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A SIMPLE METHOD FOR THE SYNTHESIS OF O^2,5'-CYCLODEOXYURIDINE

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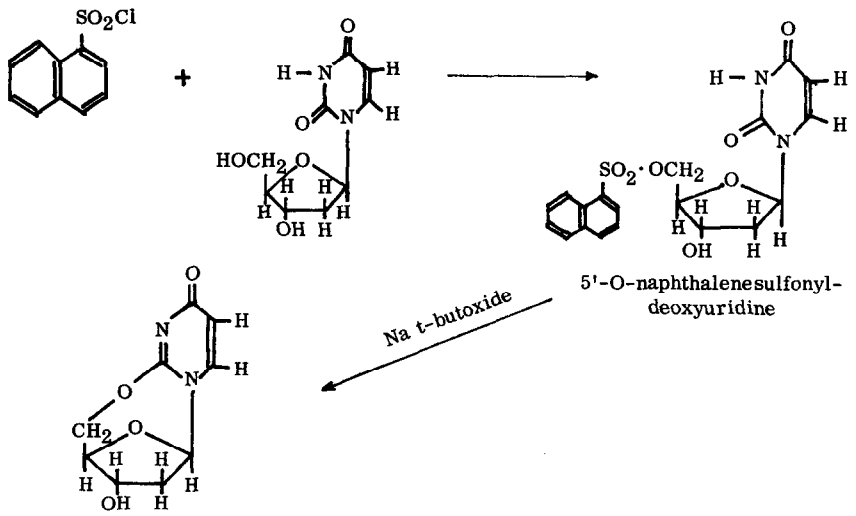
Present techniques for the synthesis of O^2,5'-cyclodeoxythymidine (1) (2) (or uridine) involve: 1) Tritylation of the 5'-hydroxyl, 2) Acetylation of the 3'-hydroxyl, 3) Removal of the 5'-trityl group, 4) Tosylation of the 5'-hydroxyl, 5) Removal of the 3'-acetyl group, 6) Formation of the O^2,5' ring by ring closure with a strong base. These techniques, which involve many steps, are time consuming and give only modest overall yields.

It occurred to us that a considerable improvement might be achieved if a large, bulky sulfonyl chloride could be found that would react exclusively with the 5'-hydroxyl of the deoxynucleoside. Even if some 3' derivative were formed it might be possible to separate it readily from the 5' derivative. The sulfonyl compound would have to be a good leaving group as well for the subsequent ring closure.

We have found that 1-naphthalenesulfonyl chloride reacts readily with deoxyuridine to give primarily the 5'-O-naphthalenesulfonyl derivative. This then is readily cyclized with sodium tert-butoxide to give O^2,5'-cyclodeoxyuridine as indicated below.



The use of sodium tert-butoxide instead of N,N'-dicyclohexyl-4-morpholinocarboxamidine to effect the cyclization is preferred since contrary to the experience of Nagyvary (3) when synthesizing the uridine cyclic derivative, the carboxamidine gave us a product which deviated in m.p. and UV spectrum from the expected one. It should be noted that the cyclodeoxyuridine has its 3'-OH unprotected. Two moles of it may be reacted with 1 mole of nucleoside 5'-monophosphate to give trinucleoside phosphates. The same principles apply to the formation of cyclic ribopyrimidines. The presently used techniques require the protection of the 2',3'-OH by an isopropylidene group. This group must be removed after the formation of trinucleoside phosphates; however the procedure for removing the isopropylidene group is likely to destroy at least some of the sensitive trinucleoside phosphates.

The use of 1-naphthalenesulfonyl chloride would perhaps allow the use of unprotected ribopyrimidines in the preparation of cyclic intermediates. Preliminary experiments indicate that 1-naphthalenesulfonyl chloride reacts with 6-azauridine to give three different naphthalenesulfonyl derivatives, presumably 5', 3' and 2' derivatives (characterized by I.R., periodate cis-glycol test and elemental analysis). These products are readily separated on thick-layer chromatography using butanol saturated with water. Further details will be reported at a later date.

