A NEW ROUTE TO THE SYNTHESIS OF CYCLITOL DERIVATIVES

ADIL A. OTHMAN, NAJIM A. AL-MASUDI and USAMA S. AL-TIMARI

Department of Chemistry, University of Basrah, P.O. Box 752, Basrah, Iraq

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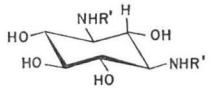
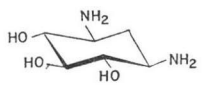
Three cyclitol derivatives, 2,4/3-triacetoxycyclohexanone diethyl dithioketal (**XVIII**), and 2,3,4-tri-O-acetyl-1-O-ethyl-2,4/1,3-cyclohexanetetrol (**XXA**) and 2,3,4-tri-O-acetyl-1-O-ethyl-1,2,4/3-cyclohexanetetrol (**XXB**), have been synthesized *via* the cyclisation of 2,3,4-tri-O-acetyl-5,6-dideoxy-D-*xylo*-hex-5-enose diethyl dithioacetal (**XIV**) and the cyclisation of 2,3,4-tri-O-acetyl-5,6-dideoxy-D-*xylo*-hex-5-enose diethyl acetal (**XV**) under ultraviolet or direct sunlight, in aqueous acetone.

Streptomycin may be the most famous in a large class of aminocyclitol antibiotics[1]. Their members are basically built of two sugar molecules and a cyclitol derivative (*e.g.* streptidine, **I**).

Other examples of this class which contain the 2-deoxystreptamine moiety (**II**) are neomycins, kanamycins (**III**), gentamicins[2] (**IV**) and ribostamycin[3] (**V**).



R'= $-\overset{NH}{\overset{\|}{C}}-NH_2$ (I)

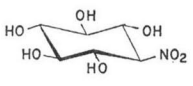


2-Deoxystreptamine (II)

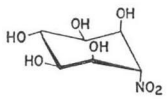
The chief supplies of the cyclitol derivatives[4] come from their natural sources[5]. While the synthesis of the various kinds of cyclitol rings and constructing their functional groups in the desired configurations can be outlined into three major lines:

1. the synthesis from non-cyclitols, non-sugars materials,[6~16]
2. the synthesis from cyclitols,[5,15,17~19]
3. the synthesis from sugar precursors[20~25].

The most important synthesis of the third type was reported by GOSHEINTZ and FISCHER[20] which involved the synthesis of a mixture of nitrocyclitols of *scyllo*-configuration (**VI**) and *muco*-configuration (**VII**) in equal proportions.



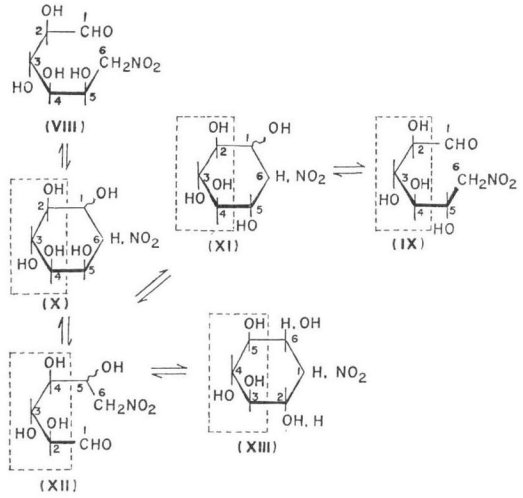
Scyllo-configuration
(**VI**)



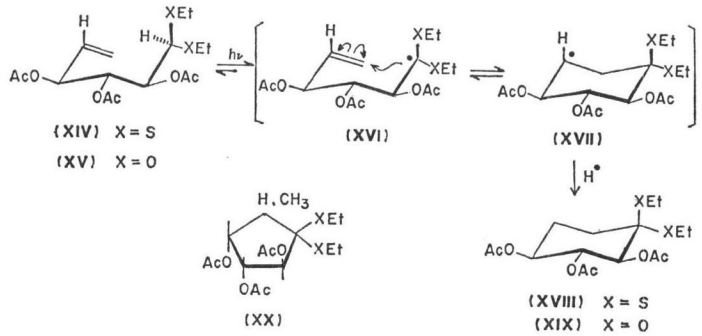
Muco-configuration
(**VII**)

The synthesis was achieved by the base catalyzed cyclisation of 6-deoxy-6-nitro-D-glucose (**VIII**) and the 6-deoxy-6-nitro-L-idose (**IX**) as in the following scheme:
In this synthesis, three asymmetric centers suffered epimerization throughout the cyclisation and opening reactions.

