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1,3-*O*-Benzylidene-L-sorbose[1)]

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It has been proposed that 1,3-*O*-benzylidene-L-sorbose (III) exists as an equilibrium mixture of a pyranose form (IIIp), a keto-form (IIIk) and a furanose form (IIIf) in solutions. The acetylation of III in pyridine afforded the acetates of IIIf; one of them (IV) is in a keto-form (IVk) in a crystalline state, and at a low temperature, while the acetates of IIIf and IIIp at higher temperatures. When a pyridine solution of III was allowed to stand for some time before acetylation, the yield of the acetate of IIIp increased. The recrystallization of III usually gave crystals of IIIf, however, while the addition of petroleum ether to the concentrated pyridine solution of III afforded a powder which was consisted mainly of IIIp. These results suggest that III exists as IIIf in a crystalline state and as an equilibrium mixture of IIIf, IIIk, and IIIp in solution; the existence of this equilibrium was also confirmed by proton magnetic resonance spectroscopy.

The 1,3-*O*-acetal of L-sorbose (I) is a key intermediate in the acetalation of I, which is an important reaction for L-ascorbic acid production.[2-4)] We have successfully isolated two examples of this kind of acetals, 1,3-*O*-ethylidene-α-L-sorbopyranose (II) from the ethylidenation[3)] and 1,3-*O*-benzylidene-L-sorbose (III) from the benzylidenation.[2)] It is quite natural that the ring structure of II has a pyranose form, for I is stable in an α-L-pyranose form.[5)] On the other hand, much attention should be paid to the surprising fact with III that a β-furanose form (IIIf) of the *cis*-decalin type is more likely than an α-pyranose form (IIIp) of the *trans*-decalin type (see Chart 2). III exists as IIIf in a crystalline state, while IIIp is considered to exist only as an equilibrium mixture with IIIf in solution. This paper will be concerned with the equilibrium of III. For this purpose, further studies of the

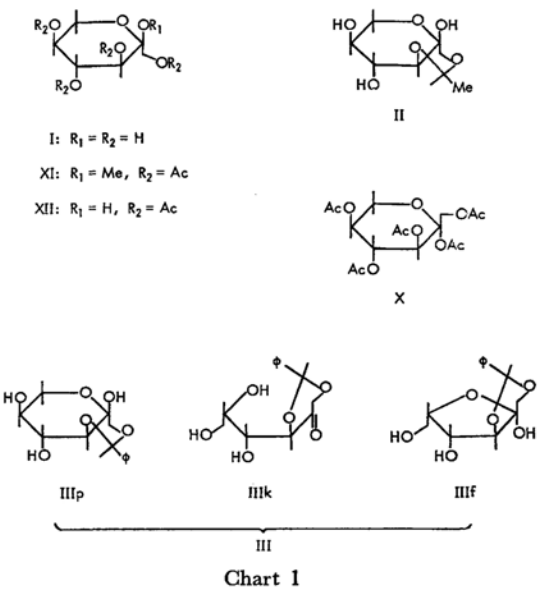

Chart 1

1) Sorboses XV. For Part XIV, See Ref. 2.

2) T. Maeda, M. Kimoto, S. Wakahara and K. Tokuyama, This Bulletin, **42**, 1668 (1969).

3) T. Maeda, M. Kiyokawa and K. Tokuyama, *ibid.*, **42**, 492 (1969).

4) T. Maeda and K. Tokuyama, *Tetrahedron Letters*, **1968**, 3079.

5) a) S. J. Angyal, "Conformational Analysis," ed. by E. L. Eliel, N. A. Allinger, S. J. Angyal and G. A. Morrison, John & Wiley, New York (1965), p. 351. b) J. C. Jochins, G. Taigel, A. Seelinger, P. Lutz and H. E. Driesen, *Tetrahedron Letters*, **1967**, 4363. c) I. Listowsky, S. Englard and G. Avigad, *Carbohyd. Res.*, **2**, 261 (1966).

acetylation of III and proton magnetic resonance spectroscopic studies were carried out.

The acetylation of III in pyridine with acetic anhydride at −5—6°C has been shown to give 4,6-di-*O*-acetyl- (V) and 2,4,6-tri-*O*-acetyl-1,3-*O*-benzylidene-β-L-sorbofuranose (VI), along with a limited amount of 4,5-di-*O*-acetyl-1,3-*O*-benzylidene-α-L-sorbopyranose (VII).[2] This fact suggests that III usually exists as IIIf in a pyridine solution at a low temperature. The acetylation at about −30°C gave strong support to this suggestion. The examination of the reaction by thin-layer chromatography (TLC) showed that a mono-acetate (IV) initially appeared and that V and VI then appeared at the expense of IV. No formation of detectable amount of VII was observed. The interuption of the reaction after 2 hr gave mainly IV, which was then converted into VI *via* V, by further acetylation, but not into VII.

