The fate of the original alcohol component of the ether has not been defined in these examples.

Experimental

Materials.—The polyhydric alcohols were all commercially available products. The reaction solvent, *N,N*-dimethylformamide, and the triethylamine were fractionally distilled commercial samples (b.p. 149–150° and 89.0°, respectively). The 2,4-dinitrofluorobenzene was used without purification as obtained from the Pierce Chemical Co., Rockford, Ill. The 2,4,6-trinitrofluorobenzene was prepared by the method of Vogel and Henne.[8]

Preparation and Properties of 2,4-Dinitrophenyl Ethers.—Examples are given of the various techniques employed in the derivatization of the polyhydric alcohols. Complete data on yields, melting points, analyses and X-ray powder diffraction patterns[9] are given in Table I; a representative infrared absorption spectrum is given in Fig. 1. The 2,4-dinitrophenyl ethers of the polyhydric alcohols were insoluble in water, diethyl ether, ethanol, benzene, chloroform, carbon tetrachloride, pyridine, ethyl acetate and acetic acid. These ethers were soluble (with wide variations in degree) in acetone, *N,N*-dimethylformamide, nitrobenzene and dimethyl sulfoxide. Their solutions showed a slight yellow color. On pouring solutions of the ethers in concd. sulfuric or nitric acids into water the ethers were recovered unchanged. Although the ethers were stable under most conditions, low order detonations resulted on heating in a direct flame or on striking them with a hammer on steel.

Tetrakis-*O*-(2,4-dinitrophenyl)-erythritol.—Erythritol (11 mmoles) was added to a stirred suspension of 10 g. of potassium carbonate powder in 50 ml. of *N,N*-dimethylformamide containing 75 mmoles of 2,4-dinitrofluorobenzene. After stirring for 40 hr., the insoluble salts were removed by filtration and washed with added solvent. The blood-red filtrate and washings were diluted with 1 liter of benzene. The yellow-orange precipitate was collected and washed with ethanol and hot water. The powder was dried (110°) and dissolved in a minimum of warm acetone. After treatment with activated carbon, the solution was concentrated and benzene added. Cooling afforded crystals which were recrystallized in the same manner to give a white product; yield 4.1 g.

If the 2,4-dinitrofluorobenzene was replaced by equimolar amounts of either 2,4,6-trinitrofluorobenzene or its chloro analog, the only product isolated was potassium 2,4,6-trinitrophenoxide in high yield. Potassium 2,4-dinitrophenoxide could also be isolated in low yield from the water washings of the 2,4-dinitrofluorobenzene crude reaction product.

Hexakis-*O*-(2,4-dinitrophenyl)-D-mannitol.—D-Mannitol, 15 g., was added to a mixture of 75 ml. of triethylamine, 75 ml. of 2,4-dinitrofluorobenzene and 180 ml. of *N,N*-dimethylformamide. After stirring for 24 hr. at room temperature, the reaction mixture (a deep red solution) was acidified with dilute hydrochloric acid, diluted to 1 liter with water and cooled. The hard mass of precipitate was separated by decantation and washed with water before drying. The dry solid was extracted twice with small volumes of cold acetone, once each with hot ethanol and hot water. After drying again, the solid was dissolved in hot *N,N*-dimethylformamide, treated with activated carbon, and benzene added (hot) until crystallization ensued. Cooling, followed by the further addition of benzene, afforded 79 g. of slightly yellow crystals, hexakis-*O*-(2,4-dinitrophenyl)-D-mannitol. The analytical sample was crystallized once more from acetone–benzene.

If 2,4,6-trinitrofluorobenzene was substituted for the dinitro analog in the above process, an intensely black mixture resulted which did not afford any solid material when processed as above or by various alternate methods. If no base was added to the reaction mixture, no reaction occurred (72 hr.) and the D-mannitol could be recovered in 85% yields by filtration. The filtrate failed to produce turbidity on addition to water. Substitution of 2,4-dinitrochlorobenzene for the fluoro analog resulted in extremely low yields of the desired fully etherified derivatives. No reaction was observed with 4-nitrofluorobenzene.

