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THE SYNTHESIS OF OPTICALLY ACTIVE DERIVATIVES OF 2,5-DIHYDROFURANS.

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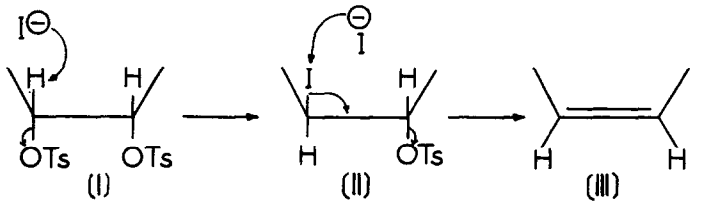
It has been suggested that 2', 3'-unsaturated nucleosides are possible intermediates in the biosynthetic pathway leading to 2'-deoxyribonucleosides (1,2), and that 2',3'-dideoxyadenosine (3,4) might inhibit selectively the biosynthesis of deoxyribonucleosides (DNA). These proposals have been responsible in recent years for the efforts directed toward the synthesis of (2,5-dihydro-2-furyl)-adenine and -pyrimidines (5,6) and (tetrahydro-2-furyl)-adenine (4,5). Structural elucidation of the antibiotic blasticidin S (7) as a 2', 3'-unsaturated derivative of cytosine has also stimulated the general interest in unsaturated nucleosides. Synthetic procedures for the introduction of 2', 3'-unsaturation in the carbohydrate moiety of pyrimidine and purine nucleosides have been reported from the corresponding 3'-O-tosyl-2'-deoxy derivative via base-catalyzed elimination reactions (5,6,8). Attempts to convert 2', 3'-thionocarbonate of ribonucleosides into the 2'3'-alkenes by the procedure of Corey and Winter (9) were unsuccessful (10,11,12).

As part of a research program in this area we report in this communication the synthesis of optically active derivatives of 2,5-dihydrofurans (VI, VII).

Contiguous sulphonyloxy groups have been converted into unsaturated derivatives by their reaction with iodide ion and zinc in both terminal and non-terminal positions in acyclic molecules (13,14) (I, II, III). The latter situation requires the use of N,N-dimethyl-formamide (DMF) as a solvent. The reaction occurs via the iodo-sulphonate (II), the stereochemistry of which is not critical because of the possibility of free rotation.



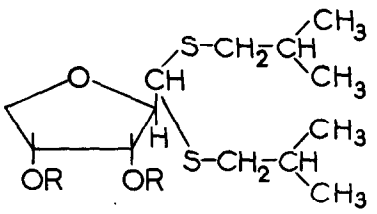
In view of the ease of nucleophilic displacements of secondary cyclic sulphonates in DMF, we have investigated the use of Tipson's reagent(14) on contiguous cyclic-disulphonyloxy compounds (V, XI).

A cis arrangement of the ester groups is now necessary, so that the intermediate iodo-sulphonyloxy compound (formed by displacement of one of the ester groups) has the necessary trans configuration for the elimination to occur.

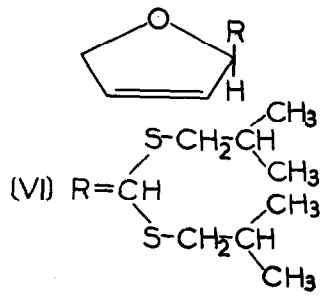
2,5-Anhydro-D-ribose diisobutyl dithioacetal (15) (IV) was reacted with tosyl chloride in pyridine to give 3,4-di-O-tosyl derivative (V), m.p. 90.5-91°, $[\alpha]_D^{29}$ - 50° (c 0.78 ; $CHCl_3$) ; (found : C, 54.03 ; H, 6.36 ; S, 21.04 $C_{27}H_{38}O_7S_4$, requires C, 53.82 ; H, 6.31 ; S, 21.26).

The di-O-sulphonate (V) could also be obtained in a one step procedure ; treatment of D-ribose diisobutyl dithioacetal (16) with tosyl chloride gave 2,5-anhydro-D-ribose diisobutyl dithioacetal (IV), which was further tosylated in situ to give 2,5-anhydro-3,4-di-O-tosyl-D-ribose diisobutyl dithioacetal (V) (86 %). In a similar way, 2,5-

anhydro-D-xylose diisobutyl dithioacetal (15), was converted into its di-O-sulphonate, m.p. 72-73°, $[\alpha]_D^{28}$ + 23° (c 1.33 ; $CHCl_3$).