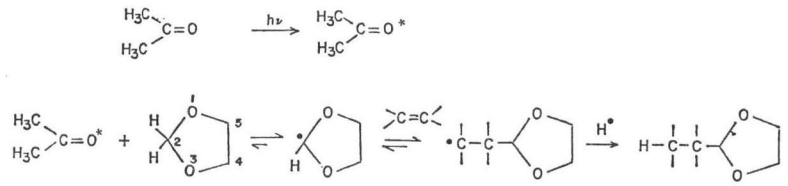
The work described in this paper shows cyclisation of two acetal olefins **XIV** and **XV** without rish of epimerization in the asymmetrical centers of the starting saccharide. This has been accomplished by the irradiation of the olefinic acetals[28] (**XIV** and **XV**) in aqueous acetone solution under ultraviolet



light of direct sunlight. The course of photochemical cyclisation is expected to proceed *via* the following pathway:



The direct excitation of acetals and addition to the olefinic bonds should require ultraviolet light of a short wave length[26,27]. But the ketone-initiated photochemical reactions of acetal and olefin are induced by light of wave lengths longer than 290 nm and involve absorption of light by ketonic compound through n-π^* transition. The next step involves an abstraction of hydrogen atoms from the acetals by the excited ketonic molecules.



Acetone-initiated Photochemical Addition of 1,3-Dioxolane to Olefin.

The hydrogen atoms at C–2 of the 1,3-dioxolane are expected to be more activated due to the combined inductive effect of oxygen 1 and 3. Thus the free radical is most likely formed at C–2 and therefore added to the olefinic bond[27] to generate another free radical. The reaction is terminated by

extraction of a hydrogen-free radical from the medium. The actual olefins **XIV** and **XV** both acquire an acetal end with active hydrogen and an olefinic bond which on cyclisation give preferencially cyclohexane rings **XVIII** and **XIX** following anti MARKOWNIKOFF's rule although the MARKOWNIKOFF's addition to give the five-membered ring adduct **XX** is not utterly excluded. However, after the 2,3,4-tri-O-acetyl-5,6-dideoxy-D-*xylo*-hex-5-enose diethyl dithioacetal (**XIV**) and the 2,3,4-tri-O-acetyl-5,6-dideoxy-D-*xylo*-hex-5-enose diethyl acetal (**XV**) were made available,[28] the cyclisation study was attempted. The irradiation of the dithioacetal olefin (**XIV**) under the sunlight for 12 days gave in addition to the starting material and a very polar substance, a compound which was moderately polar and isolated by column chromatography. This fraction was attributed to the cyclic compound **XVIII** on the following basis.

The n.m.r. spectrum of **XVIII** showed a quartet at δ 5.73 ppm for H–3 with $J_{3,2}=9$ Hz and $J_{3,4}=9$ Hz, and a doublet at δ 5.72 ppm for H–2 with $J_{2,3}=9$ Hz and a multiplet at δ 5.4 ppm for H–4. A doublet of quartet appeared at δ 2.8 and 2.75 ppm integrated for two methylene groups and therefore attributed to $-S-CH_2-CH_3$ resonance which seemed to be asymmetric towards each other. The H–5 protons appeared as a quartet centered at δ 3.85 ppm while the $2\times$H–6 protons came under the methyl signals of the ethyl groups at δ 1.25 ppm. The latter showed a broad signal which made it difficult to analyze. However, the doublet at δ 4 ppm which is usually the position of the center acetal proton completely disappeared. The infrared spectrum showed no absorption at 1640 cm^{-1} for the double bond stretching which clearly appeared in the starting acetal olefin (**XIV**).

The five-membered ring product (**XX**) was excluded from the possibility due to the absence of its expected doublet at 1.0 ppm. Also it is thermodynamically less favoured than the six-membered ring possibility.

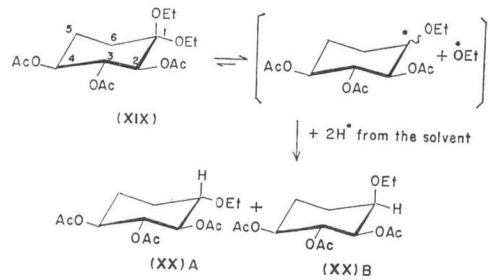
This photochemical cyclisation seemed to be sensitive to the intensity of light and to the solvent. When the irradiation was affected by a weak source of ultraviolet to make a condition similar to the sunlight, the starting material was recovered after 120 hours at 25°C. Using a stronger source of ultraviolet, cyclisation took place in dry acetone after 13 hours at 40°C. But if the irradiation was performed in aqueous acetone, a weak source of ultraviolet light was enough to effect cyclisation.