COLUMBUS 10, OHIO

(8) G. Vogel and A. Henne, unpublished work.

(9) A complete tabulation of these data is presented in the M. Sc. Thesis of B. O. Juliano, The Ohio State University, 1958.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, STANFORD UNIVERSITY]

The Acid-catalyzed Anomerization of Acetylated Aldopyranoses[1]

BY WILLIAM A. BONNER

RECEIVED SEPTEMBER 23, 1958

Three acetylated aldohexopyranoses, an acetylated 6-deoxyaldohexopyranose and three acetylated aldopentopyranoses have been studied from the viewpoint of their sulfuric acid-catalyzed anomerization in 1:1 acetic acid–acetic anhydride solvent. In each case the rate of anomerization has been found to be approximately first order in sulfuric acid concentration and first order in acetylated aldopyranose concentration. Acetylated aldopentopyranoses have been found to anomerize 8-25 times as rapidly as acetylated aldohexopyranoses, a feature which can be rationalized by steric shielding of the anomeric center by the C5 acetoxymethyl groups in the latter series. Several tentative generalizations regarding the effect of stereochemical configuration on the anomerization rates of acetylated aldohexoses and aldopentoses are pointed out. The equilibrium constant for each acetylated aldopyranose anomerization has been estimated, and it has been found that the predominant anomer at equilibrium may be qualitatively predicted by application of the Hassel–Ottar effect.

Introduction

Although the action of Lewis acids in mixtures of acetic acid and acetic anhydride on acetylated β-D-aldopyranoses has been widely used[2] as a synthetic tool for the general preparation of poly-*O*-acetyl-α-D-glycopyranoses, relatively little attention has been paid to the fundamental mechanism of this anomerization reaction. In 1951, we published[3] the results of a rather detailed kinetic study of the sulfuric acid-catalyzed anomerization of the penta-*O*-acetyl-D-glucopyranoses, (a) pointing out the approximately linear relationship between anomerization rate and acid concentration, (b) indicating the absence of a salt effect in the anomerization, (c) studying the effect of solvent composition, particularly with respect to acetic anhydride concentration, on the rate of anomerization, (d) demonstrating the specificity of the anomerization process for the anomeric center and (e) suggesting a mechanism for anomerization consisting essentially of an SN2 attack by the conjugate acid of acetic anhydride on the anomeric carbon. In 1953, Painter disclosed[4] the results of a similar study

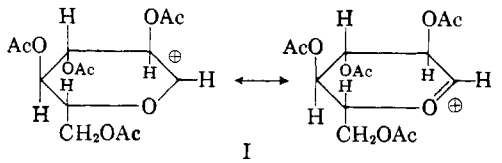
(1) We are indebted to the Quaker Oats Co. for their generous support of a portion of this research.

(2) *Cf.* ref. 3 for a number of specific examples.

(3) W. A. Bonner, THIS JOURNAL, **73**, 2659 (1951).

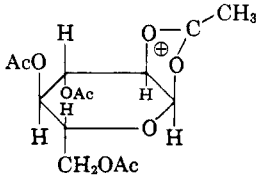
(4) E. P. Painter, *ibid.*, **75**, 1137 (1953).

employing both sulfuric and perchloric acids as anomerizing catalysts. Confirming and extending our earlier observations, he arrived, primarily on the basis of the inhibiting effect of acetic acid on the anomerization rate, at the conclusion that the C-1 carbonium ion hybrid (I), formed by a rate-deter-



