Synthesis of Deoxysugars and of Deoxynucleosides from Diol Thiocarbonates

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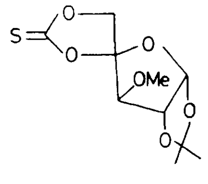
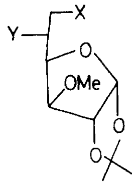
Summary Catalysed reduction of diol thiocarbonates with tributyltin hydride followed by appropriate alkaline hydrolysis affords a convenient synthesis of 2-, 3-, 4-, and 5-deoxysugars and of 2′- and 3′-deoxynucleosides.

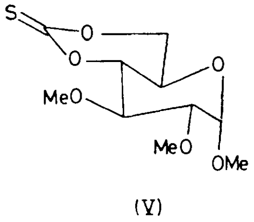
We recently reported[1] that treatment of the diol thiocarbonate (I) with methyl iodide gave quantitatively the 6-iodo-derivative (II). Reduction of the latter with chromous acetate in the presence of a thiol,[2] followed by alkaline hydrolysis, afforded the 6-deoxysugar (III) in excellent yield.



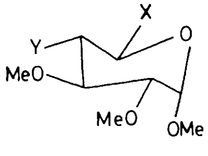
(I)



(II) X = I, Y = OCOSMe
(III) X = H, Y = OH
(IV) X = OH, Y = H

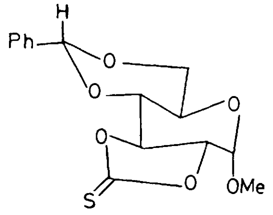


(V)

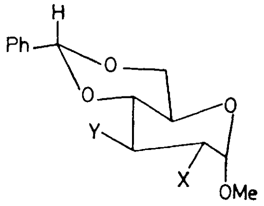


(VI) X = CH$_2$OH, Y = H
(VII) X = CO$_2$H, Y = H
(VIII) X = CO$_2$Me, Y = H
(IX) X = CH$_2$I, Y = OCOSMe
(X) X = Me, Y = OH

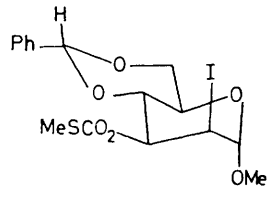
This reaction involves methylation of the sulphur and S_N2 displacement by iodide ion at the 6-position. It occurred to us that if the diol thiocarbonate group of (I) were opened in a radical fashion using tributyltin hydride[3] then a cleavage of the complementary regiospecificity should occur (secondary radical more stable than primary radical). Addition of (I) (1 mmol), tributyltin hydride (2 mmol), and azobisisobutyronitrile (0·02 mmol) in dry toluene (15 ml) to toluene (20 ml) under reflux under argon, with further additions of hydride and initiator as needed, gave, after alkaline hydrolysis, the 5-deoxysugar IV), $[\alpha]_D$ − 49° (*C*, 2·1 in CHCl$_3$), (57%). There was no



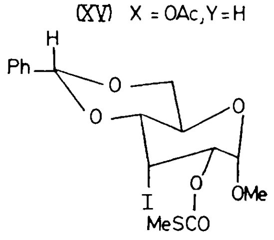
(XI)



(XII) X = H, Y = OH
(XIII) X = OH, Y = H
(XIV) X = H, Y = OAc
(XV) X = OAc, Y = H

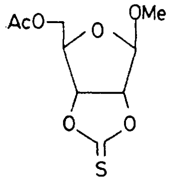


(XVI)

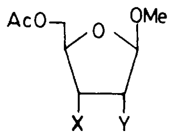


(XVII)

formation of the 6-deoxy compound (III). The compounds (III) and (IV) were characterised as their 3,5-dinitrobenzoates, m.p. 71—73 °C, $[\alpha]_D$ − 19° (*C*, 1·1 in MeOH) and m.p. 82—83 °C, $[\alpha]_D$ − 12° (*C*, 0·9 in MeOH) respectively (mixed m.p. depressed). Unlike other $\geq C{=}S$ systems,[3] an initiator was necessary for diol thiocarbonates.



