

Derivatives of 2',3'-Dithiouridine and [1- β -D-(2,3-Dithioxylofuranosyl)]uracil

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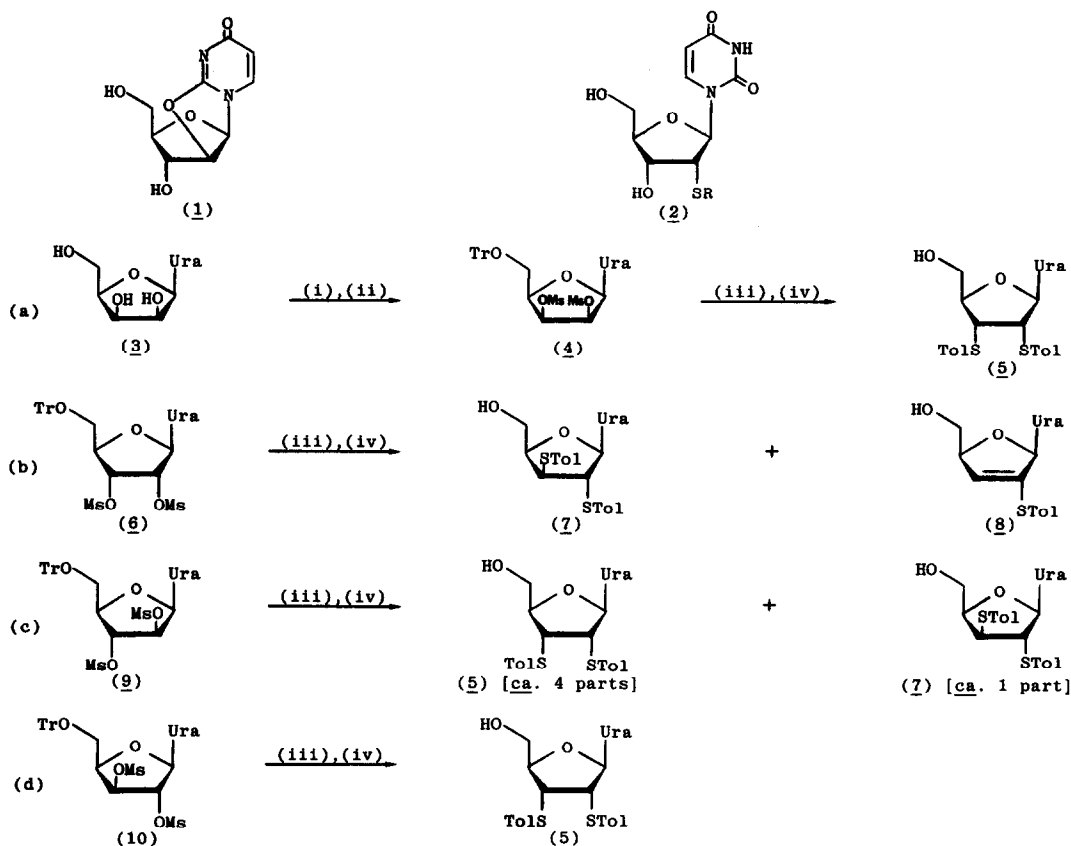
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Abstract: The synthesis of 2',3'-di-(4-tolylthio)uridine (5) and {1- β -D-[2,3-di-(4-tolylthio)xylofuranosyl]}uracil (7) from (1- β -D-lyxofuranosyl)uracil (3) and uridine, respectively, is described.

A number of years ago, we reported¹ that *S*-aryl and *S*-alkyl derivatives (2; R = aryl and alkyl, respectively) of 2'-thiouridine can easily be prepared by heating 2,2'-anhydro-(1- β -D-arabinofuranosyl)uracil (1) with aromatic and aliphatic thiols, respectively, in the presence of base. In continuation of our studies² directed towards the synthesis of 2',3'-dideoxynucleoside derivatives that are potential reverse transcriptase inhibitors³, we now report that 2',3'-di-(4-tolylthio)uridine (5) can be prepared in satisfactory yield from the 2',3'-di-*O*-mesyl-5'-*O*-trityl-derivative (4) of (1- β -D-lyxofuranosyl)uracil (3), and that the diastereoisomeric {1- β -D-[2,3-di-(4-tolylthio)xylofuranosyl]}uracil (7) can similarly be prepared from 2',3'-di-*O*-mesyl-5'-*O*-trityluridine (6).

1- β -D-Lyxofuranosyluracil⁴ (3) was heated (Scheme 1a) with a slight excess of chlorotriphenylmethane in pyridine solution at 100°C for 1 hr, and the products were allowed to react with a small excess of methanesulphonyl chloride in pyridine solution to give (4). The latter compound (4), which was isolated as a crystalline solid, m.p. 229°C, in 73% overall yield, was then heated with ca. 2.6 mol. equiv. of toluene-4-thiol and ca. 2.5 mol. equiv. of sodium hydride in *N,N*-dimethylacetamide (DMA) solution at 100°C for 30 min. After the products had been detritylated by treatment with trifluoroacetic acid (TFA, ca. 6.25 mol. equiv.) and pyrrole⁵ (ca. 20 mol. equiv.) in dichloromethane solution at room temperature for 10 min, (5) was obtained and isolated as a crystalline solid, m.p. 164°C, in 71% overall yield for the two steps starting from (4). The constitution of (5) is based on its method of preparation, and on microanalytical⁶ and NMR (¹H and ¹³C) spectroscopic evidence. It can be seen below that the alternative structure (7) may be excluded. When 2',3'-di-*O*-mesyl-5'-*O*-trityluridine (6) was allowed to react with toluene-4-thiol and sodium hydride in DMA solution under the same conditions (Scheme 1b) and the products then detritylated, a mixture of (7) and (8) was obtained. Following fractionation of this mixture by chromatography on silica gel, (7) and (8) were isolated as crystalline solids, m.p.s 170 and 141°C, in 50 and 29.5% yield, respectively. The constitution of (7) is

firmly based on an X-ray crystal structure analysis (Figure 1), and that of (8) on its unambiguous synthesis⁷ from 2'-(4-tolylthio)uridine¹ (2; R = 4-MeC₆H₄).