I

mining first-order dissociation of the penta-*O*-acetyl-D-glucopyranose, was the important anomerization intermediate. Later Lemieux, Brice and Huber, in an elegant study comparing polarimetrically determined anomerization rates with radiochemically determined C-1 acetoxy exchange rates, found[5] that the inversion rate for the $\alpha \rightarrow \beta$ process and the exchange rate for labeled C-1 acetoxy in penta-*O*-acetyl-α-D-glucopyranose were identical in a 1:1 mixture of acetic acid and acetic anhydride 0.5 *M* in sulfuric acid, while the exchange rate for penta-*O*-acetyl-β-D-glucopyranose was about 17 times as rapid as was the inversion rate for $\beta \rightarrow \alpha$. While the first of these observations supported our original suggestion of an SN2 mechanism for anomerization, the authors argued that an ionic mechanism was not rigorously excluded, and suggested that an ionic intermediate (II) involving participation by



II

the acetoxy group at C-2 was likewise important in the anomerization–exchange picture.

Since our original study[3] we have undertaken further investigation of the anomerization reaction, and report our recent observations in this and following papers. At the outset it seemed desirable to extend anomerization studies to acetylated sugars other than the penta-*O*-acetyl-D-glucopyranoses. These studies are the subject of the present paper.

Experimental

Poly-*O*-acetylaldopyranoses.—The acetylated α- and β-anomers of D-glucopyranose, the acetylated β-anomers of D-mannopyranose, D-galactopyranose, 6-deoxy-D-glucopyranose, D-xylopyranose, D-ribopyranose and the acetylated α-anomer of *L*-arabinopyranose were employed in the polarimetric studies described below. These samples, except as noted below, were prepared by acetylation of the free aldoses by methods adequately described in the literature, and were purified by recrystallization until their melting points and specific rotations were in agreement with the corresponding values found in the literature. The purified samples were dried in a vacuum desiccator prior to their use in anomerization experiments.

Tetra-*O*-acetyl-L-arabinopyranose.—Tri-*O*-acetyl-β-L-arabinopyranosyl chloride was prepared by the action of acetyl chloride containing anhydrous zinc chloride on L-arabinose, after the procedure of Brauns.[6] The crude product had m.p. 146–147° in agreement with the literature[6] and was used below after a single recrystallization from an ether–ligroin solvent. The product was dissolved in anhydrous ether, treated with an excess of silver acetate, and the mixture was stirred under reflux in the presence of glass beads for 4 hours. The solids were filtered and the solvents evaporated from the filtrate. Lacking seed crystals, the sirupy product, $[\alpha]^{25}D$ +43.2° (*c* 4.3, $CHCl_3$), could not be crystallized from the usual solvents. Since its rotation, however, was close to that described[7] in the literature, $[\alpha]^{25}D$ 42.5° ($CHCl_3$), for tetra-*O*-acetyl-α-L-arabinopyranose, the desiccated sirupy product above was employed as such in anomerization reactions as described below. The combined product from three such anomerization reactions was isolated as described below for anomeric equilibrium composition determination (Table III). On standing, the crude product partially crystallized. Recrystallized twice from dilute ethanol the resulting sturdy prisms melted constantly at 97° and had $[\alpha]^{25}D$ +146.5° (*c* 1.5, $CHCl_3$). This is the correct specific rotation ($[\alpha]^{25}D$ +147.2° ($CHCl_3$)[7]), but a newly reported melting point (lit.[7] 86°) for tetra-*O*-acetyl-β-L-arabinopyranose.

Anal. Calcd. for $C_{13}H_{18}O_9$: C, 49.06; H, 5.70. Found: C, 48.79, 48.77; H, 5.76, 5.76.

Tetra-*O*-acetyl-6-deoxy-D-glucopyranoses were prepared by the convenient reaction sequence described by Hardegger and Montavon,[8] involving finally the catalytic hydrogenation of the anomeric tetra-*O*-acetyl-6-deoxy-6-iodo-D-glucopyranoses. The products had properties corresponding closely to those described by Hardegger and Montavon.

