Tetrahedron Letters No.6, pp. 755-760, 1968. Pergamon Press. Printed in Great Britain.

ADDITION REACTIONS OF GLYCALS. III. (1) CHLORINATION OF D-GLUCAL TRIACETATE

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(Received in Japan 21 September 1967)

In 1920, Fischer, Bergmann and Schotte (2) have investigated chlorination of D-glucal triacetate (I) and isolated a crystalline "triacetyl glucal dichloride." Recently, Lemieux and Fraser-Reid (3) have clarified the structure of the dichloride as 3,4,6-tri-O-acetyl-2-chloro-2-deoxy-α-D-glucopyranosyl chloride (II). Furthermore, Lefar and Weill (4) have isolated II and another dichloride, m.p. 139-140°, the structure of which they have assigned as 3,4,6-tri-O-acetyl-2-chloro-2-deoxy-α-D-mannopyranosyl chloride, in the chlorination of I. We could isolate the possible four isomers of D-glucal triacetate dichlorides. This is the subject of this paper. The elemental analyses of all crystalline compounds obtained were satisfactory.

Firstly, I was chlorinated in a manner described in the literature (2), and the product was fractionated by a preparative thin layer chromatography (or a column chromatography) on silica gel using a mixture of benzene and ether in a ratio of 1 : 1 as a developer.

From the faster moving zone (R_f, 0.63), colorless crystalline II was obtained as silky needles in 62.5% yield (the physical constants and the nmr spectra of the products are summarized in Tables I, II, and III).

From the slower moving zone (R_f, 0.45), another dichloride was obtained as colorless needles in 12.5% yield. Its melting point and nmr spectrum were identical with those of 3,4,6-tri-O-acetyl-2-chloro-2-deoxy-α-D-mannopyranosyl chloride assigned by Lefar and Weill (4). However, we assigned it as 3,4,6-tri-O-acetyl-2-chloro-2-deoxy-β-D-mannopyranosyl chloride (III). The reasons are as follows. The rotation value was -44° (in $CHCl_3$). In the nmr spectrum the H_1 signal appeared at τ 4.37 as a doublet ($J_{1,2}$ = 1.2 cps). Lefar and Weill assigned the structure as α-D-manno configuration from the $J_{1,2}$ value. But α-D- or β-D-manno configuration cannot be assigned with certainty from the $J_{1,2}$ value because in both cases the $J_{1,2}$ values are very small (5). The chemical shifts of H_1, H_3 (τ 4.90) and H_5 (τ 6.20) are