2,3,4-Tri-O-acetyl-5,6-dideoxy-D-*xylo*-hex-5-enose diethyl acetal (**XV**) was also irradiated in aqueous acetone both under ultraviolet light and under sunlight. The results were the same. The major photolysis product was isolated by column chromatography as a colourless syrup. Its infrared spectrum showed no olefinic band.

From the previous photolysis work on the diethyl dithioacetal (**XIV**), the result of the irradiation of **XV** ought to be the 2,4/3-triacetoxycyclohexanone diethyl ketal (**XIX**). The n.m.r. spectrum of the photolysis product showed a quartet at δ 5.38 ppm attributed to H–3 proton of $J_{3,2}=8$ Hz and $J_{3,4}=8$ Hz. The triplet centered at 5.16 ppm was not expected for H–2 proton unless C–1 acquired a proton, $J_{2,1}=6$ Hz and $J_{2,3}=8$ Hz. H–4 appeared as a double triplet centered at δ 5 ppm. It seemed reasonable from the analysis of the n.m.r. spectrum that the photoproduct cannot be actually described by structure **XIX**, but, one $-O-CH_2-CH_3$ must have been lost during the course of the reaction. This fact seemed to be evidenced by the appearance of the H–1 as it expected at δ 4.2 ppm as a broad triplet. The $-CH_2-$ protons appeared as a split quartet at δ 3.6 ppm and integrated for two protons only suggesting the presence of one ethoxyl group at C–1 in different environment. The signals for $-CH_3$ of ethoxyl group also appeared as a split triplet to strengthen the proposition that the photoproduct was a mixture of isomers (**XXA,B**). H–5 showed at δ 2.5 ppm as a broad triplet.

H–6 protons at δ 1.6 ppm showed as quartet.

The appearance of only one ethoxyl group in the n.m.r. spectrum of the photoproduct from **XV** might be explained to take place *via* the following route:



One of the ethoxyl groups of **XIX** might have been replaced by prolonged irradiation and due to the aggregation of many oxygen atoms at a small space of C–1 and 2.

The irradiation in aqueous acetone under the sunlight has given the same pattern of the reaction products shown under the direct ultraviolet light.

Since the irradiations were performed under relatively higher temperatures (30~60°C), a proof has to be provided to show that the change taken place on the starting material was effected only by ultraviolet light. The diethyl acetal olefin (**XV**) was heated in dark in an aqueous acetone under reflux for 10 hours and the reaction was followed by t.l.c. which showed two spots only. One non-polar component Rf 0.86 and the other one was very polar (Rf 0) and none of them were corresponding to the photoproducts.

Experimental

Ultraviolet irradiations were carried out by using a mercury lamp (1.1 A). Photolyses were performed in solution under normal atmosphere. Reaction containers were specified in each individual experiment.

Eluent used in thin-layer chromatography (t.l.c.) or in column chromatography was benzene – ethyl acetate, 1: 1.

Nuclear magnetic resonance (n.m.r.) spectrometer operating at 90 MHz.

Photolysis of 2,3,4-tri-O-acetyl-5,6-dideoxy-D-*xylo*-hex-5-enose diethyl dithioacetal (**XIV**) (under sunlight)

Diethyl dithioacetal olefin (**XIV**; 500 mg) of Rf 0.73 in 1% aqueous acetone (50 ml) was irradiated under direct sunlight in a Pyrex glass test tube for 12 days. The photolytic reaction was followed by t.l.c. which showed the development of two spots in addition to some of the starting material, one at Rf 0.39 and the other at the base line. The aqueous acetone solution was dried over anhydrous $CaCl_2$ and the acetone was evaporated under reduced pressure at room temperature to give a syrupy mixture (450 mg).

The syrup was absorbed into a column filled with silica gel (40 g), diluted with benzene – ethyl acetate, 1: 1. The first fraction was the starting acetal olefin (**XIV**, 200 mg). The second fraction was a colourless syrup (180 mg). The third fraction did not come down by this eluent. The I.R. of the second fraction showed no band at 1640 cm^{-1}. N.m.r. spectrum in $CDCl_3$ showed δ 5.73 (q) for H–3 $J_{3,2}$=9 Hz and $J_{3,4}$=9 Hz; δ 5.72 (d) for H–2, $J_{2,3}$=9.0 Hz; δ 5.4 (m) for H–4; δ 2.8 (q) and 2.75 (q) for 2 (CH_2); δ 3.85 (quartet) for H–5 and δ 1.25 (dt) and (m) for 2(CH_3) and 2(H–6). On the basis of n.m.r. this fraction is attributed to the 2,4/3-triacetoxycyclohexanone diethyl dithioketal (**XVIII**).