(XVIII)

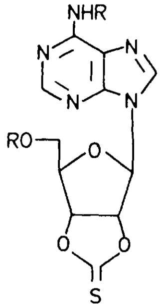


(XIX) Y = H, X = OAc

(XX) Y = OAc, X = H

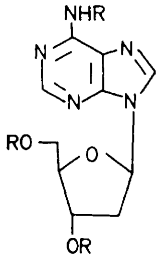
(XXI) Y(*epi*) = I, X = $\mathrm{O\overset{O}{\overset{\|}{C}}SMe}$

(XXII) Y = $\mathrm{O\overset{O}{\overset{\|}{C}}SMe}$, X (*epi*) = I



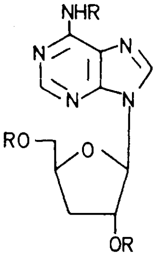
(XXIII) R = H

(XXIV) R = Ac



(XXV) R = H

(XXVII) R = $\mathrm{\overset{O}{\overset{\|}{C}}Me}$



(XXVI) R = H

(XXVIII) R = $\mathrm{\overset{O}{\overset{\|}{C}}Me}$

Similarly the diol thiocarbonate (V)[4] gave the 4-deoxysugar (VI), $[\alpha]_D$ + 70° (*C*, 1·0 in MeOH) (61%), characterised as the known toluene-*p*-sulphonate[5] and by oxidation with PtO_2–O_2 to the acid (VII) giving a methyl ester (VIII), $[\alpha]_D$ + 59° (*C*, 1·07 in $CHCl_3$). As expected, treatment of the thiocarbonate (V) with methyl iodide afforded the iodo-derivative (IX). This, on reduction with the chromous acetate–thiol reagent followed by alkaline hydrolysis gave the 6-deoxysugar (X), $[\alpha]_D$ + 119° (*C*, 1·2 in $CHCl_3$).

Similarly, the diol thiocarbonate (XI)[6] gave a mixture of the 2-deoxy-derivative (XII)[7] (30%) and the 3-deoxy-derivative (XIII)[3] (60%). These compounds were separated by chromatography of their acetates (XIV)[8] and (XV), m.p. 134—136 °C, $[\alpha]_D$ + 69° (*C*, 1·3 in $CHCl_3$), respectively.

Alternatively, the diol thiocarbonate (XI) was treated with methyl iodide to give the mixed iodides (XVI) and (XVII) in quantitative yield. Reduction with the chromous acetate-thiol reagent and alkaline hydrolysis gave the same mixture of deoxy-derivatives (XII) and (XIII) in the same good overall yield.

Likewise, the reaction of the ribofuranose thiocarbonate (XVIII), m.p. 104—106 °C, $[\alpha]_D$ − 60·01 (*C*, 0·59 in $CHCl_3$), with the tin hydride under the set conditions, followed by alkaline hydrolysis and acetylation gave the known 2-deoxy-derivative (XIX)[9] (60%) and the 3-deoxyderivative (XX)[9] (40%). The reaction of (XVIII) with methyl iodide gave the mixed iodides (XXI) and (XXII) in good yield. Reduction with the chromous acetate–thiol reagent, alkaline hydrolysis, and acetylation gave the same 2-deoxy-derivative (XIX) and the 3-deoxy-derivative (XX) in the ratio of 2 : 1 as indicated by n.m.r. and optical rotational data.

The reaction was successfully explored in the nucleoside area also. Thus, the known diol thiocarbonate (XXIII)[10] was converted into the diacetate (XXIV), m.p. 140—143 °C, $[\alpha]_D$ −27·5° (*C*, 0·8 in MeOH), which on treatment with tributyltin hydride in the presence of azobis-isobutyronitrile in dimethylacetamide as solvent, followed by alkaline hydrolysis, gave the known 2′-deoxyadenosine (XXV)[11a,b] (60%) and 3′-deoxyadenosine (XXVI)[12] (31%). These compounds were further characterised as their acetates (XXVII)[11b] and (XXVIII), m.p. 140—142 °C, $[\alpha]_D$ −18° (*C*, 0·7 in MeOH), respectively.

These two complementary methods of deoxygenation have potential application in the chemistry of aminoglycoside antibiotics.

All compounds had n.m.r., i.r., u.v., and mass spectra in accordance with the assigned structures. New compounds gave correct microanalyses.

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