Chart I

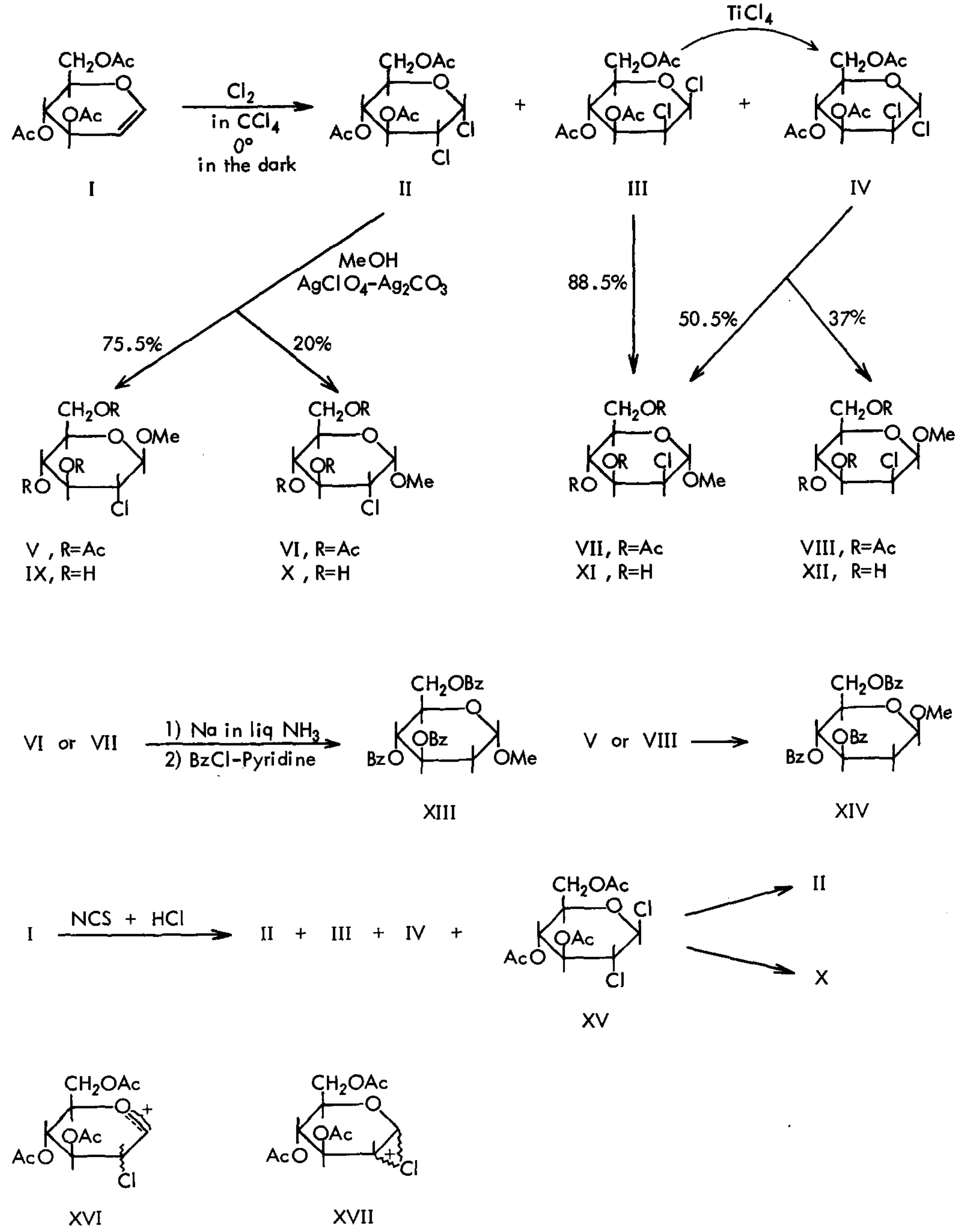
TiCl4
CH2OAc
AcO
OAc
Cl2
in CCl4
0°
in the dark
Cl
I
II
III
IV
MeOH
AgClO4-Ag2CO3
75.5%
20%
88.5%
50.5%
37%
CH2OR
RO
OR
OMe
V, R=Ac
IX, R=H
VI, R=Ac
X, R=H
VII, R=Ac
XI, R=H
VIII, R=Ac
XII, R=H
VI or VII
1) Na in liq NH3
2) BzCl-Pyridine
CH2OBz
BzO
OBz
XIII
V or VIII
XIV
I
NCS + HCl
II + III + IV +
XV
II
X
XVI
XVII

TABLE I
Physical Properties of Four Isomeric Dichlorides

	II	XV	III	IV
m.p. (°C)[a]	99-100	122.5-123	145.5-146	62-62.5
$[\alpha]_D^{temp}$ (in $CHCl_3$)[b]	^{23} +227.6°	^{24} +42.7°	^{23} -44°	^{24} +62.7°

[a] Melting points were measured using a monoscope (H. Boch, Frankfurt, Germany) and uncorrected.