Photolysis of 2,3,4-tri-O-acetyl-5,6-dideoxy-D-*xylo*-hex-5-enose diethyl dithioacetal (**XIV**). (under ultraviolet light)

1. In dry acetone:

The diethyl dithioacetal olefin (**XIV**, 150 mg) in dry acetone (16 ml) was irradiated under ultraviolet light in quartz cell at 25°C for 5 days. T.l.c. showed no change in starting material and no development of any other spot. If the temperature raised to 40°C the reaction started after 3 hours of irradiation.

2. In aqueous acetone:

The diethyl dithioacetal olefin (**XIV**; 150 mg) in % aqueous acetone (16 ml) was irradiated under ultraviolet light in a quartz cell at 25°C. T.l.c. showed the beginning of development of other two spots after 45 hours. The irradiation was continued for further 3 days to give the same pattern of spots on t.l.c. shown in the irradiation under sunlight. The reaction mixture was worked up in the usual way to give identical I.R. and n.m.r. spectra to above.

Photolysis of 2,3,4-tri-O-acetyl-5,6-dideoxy-D-*xylo*-hex-5-enose diethyl acetal (**XV**) (under ultraviolet light):

1. In aqueous acetone:

The diethyl acetal olefin (**XV**, 250 mg) in 1% aqueous acetone (20 ml) was irradiated under direct sunlight in a Pyrex tube for 10 days. The proceeding of the reaction was followed by t.l.c. which indicated that most of the starting material was consumed to give rise to a moderately polar component of Rf 0.54 and other more polar component Rf 0.35 which was very faint. The aqueous acetone was dried over anhydrous $CaCl_2$, then it was evaporated under reduced pressure at room temperature to give a syrupy mixture (200 mg). The syrup was absorbed into a column of silica gel (20 g) to give three fractions. The less polar compound was the diethyl acetyl olefin (**XV**, 100 mg). The second function of two overlapped compounds of Rf 0.54 was a syrup (70 mg) which was attributed to the mixture of 2,3,4-tri-O-acetyl-1-O-ethyl-2,4/1,3-cyclohexanetetrol (**XXA**) and 2,3,4-tri-O-acetyl-1-O-ethyl-1,2,4/3-cyclohexanetetrol (**XXB**) on the basis of the I.R. and n.m.r. spectra.

I.R. data ν_{max}^{neat}: no absorption attributable to OH groups, 2990, 2915 (CH_2 stretching), 1740, 1715 cm^{-1} (carbonyl group); 1165, 1050 cm^{-1} (C–O–C stretching).

N.m.r. data:

δ 5.38 (q) for H–3, $J_{3,2}$=8 Hz and $J_{3,4}$=8 Hz; δ 5.16 (t) for H–2 $J_{2,1}$=6 Hz and $J_{2,3}$=8 Hz; δ 5 (dt) for H–4; δ 4.2 (t) for H–1 and 2×CH_3; δ 3.6 (split q) for (CH_2); δ 2.5 (t) for H–5 and δ 1.6 ppm (quartet) for H–6.

The third fraction was a trace of syrup, unidentified.

2. In dry acetone:

The olefin (**XV**, 200 mg) in dry acetone (25 ml) was irradiated under u.v. light in a quartz cell at 40°C. T.l.c. showed no change in the starting material.

Photolysis of 2,3,4-tri-O-acetyl-5,6-dideoxy-D-*xylo*-hex-5-enose diethyl acetal (**XV**) (under sunlight).

2,3,4-Tri-O-acetyl-5,6-dideoxy-D-*xylo*-hex-5-enose diethyl acetal (**XV**; 1 g) in 1% aqueous acetone (60 ml) was irradiated under direct sunlight in a Pyrex glass test tube for 5 days. T.l.c. showed the same products as above and after working up as in ultraviolet reaction, gave the starting material (**XV**; 120 mg), and a syrup of unseparable isomers of **XX** A and B (482 mg; 56%).

Thermolysis of 2,3,4-tri-O-acetyl-5,6-dideoxy-D-*xylo*-hex-5-enose diethyl acetal (**XV**) (in aqueous acetone).

The olefin (**XV**) was heated in aqueous acetone on a water bath (temperature 40°C) for 10 hours in dark. T.l.c. showed that most of the starting material was changed into a very mobile spot relating to neither of the spots mentioned in the photolysis work.

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