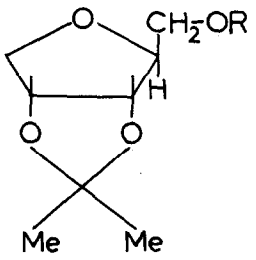


(IV) R = H
(V) R = OTs

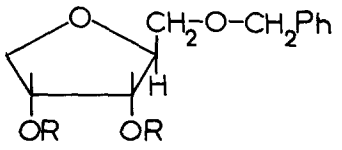


(VI)

(VII) $R=CH_2-O-CH_2Ph$
(VIII) $R=CH_2N_3$



(IX) R = H
(IXa) $R=CH_2Ph$



(X) R = H
(XI) R = Ts

When the ditosylate (V) was heated with sodium iodide-N,N-dimethylformamide-zinc dust at 168° for 5.5 hours, t.l.c., indicated the disappearance of the starting di-ester and the formation of a new product. The resulting oil (89 %) could be distilled and analyzed for (2R)-2-(aldehydo-diisobutyl dithioacetal)-2,5-dihydrofuran (VI), b.p. 103-105°/0.1 mm, $[\alpha]_D^{30}$ + 95.5 (c 1.36 ; $CHCl_3$), n_D^{26} 1.5065, (found : C 59.97 ; H, 9.35 ; S, 24.18 $C_{13}H_{24}OS_2$, requires C, 59.98; H, 9.25 ; S, 24.58).

The N.M.R. spectrum of (VI) shows unambiguously a broad-two proton signal at 5.99 p.p.m. due to the vinyl protons at C-3 and C-4, and consequently excludes the alternative structure having the unsaturation at C-2 and C-3.

The second unsaturated system (VII) was elaborated from 2,5-anhydro-3,4-O-isopropylidene-D-ribitol (IX) (17). The latter was treated with powdered potassium hydroxide and benzyl chloride to give the oily O-benzyl derivative (IX a), b.p. 125-127°/0.2 mm, $[\alpha]_D^{30}$ - 28.6° (c 1.78 ; $CHCl_3$), n_D^{26} 1.5010, (found : C, 68.42 ; H, 7.84 $C_{15}H_{20}O_4$, requires C, 68.18 ; H, 7.63).

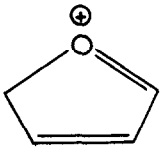
Acid hydrolysis of compound (IX a) afforded 2,5-anhydro-1-O-benzyl-D-ribitol (X), which with tosyl chloride in pyridine, gave the crystalline disulphonate (XI), m.p. 87-88°, $[\alpha]_D^{30}$ - 38° (c, 1 ; $CHCl_3$) ; (found : C, 58.64 ; H, 5.28 ; S, 12.09 $C_{26}H_{28}O_8S_2$, requires C, 58.64 ; H, 5.30 ; S, 12.02).

Treatment of the disulphonate (XI) with sodium iodide-N,N-dimethylformamide-zinc dust at 170° for 5.5 hours gave a liquide (82 %) formulated as (2R)-2-(benzyloxymethyl)-2,5-dihydrofuran (VII), b.p. 80-82°/0.1 mm, $[\alpha]_D^{29}$ + 67° (c 4.31 ; $CHCl_3$), n_D^{22} 1.5208, (found : C, 75.63 ; H, 7.32 $C_{12}H_{14}O_2$, requires C, 75.76 ; H, 7.42). The N.M.R. spectrum of (VII) showed in the region of 5.9 p.p.m. a broad two proton doublet, due to the vinylic hydrogens at C-3 and C-4.

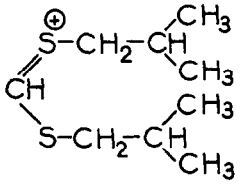
Applying the same approach, -described above - the synthesis of (2R)-2-(azidomethyl)-2,5-dihydrofuran (VIII) was also realized.

Compounds (VI, VII) did not show molecular ion peaks in their mass spectra, but the appearance of certain significant fragment ion peaks, confirms the assigned structures. Thus, compound (VI) shows peaks at m/e 69 and m/e 191 (M-69) corresponding to ions a and b, respectively.

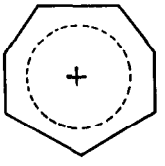
Similarly, compound (VII) exhibits in its mass spectrum the peaks at m/e 69, m/e 91, m/e 121, m/e 122, due to the ions a, c, d and e, respectively.



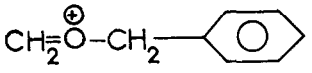
a, m/e 69



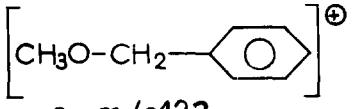
b, m/e 191



c, m/e 91



d, m/e 121



e, m/e 122

Further studies on the scope of this approach are currently in progress.

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Acknowledgments

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