[b] Rotations were measured using Perkin Elmer Type 141 Polarimeter (Bodensee, Germany).

assumed to be too high for α-D-manno configuration in comparison with those of II. When the structure of this compound is assigned as β-D-manno configuration all the contradictions disappear. We also clarified the structure chemically. Treatment of III with titanium tetrachloride afforded an isomeric dichloride as colorless prisms in 90% yield. In its nmr spectrum, the H_1 signal appeared at τ 3.83 as a doublet ($J_{1,2}$ = 1.4 cps), and the chemical shifts of the H_3 and H_5, which were not resolved well, were similar to those of the H_3 and H_5 of II. From this result the structure of this compound was assigned as 3,4,6-tri-O-acetyl-2-chloro-2-deoxy-α-D-mannopyranosyl chloride (IV). The rotation value also supported this assignment.

Methanolysis of III in methanol with silver perchlorate and silver carbonate as catalysts gave a sirupy methyl 3,4,6-tri-O-acetyl-2-chloro-2-deoxy-α-D-mannopyranoside (VII), $[\alpha]_D^{23}$ +37.4° (in $CHCl_3$), (lit.(6), $[\alpha]_D$ +45.2° (in $CHCl_3$)), in 89% yield. Deacetylation of VII gave a sirupy methyl 2-chloro-2-deoxy-α-D-mannopyranoside (XI), $[\alpha]_D^{24}$ +81.1° (in CH_3OH). Reduction of VII with metallic sodium in liquid ammonia and benzoylation of the product afforded methyl 3,4,6-tri-O-benzoyl-2-deoxy-α-D-glucopyranoside (XIII) (7).

Methanolysis of IV gave two products, which were isolated by a preparative thin layer chromatography. From the faster moving zone, VII was obtained in 50.5% yield. From the slower moving zone, methyl 3,4,6-tri-O-acetyl-2-chloro-2-deoxy-β-D-mannopyranoside (VIII), m.p. 120.5-121°, $[\alpha]_D^{22.5}$ -86.9° (in $CHCl_3$), was obtained in 37% yield. In its nmr spectrum, the H_1 signal appeared at τ 5.37 as a doublet ($J_{1,2}$ = 1.0 cps), the H_2 signal appeared at τ 5.53 as a quartet ($J_{2,3}$ = 3.5 cps) and the methyl signal appeared at τ 6.42 as a singlet. Hydrolysis of VIII with methanolic ammonia gave methyl 2-chloro-2-deoxy-β-D-mannopyranoside (XII), m.p. 134-134.5°, $[\alpha]_D^{24}$ -78.6° (in CH_3OH). Reduction of VIII with metallic sodium in liquid ammonia and benzoylation of the product gave methyl 3,4,6-tri-O-benzoyl-2-

deoxy-β-D-glucopyranoside (XIV) (7).

These results apparently indicate that the above assignments are correct.

Methanolysis of II gave methyl 3,4,6-tri-O-acetyl-2-chloro-2-deoxy-β-D-glucopyranoside (V), m.p. 154-155°, $[\alpha]^{23}_{D}$ +48.6° (in $CHCl_3$) (lit., m.p. 149-150°, (2,6), $[\alpha]_D$ +40.2° (2), +53° (in $CHCl_3$) (6)). Hydrolysis of V with methanolic ammonia gave methyl 2-chloro-2-deoxy-β-D-glucopyranoside (IX), m.p. 168-169°, $[\alpha]^{24}_{D}$ -11.9° (in H_2O) (lit., m.p. 164-165°, (2,6), $[\alpha]_D$ -12.9° (in H_2O) (6)). From the mother liquor of V another glucoside, methyl 2-chloro-2-deoxy-α-D-glucopyranoside (X), m.p. 143-143.5°, $[\alpha]^{24}_{D}$ +182.6° (in CH_3OH), was obtained by deacetylation with methanolic ammonia. Acetylation of X gave a sirupy methyl 3,4,6-tri-O-acetyl-2-chloro-2-deoxy-α-D-glucopyranoside (VI), $[\alpha]^{24}_{D}$ +171.2° (in $CHCl_3$). In its nmr spectrum, the H_1 signal appeared at τ 5.16 as a doublet ($J_{1,2}$ = 3.5 cps), the H_2 signal appeared at τ 6.08 as a quartet ($J_{2,3}$ = 10.5 cps), and the methyl signal appeared at τ 6.53 as a singlet. Reduction of VI with metallic sodium in liquid ammonia and benzoylation of the product gave XIII.