Anomerization Experiments.—A solvent mixture containing equal volumes of C.P. acetic anhydride and C.P. acetic acid was prepared, and a portion placed in a 10-ml. volumetric flask; C.P. sulfuric acid (0.55 ml.) was added to the flask, rinsing the pipet well. The resulting solution was thermostated at 25.0 ± 0.1°, then diluted to the mark with solvent mixture, providing an anomerization reagent 1.0 *M* in sulfuric acid. The appropriate weight of poly-*O*-acetylaldopyranose was transferred to a 10-ml. volumetric flask and dissolved in a small volume of the above solvent mixture. After thermostating, an appropriate volume of the above 1.0 *M* sulfuric acid anomerization reagent was added, the contents were diluted to 10.0 ml. with solvent mixture, and the stopwatch was started. The reaction mixture was transferred to an all-glass, jacketed 2-dm. polarimeter tube through whose jacket 25.0 ± 0.1° water was circulated, and optical rotation observations were made at measured time intervals. The first-order rate constants recorded in the tables were calculated as previously[3] at the measured time intervals by the relationship

$$k\alpha + k\beta = \frac{2.3}{t} \log \frac{r_0 - r_e}{r_t - r_e}$$

where r_0 is the observed rotation at zero time, r_t that at the measured time t and r_e that at final equilibrium. The value for r_0 was obtained either by extrapolation of the mutarotation curve to zero time or by observing the rotation of a similar mixture lacking the sulfuric acid catalyst, the two methods giving concordant results. The rate constants given in the tables are the averages of five to twelve individual constants calculated for each run. The precision of these figures was generally comparable to that described in our earlier study.[3]

On completion of the anomerization the reaction mixture was diluted with water and allowed to stand a few minutes, whereupon the product was extracted into chloroform. The extract was washed with water, then sodium bicarbonate solution, then dried over anhydrous sodium sulfate, filtered and stripped of solvent *in vacuo*. The residue, generally in nearly quantitative yield, was dried *in vacuo* over phosphoric anhydride, during which time it usually crystallized. The equilibrium composition of the anomerized product was determined by measuring the specific rotation of the above crude sample after the manner which we employed previously.[3] We have generally retained the use of this method for estimating anomerization equilibria, although Painter has argued[4] that the observed rotation of the

(5) R. U. Lemieux, C. Brice and G. Huber, *Can. J. Chem.*, **33**, 134 (1955).

(6) D. H. Brauns, THIS JOURNAL, **46**, 1484 (1924).

(7) C. S. Hudson and J. K. Dale, *ibid.*, **40**, 995 (1918).

(8) E. Hardegger and R. M. Montavon, *Helv. Chim. Acta*, **29**, 1199 (1946).

final equilibrated reaction mixture is a better criterion of equilibrium composition than is the specific rotation of the isolated anomerized product. Lemieux and co-workers have confirmed[5] the slight discrepancies in estimated anomerization equilibrium values obtained by the two methods for the penta-*O*-acetyl-D-glucose (*ca.* 86% α- and 14% β-anomer by the reaction mixture rotation criterion *versus ca.* 83% α- and 17% β-anomer by the crude product specific rotation criterion[5]), and have substantiated the equilibrium composition of the isolated product by isotopic dilution analysis. We have continued to use primarily the rotation of the isolated product as the criterion for anomeric equilibrium composition both because of Lemieux' confirmation of its validity and because the method may be based on literature values of specific rotations (usually in chloroform) and does not require the measurement of the rotations of the less available α-anomers in the anomerization solvent (1:1 acetic acid–acetic anhydride) employed.

Results

In Table I it is seen that the approximately linear relationship between anomerization rate and sulfuric acid concentration, previously observed for penta-*O*-acetyl-D-glucopyranose anomerizations with both sulfuric[3,4] and perchloric[4] acids, applies also to a large number of acetylated hexoses and pentoses. As previously observed,[3] with both acetic anhydride and 1:1 acetic acid–acetic anhydride solvents, one notes generally in Table I (last column) a slight negative departure from this linearity at lower sulfuric acid concentrations, a feature also evident in Painter's data with perchloric catalyst.[4]