5'-O-naphthalenesulfonyldeoxyuridine

Deoxyuridine (0.917 g; 4.03 mmole) was dissolved in 20 ml of dry pyridine, then 0.929 g (4.1 mmole) of 1-naphthalenesulfonyl chloride was added. The resulting yellow solution was kept in a dry box under nitrogen at room temperature for 2 days. The dark brown reaction solution was evaporated to dryness under reduced pressure. Absolute methanol was added and removed by evaporating under vacuum in order to remove pyridine. This was repeated. A yield of 2.33 g of crude products were obtained. This was then dissolved in 5 ml of acetone and applied to 25 thick-layer chromatography plates (20 cm x 20 cm with 1 mm thickness Silica Gel PF_{254}), using n-butanol saturated with water as solvent. Bands were located by U.V. lamp. There were four bands detected on the chromatogram. The major band at Rf 0.66 (Rf 0.41 for deoxyuridine as a standard) was scraped off, the silica gel filtered from acetone and washed with acetone four times. The combined filtrate and washings were evaporated, giving 0.474 g (28% yield) of white flaky glass, which at 75-77° became semi-solid, at 156° decomposed. The other bands had Rf values of 0.0, 0.76 and 0.41. The band with Rf 0.0 may be 1-naphthalenesulfonic acid, because known 1-naphthalenesulfonic acid has Rf 0.0. The band with Rf 0.76 appears to be 3'-O-naphthalenesulfonyldeoxyuridine (identified by I.R.). The band with Rf 0.41 has the least U.V. absorbing intensity and is unreacted deoxyuridine (identified by chromatography, Rf value and mixed m.p.). The sample for elemental analysis was obtained by rechromatographing two additional times and then crystallizing from acetone-ether. This product had a m.p. of 156-157° (decomposed); I.R.: ν_{max}^{KBr} 1655 and 1620 (two amide C=O), 1335 and 1160 cm^{-1} (S=O).

Calculated values for $C_{19}H_{18}O_7N_2S$: C, 54.54; H, 4.34; N, 6.70; S, 7.66. Found: C, 54.26; H, 4.55; N, 6.48; S, 7.50.

O^2,5'-cyclodeoxyuridine

Sodium tert-butoxide (4) (0.34 ml of a 0.5 M solution in t-butyl alcohol; 0.17 mmole) was added to a solution of 5'-O-naphthalenesulfonyldeoxyuridine (0.065 g; 0.17 mmole) in 5 ml of dry dimethylformamide. The reaction flask was stoppered with a calcium sulfate drying tube and kept at 100° for 1 1/2 hr. The light brown reaction solution was evaporated to dryness under reduced pressure. A yield of 0.082 g of crude product was obtained. This was then dissolved in 0.3 ml of absolute methanol and applied to 2 thick-layer chromatography plates (1 mm thickness Silica Gel PF_{254}), using n-butanol saturated with water as solvent. The major band at R_f 0.16 (R_f 0.40 for deoxyuridine as a standard) was scraped off, the silica gel filtered from absolute methanol and washed with absolute methanol four times. The combined filtrate and washings were evaporated, giving 0.028 g (79% yield) of white powder, which at 195-197° became semi-solid, then darkened gradually. The sample for analysis was obtained by separation on a thick-layer chromatograph and then twice crystallized from absolute methanol. This sample became semi-solid at 199-200°, then darkened gradually; I.R.: ν_{max}^{KBr} 3400 (OH), 1630 cm^{-1} (C=O). U.V.: λ_{max}^{EtOH} 236 mμ (ε =11900), λ_{min}^{EtOH} 212.5 mμ (ε =3660) (5).

Calculated values for $C_9H_{10}O_4N_2$: C, 51.44; H, 4.76; N, 13.33. Found: C, 51.20; H, 4.96; N, 13.16.

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