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

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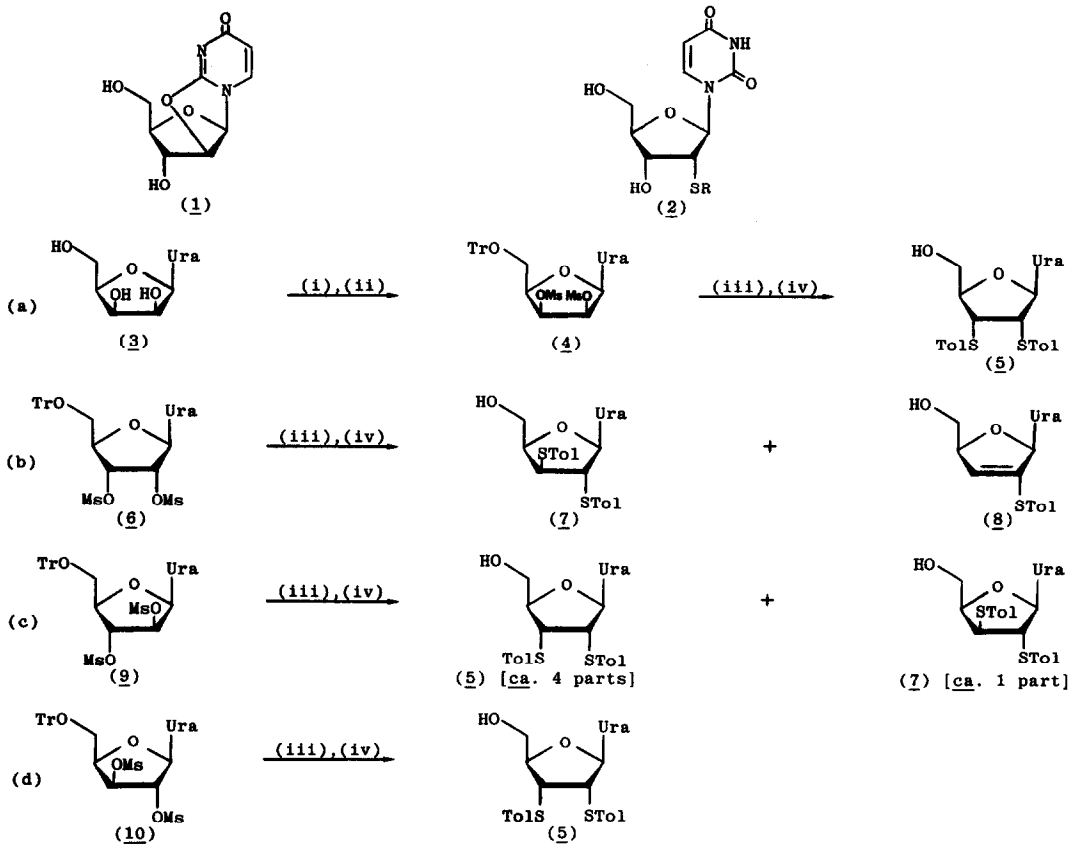
Abstract: The synthesis of 2',3'-di-(4-tolylthio)uridine (5) and {1-β-D-[2,3-di-(4-tolylthio)xylofuranosyl]}uracil (7) from (1-β-D-lyxofuranosyl)uracil (3) and uridine, respectively, is described.

A number of years ago, we reported[1] 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 studies[2] directed towards the synthesis of 2',3'-dideoxynucleoside derivatives that are potential reverse transcriptase inhibitors[3], 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-Lyxofuranosyluracil[4] (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 pyrrole[5] (*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 microanalytical[6] and NMR (^{1}H and ^{13}C) 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 synthesis[7] from 2'-(4-tolylthio)uridine[1] (2; R = 4-MeC_6H_4).



Scheme 1 Ura = uracil-1-yl Tol = 4-MeC_6H_4

Reagents: (i) Ph_3CCl, C_5H_5N, 100°C; (ii) CH_3SO_2Cl, C_5H_5N, RT; (iii) 4-MeC_6H_4SH, NaH, $MeCONMe_2$ (DMA), 100°C; (iv) CF_3CO_2H (TFA), pyrrole, CH_2Cl_2, RT.

In order to complete this study, 1-β-D-arabinofuranosyluracil[8] and 1-β-D-xylofuranosyluracil[9] 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 yield[11].

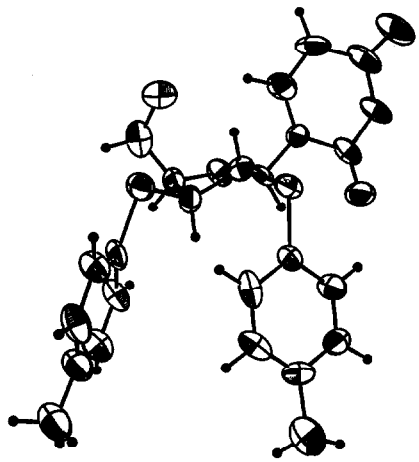
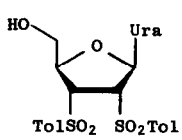
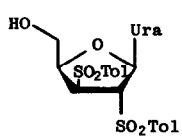


Figure 1. Computer-drawn plot of the molecular structure of (7).

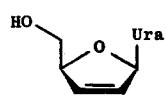
In consideration of the general overall stereochemistry of the reactions between toluene-4-thiolate ions and the isomeric 2',3'-di-*O*-mesyl-5'-*O*-trityl derivatives [(4), (6), (9) and (10)], all four products would be expected to have 2'-α-(4-toluenethio) substituents. In the cases of substrates (4) 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 derivatives[12]. 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 derivative[12].



(11)



(12)



(13)

Ura = uracil-1-yl Tol = 4-MeC_6H_4

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'-dideoxyuridine[13] (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, CH_2Cl_2, RT] and in 89% yield from the 3'-*O*-mesyl-5'-*O*-trityl derivative of 2'-(4-tolylthio)uridine (2; R = 4-MeC_6H_4); it was identical [TLC ($CHCl_3$-MeOH, 9:1 v/v), ^{1}H- and ^{13}C-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 ^{1}H-NMR spectroscopy; after the mixture had been allowed to react with an excess of 3-chloroperbenzoic acid in CH_2Cl_2 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-xylofuranosyluracil[9] is much less readily accessible than 1-β-D-lyxofuranosyluracil[4] (3).
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