TABLE I

DEPENDENCE OF ANOMERIZATION RATES OF ACETYLATED ALDOPYRANOSES ON SULFURIC ACID CONCENTRATION IN 1:1 ACETIC ACID–ACETIC ANHYDRIDE AT 25.0°

Acetylated aldopyranose, concn. = 0.1 *M*	$[H_2SO_4]$, mole/l.	$k\alpha + k\beta$, min.$^{-1}$	$k\alpha + k\beta/[H_2SO_4]$, l./mole-min.
α-D-Glucose	0.50	0.0342	0.0684
β-D-Glucose	.10	.00534	.0534
β-D-Mannose	.50	.0334	.0668
	.25	.0150	.0600
β-D-Galactose	.50	.0788	.1572
	.25	.0338	.1351
	.10	.0114	.114
6-Desoxy-β-D-glucose	.50	.375	.750
	.10	.0569	.569
β-D-Xylose	.50	.810	1.620
	.25	.419	1.675
	.05	.0703	1.405
β-D-Ribose	.50	.284	0.568
	.25	.143	0.572
α-L-Arabinose	.50	.650	1.300
	.25	.289	1.157

Table II indicates that the first-order dependence of anomerization rate upon concentration of acetylated aldose, previously noted[3,4] for the penta-*O*-acetyl-D-glucopyranoses, is a general one. The relationship

$$\text{rate} = (k\alpha + k\beta)\,[\text{acetylated aldose}]$$

required at a given catalyst concentration by any of the anomerization mechanisms which have been proposed is seen to be quite general among the acetylated aldopentoses and aldohexoses studied. This fact is indicated by the essential independence of the *specific* anomerization rate of each acetylated aldose on concentration over a several fold range of acetylated aldose concentration.

TABLE II

INDEPENDENCE OF SPECIFIC RATE OF ANOMERIZATION ON CONCENTRATION OF ACETYLATED ALDOPYRANOSE IN 1:1 ACETIC ACID–ACETIC ANHYDRIDE 0.5 *M* IN SULFURIC ACID AT 25°

Acetylated aldopyranose	Concn. mole/l.	$k\alpha + k\beta$, min.$^{-1}$
β-D-Glucose[a]	0.20	0.0362[c]
	.10	.0326[c]
	.05	.0356[c]
α-D-Glucose[a]	.20	.0387
	.10	.0341
	.05	.0343
	Av.	.0352
β-D-Mannose[a]	.20	.0342
	.10	.0326
	Av.	.0334
β-D-Galactose[a]	.20	.0788
	.10	.0789
	Av.	.0788
β-D-Xylose[b]	.20	.418
	.10	.420
	Av.	.419
β-D-Ribose[b]	.20	.144
	.10	.143
	Av.	.143
α-L-Arabinose[b]	.20	.270
	.10	.309
	Av.	.289

[a] Catalyst conc., 0.50 *M*. H_2SO_4. [b] Catalyst conc., 0.25 *M*. H_2SO_4. [c] Data from Ref. 3.

Finally, in Table III are presented the anomerization equilibrium constants pertaining to the various acetylated hexopyranoses and pentopyranoses studied, as well as the individual rate constants applying to each

$$\alpha \underset{k\beta}{\overset{k\alpha}{\rightleftharpoons}} \beta$$

anomerization. The individual rate constants in Table III are, of course, open to the errors inherent in estimating the values for K_{eq} (*cf.* Experimental). The magnitude of the discrepancies occasioned by the alternative methods of estimating K_{eq} is suggested in Table III by the examples of D-glucose, D-mannose and 6-deoxy-D-glucose. In each case noted the equilibrated reaction mixture criterion gives a lower value for K_{eq} than does the specific rotation of the crude product criterion. This is the direction of error which might be expected if an optically inactive impurity (*e.g.*, residual solvent) were present in the crude anomerized product whose specific rotation was used as a criterion for K_{eq}.

