reaction of trimethylchlorosilane with 5-allyluracil (5, 6) in dioxane. Fusion of this blocked pyrimidine with 3,5-di-(*p*-chlorobenzoyl)-2-deoxy-D-ribofuranosyl chloride (7) at 125-130° *in vacuo* gave a 23% yield of crystalline, chromatographically pure 5-allyl-1-[3,5-di-*O*-(*p*-chlorobenzoyl)-2-deoxy-β-D-ribofuranosyl]uracil. Removal of the *p*-chlorobenzoyl groups in the usual manner gave 60% yield of analytically pure 5-allyl-2'-deoxyuridine.

EXPERIMENTAL

The melting points reported were determined on a Kofler Heizbank and are corrected. The ultraviolet spectra were determined in aqueous solution with a Cary Model 14 spectrophotometer. The infrared spectra were determined in pressed potassium bromide disks with a Perkin-Elmer Model 521 spectrophotometer.

5-Allyl-2,4-bis(trimethylsilyloxy)pyrimidine.

5-Allyluracil (3 g., 19.7 mmoles) was suspended in spectro-quality dioxane (50 ml.) in a previously dried flask. Trimethylchlorosilane (5.02 ml., 4.26 g., 39.4 mmoles) was added, and the mixture was stirred continuously during the dropwise addition of a solution of triethylamine (5.5 ml., 3.98 g., 39.4 mmoles) in dioxane (20 ml.). After the addition was complete, the reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was filtered under anhydrous conditions, and the insoluble solid was washed with fresh dioxane (10 ml.). The filtrate and washings were pooled and concentrated to about 10 ml. The concentrate was filtered directly into the distillation flask and the residual dioxane removed. The crude oil was distilled at 140-142°/12 mm., bath temperature 170°, yield 5.11 g. (87%). This material was used in the next step without further purification.

5-Allyl-1-[3,5-di-*O*-(*p*-chlorobenzoyl)-2-deoxy-β-D-ribofuranosyl]uracil (2).

Using anhydrous conditions, 5-allyl-2,4-bis(trimethylsilyloxy)pyrimidine (2.92 g., 9.9 mmoles) and 3,5-di-*p*-chlorobenzoyl-2-deoxy-D-ribofuranosyl chloride (4.6 g., 10.7 mmoles) were mixed in a round bottom flask. Under anhydrous conditions, the reaction mixture was evacuated to 25 mm. and heated in a bath at 125-130° with continuous stirring for 30 minutes.

The reaction melt was cooled to room temperature and triturated with 9 ether:1 chloroform (50 ml.). The insoluble 5-allyluracil was removed by filtration and washed with fresh solvent. The filtrate and washings were evaporated to dryness *in vacuo*. The resulting glass was triturated with ether (50 ml.) containing a little ethanol (1-2%) and the crystals that formed were collected by filtration, washed with ethanol and ether and dried *in vacuo*; yield 1.15 g. (21%) of essentially pure β anomer. Chromatographically pure material was obtained by dissolving the isolated product in chloroform (3 ml.), filtering the solution through dry Celite to clarify and diluting the filtrate with ether. The crystals that precipitated from the ether solution were collected by filtration, washed with fresh solvent and dried; yield 880 mg. (16%), m.p. 150-152°. Thin-layer chromatography on silica gel H (Merck) using 3 chloroform:1 ethyl acetate as the eluant (and sodium metaperiodate oxidation followed by basic permanganate as the detector) gave good separation of the anomers as well as the starting compounds. (β anomer): $\bar{\nu}$ max in cm^{-1} : 3275, 3070, 2980, 2920 (CH); 1725, 1705 (benzoyl C=O); 1680 (ring C=O); 1590 (C=C); 1115, 1100, 1085 (C-O-C).

Additional pure β anomer (185 mg., 3%) was obtained from the recrystallization filtrate by evaporation of the filtrate to dryness and trituration of the residue with ether to remove the small amount of α anomer. Fractional precipitation of material from the original filtrate (after evaporation to dryness) from ethanol gave a purified anomeric mixture (1.3 g.) which was dissolved in ether (20 ml.), seeded with pure β anomer and allowed to stand at room temperature for several days. The crystals that formed were collected by filtration, washed with fresh ether, and dried to give 230 mg. (4%) of pure β anomer. The total yield was 1.3 g. (23%).

5-Allyl-2'-deoxyuridine (2).

A solution of 5-allyl-1-[3,5-di-*O*-(*p*-chlorobenzoyl)-2-deoxy-β-D-ribofuranosyl]uracil (800 mg., 1.47 mmoles) in ethanolic ammonia (30 ml.) was placed in a glass-lined bomb and heated at 100° for 4 hours. The reaction solution was filtered through dry Celite and the filtrate was evaporated to dryness. The resulting residue was partitioned between chloroform and water and the water layer was washed with fresh chloroform two times before it was evaporated to dryness *in vacuo*. The residue was dissolved in ethanol and evaporated to dryness several times before the oil was induced to crystallize by scratching. The crude product (370 mg. (94%)) was dissolved in ethyl acetate (15 ml.), the solution filtered, and the filtrate was allowed to stand until crystallization was complete. The crystals were collected by filtration, washed and dried; yield 190 mg. (48%); m.p. 126-128°, $[\alpha]_D^{25} + 11.8 \pm 0.2$ (C = 0.44 g./100 ml. H₂O). Thin-layer chromatography on silica gel H using 9 chloroform:1 methanol

as the eluant and the Dische deoxyribose spray as the detector gave a single spot. λ max in $\text{m}\mu$ ($\epsilon \times 10^{-3}$), pH 1-267 (9.8); pH 7-266.5 (9.8); pH 13-266 (7.2). $\bar{\nu}$ max in cm^{-1} : 3440 (OH); 3200, 3020, 2930, 2820 (CH); 1680 (C=O), 1090, 1070, 1050 (COC).

Anal. Calcd. for C₁₂H₁₈N₂O₅: C, 53.72; H, 6.01; N, 10.45. Found: C, 53.52; H, 5.69; N, 10.62.

The isolation of a second and third crop of pure material on concentration of the filtrate from above gave a total yield of 60%.

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