Methanolysis of the mother liquor after getting crystalline II described above, which did not contain III at all in its nmr spectrum and thin layer chromatography, gave mainly two spots on a thin layer plate. The product was separated by a preparative thin layer chromatography on silica gel. From the faster moving zone, which contained V, VI and VII, V was obtained in 3.7% yield (calculated from I used). From the faster moving zone, VIII was obtained in 1.9% yield (calculated from I used). The result showed that in the chlorination of I IV was produced in about 5% yield.

Chlorination of I with hydrogen chloride and N-chlorosuccinimide in ether (8) gave a chlorinated mixture. In one run, II, III, IV and XV were isolated in 15.7, 4.4, 1.4 and 10.7% yields, respectively, by repeating preparative thin layer chromatography of the product. The structure of XV was assigned as 3,4,6-tri-O-acetyl-2-chloro-2-deoxy-β-D-glucopyranosyl chloride. In its nmr spectrum, the H_1 signal appeared at τ 4.70 as a doublet ($J_{1,2}$ = 9.0 cps), and the H_2 signal appeared at τ 6.07 as a quartet ($J_{2,3}$ = 9.6 cps). Treatment of XV with titanium tetrachloride gave II in 70% yield. Methanolysis of XV and deacetylation of the product gave X in 60% yield.

The quantitative analyses of the chlorination products of I using gas-liquid chromatography are in progress.

We would like to propose that the chlorination of I in a manner described by Fischer et al. (2) mainly

TABLE II
Chemical Shifts of Methine and Methylene Protons (τ)[a]

	H_1		H_2		H_3	H_4	H_5	H_6
	e	a	e	a	a	a	a	
II	3.84d			5.82q	4.45q	4.90t	~5.50m	~5.83m
XV		4.70d		6.07q	4.72t	4.95t	~6.10m	~5.81m
III		4.37d	5.42q		4.90q	4.56t	~6.20m	5.77d
IV	3.83d		5.35		~4.48m		~5.60m	~5.77m

[a] Nmr spectra were measured with a Varian A60 spectrometer in deuteriochloroform using tetramethylsilane as an internal standard. Observed multiplicities: d, doublet; t, triplet; q, quartet; m, multiplet. In the case of complex, overlapping, or incompletely-resolved multiplets, the chemical shifts given may be approximate (~) values; e, equatorial; a, axial.

TABLE III
First-Order Coupling Constants of Protons (cps)

	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$
II	3.5	10	9	9
XV	9.0	9.6	9.6	9.6
III	1.2	3.5	9.5	9.5
IV	1.4	3.0		

proceeds by way of a four-centered transition state or a concerted mechanism. The four isomers of dichlorides thus obtained were not affected to a detectable extent when subjected to the condition of chlorination. This result indicated that this reaction was kinetically controlled. We cannot much argue about the mechanism from the predominant formation of II (3) because II can be formed by way of a four-centered transition mechanism as well as by way of an axial attack of chlorine anion at C_1 of an oxocarbonium ion intermediate (XI). However, the fact that III was predominantly obtained over IV in the products with D-manno configurations, can only be explained by way of the four-centered transition state because III can not be expected to form from the oxocarbonium ion intermediate (XVI) or chloronium ion intermediate (XVII). This proposal also offers a precise explanation for the preferable formation of II over III (the ratio of II : III is about 5 : 1) since the approach of the reagent from a direction to form III was unfavored owing to the so-called "Δ^2-effect" (9) and dipole-dipole interaction, but there is no such effects to form II. The formation of IV probably showed that a part of the reaction proceeds by way of the oxocarbonium ion (XVI) or the chloronium ion (XVII) intermediates.

Although until recently cis-addition of chlorine to an olefin has been regarded as exceptional, it is known that in several cases (10) cis-addition of chlorine occurred.

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