Discussion

The data in Tables I and II indicate that the kinetic factors previously observed[3,4] in the case of the penta-*O*-acetyl-D-glucoses also apply quite generally to other acetylated hexoses and pentoses. Consequently, any mechanism found applicable to a specific anomerization reaction can reasonably be thought of as generally valid for other acetylated aldopyranose anomerizations. Comparison of the spe-

TABLE III

EQUILIBRIUM CONSTANTS AND INDIVIDUAL RATE CONSTANTS FOR ANOMERIZATIONS OF ACETYLATED ALDOPYRANOSES IN 1:1 ACETIC ACID–ACETIC ANHYDRIDE 0.5 *M* IN SULFURIC ACID AT 25°

Acetylated aldopyranose	Equilibrated product: $[\alpha]^{25}D$ ($CHCl_3$)	Equilibrated product: % α	Equilibrated product: % β	K_{eq} %β/%α	$k\alpha$,[c] min.$^{-1}$	$k\beta$,[c,d] min.$^{-1}$
D-Glucose	85.6°	84.0[a]	16.0[a]	0.191	0.0054	0.0283
	(88.0)[b]	(88.0)[b]	(12.0)[b]	(.137)	(.0041)	(.0296)
D-Mannose	43.2	86.0	14.0	.163	.0047	.0287
		(94.0)	(6.0)	(.064)	(.0020)	(.0314)
D-Galactose	89.6	79.0	21.0	.266	.0166	.0622
6-Deoxy-D-glucose	104.2	82.5	17.5	.212	.066	.309
		(88.5)	(11.5)	(.130)	(.043)	(.332)
D-Xylose	65.5	78.5	21.5	.274	.181[e]	.657[e]
D-Ribose	−31.9	22.5	77.5	3.45	.220	.064
L-Arabinose	97.4	47.0	53.0	1.128	.345	.305

[a] Equilibrium data based on specific rotation of the isolated anomerized products. [b] Figures in parentheses are equilibrium data based on the observed rotations of the final anomerized reaction mixtures. [c] Based on averages of $k\alpha + k\beta$ values in the present and previous work.[3] [d] Calculated by the relationship $k\beta = (k\alpha + k\beta)/(1 + K_{eq})$. [e] Measurement actually made with 0.25 *M* sulfuric acid catalyst; present values found by doubling the figures so obtained.

cific rates of anomerization (Tables I and III) for acetylated aldohexoses with acetylated aldopentoses indicates clearly that the latter class of compounds undergoes anomerization roughly eight to twenty-five times as rapidly as the former. Lemieux has similarly found[9] a considerable (8-fold) enhancement in the reactivity of acetylated aldopentoses over acetylated aldohexoses in regard to the rates of exchange of their C1 acetoxy groups with stannic trichloride acetate-C^{14}. It seems most reasonable to attribute such rate enhancements in the acetylated pentopyranose series to the simple absence of steric shielding. Examination of Fisher–Hirschfelder models of the acetylated aldoses in question demonstrates clearly that in most of the possible conformations an acetoxymethyl group attached to C5 interferes to a greater or lesser extent with the access path of a reagent attacking the anomeric center at C1. Since the anomerization reaction is specific at C1[3,5,9] it follows that a hydrogen (as in pentoses) rather than an acetoxymethyl group (as in hexoses) at C5 should lead to a rate enhancement. This purely steric explanation is borne out by the further example of tetra-*O*-acetyl-6-deoxy-D-glucopyranose, whose methyl group at C5 is intermediate in bulk between that of hydrogen and of acetoxymethyl. In this case the anomerization rate is intermediate between those typical for acetylated aldohexoses on the one hand and acetylated aldopentoses on the other.