Scheme 1 Ura = uracil-1-yl Tol = 4-MeC₆H₄

Reagents: (i) Ph₃CCl, C₅H₅N, 100°C; (ii) CH₃SO₂Cl, C₅H₅N, RT; (iii) 4-MeC₆H₄SH, NaH, MeCONMe₂ (DMA), 100°C; (iv) CF₃CO₂H (TFA), pyrrole, CH₂Cl₂, RT.

In order to complete this study, 1-β-D-arabinofuranosyluracil⁸ and 1-β-D-xylofuranosyluracil⁹ were each converted in two steps [tritylation and mesylation, corresponding to steps (i) and (ii) in Scheme 1a] into the corresponding 2',3'-di-O-mesyl-5'-O-trityl derivatives [(9) and (10)] which had m.p.s 178-180 and 138-141°C, respectively. When the arabino-derivative (9) was allowed to react with toluene-4-thiol and sodium hydride in DMA solution at 100°C and the products then detritylated (Scheme 1c), an approximately 4:1 mixture of (5) and (7) was obtained in ca. 80% combined yield.¹⁰ When the xylo-derivative (10) was subjected to the same two-step process (Scheme 1d), (5) was obtained as the sole nucleoside product in 69% isolated overall yield¹¹.

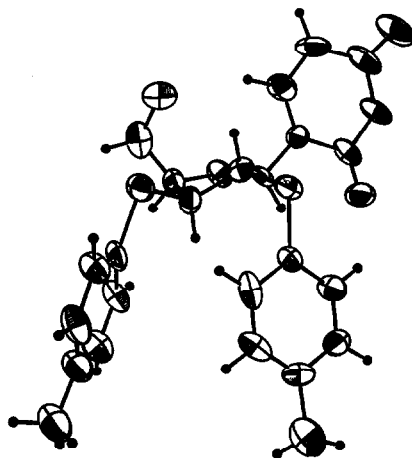
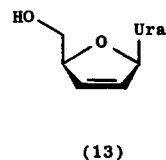
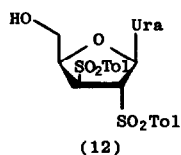
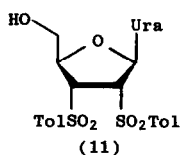


Figure 1. Computer-drawn plot of the molecular structure of (7).

In consideration of the general overall stereochemistry of the reactions between toluene-4-thiolate ions and the isomeric 2',3'-di-*O*-mesyl-5'-*O*-trityl derivatives [(4), (6), (9) and (10)], all four products would be expected to have 2'- α -(4-toluenethio) substituents. In the cases of substrates (4) and (9), this would result from direct nucleophilic attack at C-2' with inversion of configuration; in the cases of substrates (6) and (10), this would result from the intermediacy of 2,2'-anhydronucleoside derivatives¹². It would further appear that 2'- α -(4-toluenethio) substituents do not participate in reactions at C-3' and that a 3'- β -(4-toluenethio) substituent can result only by direct nucleophilic attack leading to inversion at C-3' [e.g., in the reactions of (6) and (9)]. It seems likely that the conversion of (9) into (5) involves the intermediacy of a 2,3'-anhydronucleoside derivative¹².



Ura = uracil-1-yl

Tol = 4-MeC₆H₄

When the bis-thioethers [(5) and (7)] were allowed to react with an excess of 3-chloroperbenzoic acid in dichloromethane solution, the corresponding bis-sulphones [(11) and (12)], m.p.s 282-284 and 226-228°C, respectively, were obtained. Finally, when (5) and (7) were heated, under reflux, with 2.0 mol. equiv. of tri-*n*-butyltin hydride in the

presence of azobis-isobutyronitrile in anhydrous dioxane solution, 2',3'-didehydro-2',3'-dideoxyuridine¹³ (**13**) was obtained in 76 and 91% isolated yield, respectively. We are actively engaged in further studies relating to the chemistry of 2',3'-dithionucleoside derivatives.

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6. Satisfactory microanalytical data were obtained for all new crystalline compounds described.
7. Authentic compound (**8**), m.p. 141-143°C, was prepared in two steps [(i) *N*¹,*N*¹,*N*³,*N*³-tetramethylguanidine, DMA, 100°C, 10 min; (ii) TFA, pyrrole, CH₂Cl₂, RT] and in 89% yield from the 3'-*O*-mesyl-5'-*O*-trityl derivative of 2'-(4-tolylthio)uridine (**2**; R = 4-MeC₆H₄); it was identical [TLC (CHCl₃-MeOH, 9:1 v/v), ¹H- and ¹³C-NMR] to the minor product obtained from (**6**) [Scheme 1b].
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10. As it did not prove possible to fractionate this mixture by chromatography on silica gel, its composition was determined by ¹H-NMR spectroscopy; after the mixture had been allowed to react with an excess of 3-chloroperbenzoic acid in CH₂Cl₂ solution, the resulting sulphones [(**11**) and (**12**)] were readily separated and isolated in ca. 63 and 21% yield, respectively.
11. Although only one bis-thioether (**5**) was obtained from (**10**), this route is not particularly useful synthetically as 1-β-D-xylofuranosyluracil⁹ is much less readily accessible than 1-β-D-lyxofuranosyluracil⁴ (**3**).
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