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THE SYNTHESIS OF FUNCTIONALLY SUBSTITUTED OPTICALLY ACTIVE DERIVATIVES OF IMINO-2, 5-DIHYDROFURANS.(1,2)

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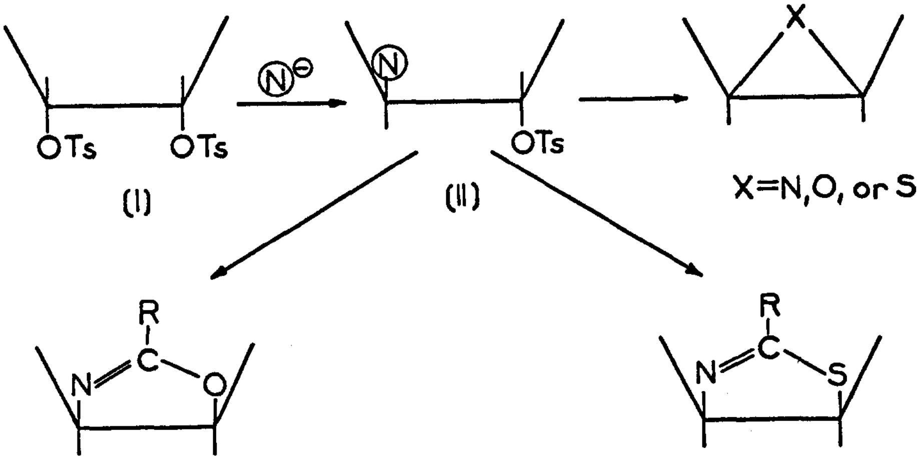
As a joint programme in our laboratories we have undertaken an investigation into methods of modifying the ribofuranose moiety in nucleosides and related compounds. Most work previously carried out in this field has used the opening of the 2,'3'-epoxide grouping as the initial step in introducing the required functional group (3).

We wish now to present a new approach to such synthesis namely the direct displacement of a sulphonyloxy group. Scheme I outlines the general method: selective displacement in a furanoid cis-sulphonyloxy system (I) with a nucleophile Ⓝ gives the key intermediate (II). Such an intermediate, with a trans arrangement of groups, could lead to a variety of derivatives, as shown, depending on the nature of Ⓝ .



SCHEME 1.

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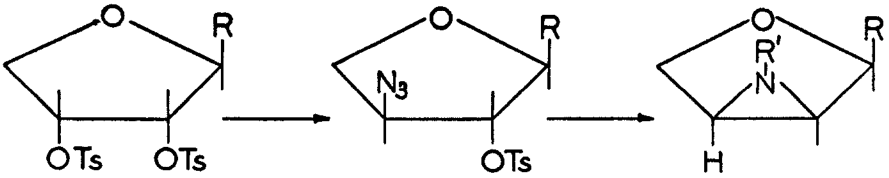
In view of the chemotherapeutic interest in molecules containing an aziridine (epimine) ring, (4), the above scheme has been utilized to produce this functional group. Recent investigations into this class of compound have led to epimines on 5-10 membered rings (5), epimino steroids (6), and epimino-carbohydrates (7). The one synthetic method that has been used successfully in both the steroid (6b) and carbohydrate fields (7a) utilizes a *trans*-azido-tosyloxy intermediate prepared by epoxide ring opening and tosylation. Scheme I allows ready access to this type of intermediate, avoiding the use of epoxides.

As a model for nucleoside studies we have used the readily accessible 2-substituted tetrahydrofuran. The ditosylate (III) (1) was heated with sodium azide in dimethylformamide for 1.5 hr. at 125°, when t.l.c. showed that it had been converted into a new product. The resulting oil (86%) could not be crystallized but infrared [2120 cm^{-1}(N$_3$); 1600 cm^{-1}(Ts)] and n.m.r. data were fully consistent with its being (4S)-azido-(2R)-formyl-(3R)-tosyloxy-tetrahydrofuran di-isobutyl dithioacetal (IV).

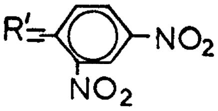
Rearward displacement is assumed to have occured at C-4 rather than C-3 because of the presence of the bulky group on C-2 (even if displacement had occured at C-3, the following steps are not affected).

The *trans* configuration about C-3 and C-4 was established by treatment of (IV)

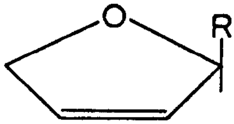


(III) (IV) (V) R'= H;

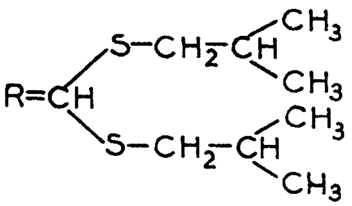
(VI) R'=



(VII) R'= Ac



(VIII)



with methalonic hydrazine hydrate and Raney nickel (of low activity) according to the procedure of Guthrie and Murphy (7a). (3S, 4S)- Imino-(2R)-formyl-2, 5-dihydrofuran di-isobutyl dithioacetal (V) (83%) was isolated as a distillable oil, b.p. 115-117°/003 mm, $[\alpha]_D^{27}$ + 2.7 (C 1.3, $CHCl_3$), n_D^{24} 1.5134, (found: C, 56.61; H, 9.31; N, 4.84; S, 23.13 $C_{13}H_{25}ONS_2$, requires C, 56.70; H, 9.15; N, 5.09; S, 23.17), characterized as its crystalline *N-2,4-dinitrophenyl derivative* (VI), *m.p.* 98,5-99°, $[\alpha]_D^{25}$ - 258°(*c* 0.5; $CHCl_3$); (found: C, 51.75; H, 6.14; N, 9.20; S, 14.76 $C_{19}H_{27}N_3O_5S_2$, requires C, 51.70; H, 6.17; N, 9.50; S, 14.50).

Pyrolytic rearrangement of N-acyl epimines are well known (5a). Generally, they rearrange at about 100° to 2-oxazolines during attempted distillation. Surprisingly, the N-acetyl-imine (VII) which was prepared in the usual way could be distilled without decomposition, b.p. 135-137°/0.03 mm, $[\alpha]_D^{27}$ + 17.8° (c 0.7; $CHCl_3$) n_D^{25} 1.5125, (found: C, 56.52; H, 8.30; N, 4.46; S, 20.38) $C_{15}H_{27}O_2NS_2$, requires C, 56.76; H, 8.58; N, 4.41; S, 20.18).

Epimines, with the nitrosating agent, sodium nitrite-acetic acid, yield olefines and nitrous oxide (6b, 8). The latter reaction is an excellent way of characterizing epimines and also provides an alternative procedure for preparing alkenes. The free epimine (V) was readily converted by the above method to (2R)-formyl-2, 5 -dihydrofuran di-isobutyl dithioacetal (VIII)(82%), identical with an authentic sample, recently prepared in our laboratory (1).

Compounds (V and VI) showed the molecular ion peaks in their mass spectra. The appearance of certain significant fragment peaks confirm the assigned structures.

The synthetic approach to nucleosides outlined in this Communication is currently under active investigation.

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