In the hexose series the epimeric structure at C2 appears to have little effect on the specific anomerization rate. Thus (Tables I and II) the anomerization rates of acetylated D-glucose and D-mannose under conditions of comparable catalyst concentration are identical within experimental error. In the pentose series, however, the epimeric configuration at C2 appears to have greater anomerization rate significance, acetylated arabinose anomerizing at 2.3 times the rate of the epimeric acetylated ribose under similar conditions. That the relative configuration at C3 is also of importance in determining anomerization rate is seen (Tables I and II) by the almost 3-fold difference in rate between acetylated D-xylose and acetylated D-ribose. Similarly, Lemieux[9] has found that the configuration at C3 "has the overriding influence" on the reactivity of 1,2-*trans* acetylated aldoses with regard to C1 acetoxy exchange with stannic trichloride acetate-C^{14} in chloroform. The effect of configurational inversion at C4 on anomerization rate appears slightly less important but still significant. Thus (Tables I and II) it is seen that acetylated D-galactose anomerizes at slightly over twice the rate of the C4 epimeric acetylated D-glucose.

The above comparisons are made to indicate that the relative configurations of any of the carbon atoms C2 through C4 in the acetylated hexopyranose or pentopyranose chain may have a noticeable effect on the specific rate of anomerization. Unfortunately, the number of examples studied is too small to permit the establishment of completely valid generalizations with regard to the effect of configuration on anomerization rate, and the relationships pointed out above are, of course, to be interpreted as only apparent and tentative.

As regards the position of equilibrium in the anomerizations listed in Table III, it may be stated that the determining factor appears to be the Hassel–Ottar effect.[10] This empirical generalization, first discovered[10] in connection with the poly-*O*-acetylglycopyranosyl halides and later extended[11] to the alkyl glycopyranosides, states that that aldopyranoside anomer (whose ring size remains intact) will predominate at equilibrium whose two chair forms can be represented by the conformational relationships

For aldohexoses: $C1_{eq} - C5_{ax} \rightleftarrows C1_{ax} - C5_{eq}$

For aldopentoses: $C1_{eq} - C3_{ax} \rightleftarrows C1_{ax} - C3_{eq}$

while that anomer will be less abundant at equilibrium whose two chair forms can be represented by

For aldohexoses: $C1_{ax} - C5_{ax} \rightleftarrows C1_{eq} - C5_{eq}$

For aldopentoses: $C1_{ax} - C3_{ax} \rightleftarrows C1_{eq} - C3_{eq}$

Application of the Hassel–Ottar generalization to the acetylated aldohexo- and aldopentopyranoses

(9) R. U. Lemieux and C. Brice, *Can. J. Chem.*, **34**, 1006 (1956).

(10) O. Hassel and B. Ottar, *Acta Chem. Scand.*, **1**, 929 (1947).

(11) M. L. Wolfrom and A. Thompson, Chap. IV in W. Pigman, "The Carbohydrates," Academic Press, Inc., New York, N. Y., 1957, pp. 210 ff.

in Table III leads to a correct qualitative prediction of the predominant anomer at equilibrium in every case. This generalization, previously found applicable in the cases of poly-*O*-acetylglycopyranosyl halides and alkyl glycopyranosides, thus also appears valid in the case of poly-*O*-acetylglycopyranoses.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF CALIFORNIA, LOS ANGELES, AND THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF SYDNEY, AUSTRALIA]

Allylic Rearrangements. XLII. The Preparation and Some Reactions of 3β-Chlorocholest-4-ene and 3α-Chlorocholest-4-ene[1]

BY W. G. YOUNG, R. E. IRELAND, T. I. WRIGLEY, C. W. SHOPPEE, B. D. AGASHE AND G. H. R. SUMMERS

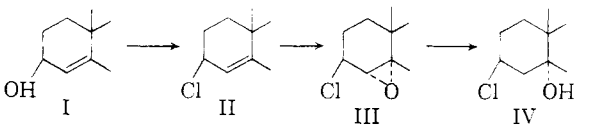
RECEIVED JUNE 23, 1958

The allylic chlorides named above have been prepared from 3β-hydroxycholest-4-ene and 3α-hydroxycholest-4-ene, respectively, and their structures established. The chlorides, by solvolysis in ethanol–dioxane (1:1) at 25°, exhibit kinetics of the first order with respect to the steroid and show closely similar rate constants (3β > 3α). The products of solvolysis under various conditions have been examined.

3β-Chlorocholest-4-ene (I, Cl quasiequatorial) was the sole isolatable product obtained by treatment of 3β-hydroxycholest-4-ene (I) with thionyl chloride in ether at 0° using the procedure of Plattner, *et al.*[2] A plot of the first-order kinetics obtained from solvolysis of the total product in alcohol–dioxane (1:1) at 25° gave a stright line between the limits 0–75% reaction. Beyond this point there was considerable drift in the rate, probably due to the presence in minor amount of a second allylic chloride. However, after several recrystallizations of this crude material, purer 3β-chlorocholest-4-ene (II) was obtained, as indicated by the almost complete elimination of this drift. The same chloride (II) was also obtained by use of phosphorus pentachloride in carbon tetrachloride; this result recalling the conversion of 7α-hydroxycholest-5-en-3β-yl acetate into 7α-chlorocholest-5-en-3β-yl acetate, with both thionyl chloride in ether and phosphorus pentachloride.[3]

The structure of the chloride II was established by conversion with perbenzoic acid to the 4α, 5α-epoxide (III), and reduction thereof with lithium aluminum hydride in ether to the known 3β-chloro-5α-cholestan-5-ol (IV).[4] This, by hydrogenation with platinum in ethyl acetate, gave 5α-cholestane. The 3β-configuration and quasiequatorial conformation[5] of the chlorine atom in II is confirmed by the infrared absorption spectrum, which exhibited a strong band at 760 cm.$^{-1}$ associated with the C-Cl stretching vibration (equatorial Cl, 736–856 cm.$^{-1}$; axial Cl, 646–730 cm.$^{-1}$[1,6a,b]).

Solvolysis of pure 3β-chlorocholest-4-ene in aqueous acetone at 45–55° in the presence of sodium bicarbonate, or in moist ether at 20° in the presence of silver hydroxide, gave cholesta-3,5-diene (*ca.* 15%), and 3β-hydroxycholest-4-ene (I) and 3α-hydroxycholest-4-ene (V) in approximately equal proportions (*ca.* 40% of each isomer). These reactions thus appear to proceed by an $S_{N}1$ heterolysis; the carbonium ion produced can acquire extra stability by resomerism and may therefore be sufficiently long-lived to assume its stable plane-trigonal form, so that the ultimate attack by the substituting agents affords an almost completely racemized product. However, use of potassium acetate in acetic acid at 20° afforded cholesta-3,5-diene (*ca.* 15%), with a marked preponderance of 3α-acetoxycholest-4-ene (70%) over the 3β-epimer (<10%); this predominant inversion of configuration suggests the incursion of $S_{N}2$ displacement despite the relatively weak nucleophilic power of the anion (OAc^{-}) involved.



Unlike its β-epimer, 3α-hydroxycholest-4-ene (V) could form a quasiaxial chlorosulfinate in which the chlorine would have relatively unhindered approach to C_5 enabling the operation of an $S_{N}1'$ mechanism. However, 3α-chlorocholest-4-ene (VI) was the major product from the reaction of the allylic alcohol (V) with thionyl chloride. Solvolysis of the total product and a plot for first-order kinetics gave a straight line between the limits 0–70% beyond which point there was considerable drift, presumably due to the presence of a second non-isolable allylic chloride, the rate of solvolysis of which was considerably slower than that of 3β-chlorocholest-4-ene (II). This minor product may be 5α-chlorocholest-3-ene (IX) resulting from an $S_{N}1'$ reaction. Lithium aluminum hydride reduction of the allylic chloride mixture afforded solely cholest-4-ene. The infrared spectrum of this total product showed no absorption at 773 and 671 cm.$^{-1}$ expected for cholest-3-ene,[7] the

(1) This investigation was commenced independently at the University of California (W.G.Y., R.E.I., T.I.W.) and at the University of Wales (C.W.S., B.D.A., G.H.R.S.); learning of each others' work we decided to publish our results jointly.

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