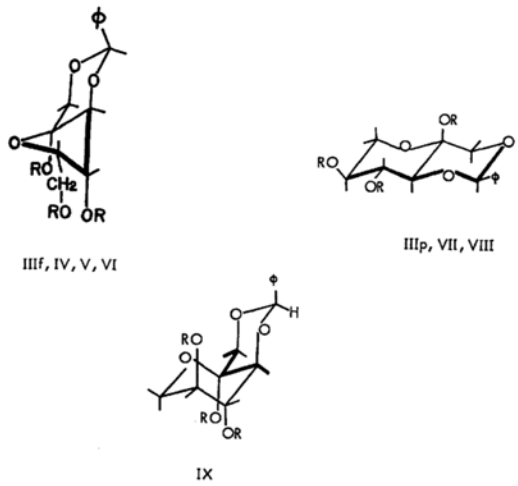

Chart 2

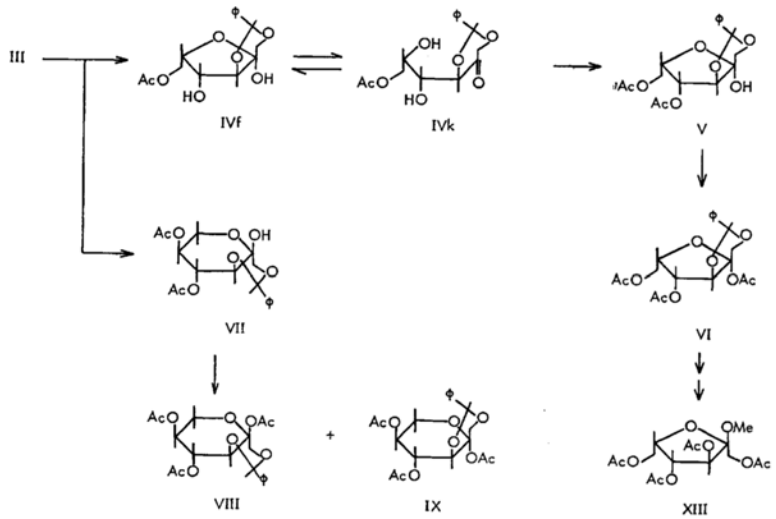

Chart 3

In view of the above facts, possibility of a pyranose structure for IV may be excluded. As the primary hydroxyl group at the C_6 position of IIIf must be more reactive for the acetylation than the secondary one at C_4,[6] the structure of IV is determined to be 6-*O*-acetyl-1,3-*O*-benzylidene-β-L-sorbofuranose. The PMR spectrum of IV in chloroform-d showing the absence of a proton on a tertiary carbon bearing an acetoxyl group (AcO$\underset{|}{\underline{C}}$H), confirmed this structure (Fig. 1).

The behavior of IV is very interesting. The infrared (IR) spectrum of IV in a KBr disk, showing two strong absorption bands at 1720 and 1740 cm^{-1} due to carbonyl groups (Fig. 2), and the optical rotatory dispersion (ORD), showing no Cotton effect[7] (Fig. 3), made it clear that IV exists as a keto-form (IVk) in a crystalline state to a considerable extent and as a furanose form (IVf) in solution.

The acetylation of III, IV, and V with acetic anhydride in pyridine gave VI as the final product, even though weak conditions were used.[8] This unexpected acetylation of a tertiary hydroxyl group was not observed in the case of VII. For the formation of the 2-*O*-acetyl derivative of VII

6) R. H. Adkins, *J. Am. Chem. Soc.*, **49**, 2517 (1927); **55**, 299 (1933); **56**, 442 (1934).

7) Acyclic ketoses are known to show a Cotton effect. See T. Sticzay, C. Reciar, K. Babor, M. Fedoroňks and K. Linek, *Carbohyd. Res.*, **6**, 418 (1968).

8) This type of abnormal acetylation has been reported on a Noranisation-derivative by Hirata *et al.*, however, a longer reaction period was required. K. Yamada, S. Takada, S. Nakamura and Y. Hirata, *Tetrahedron*, **24**, 1267 (1968).

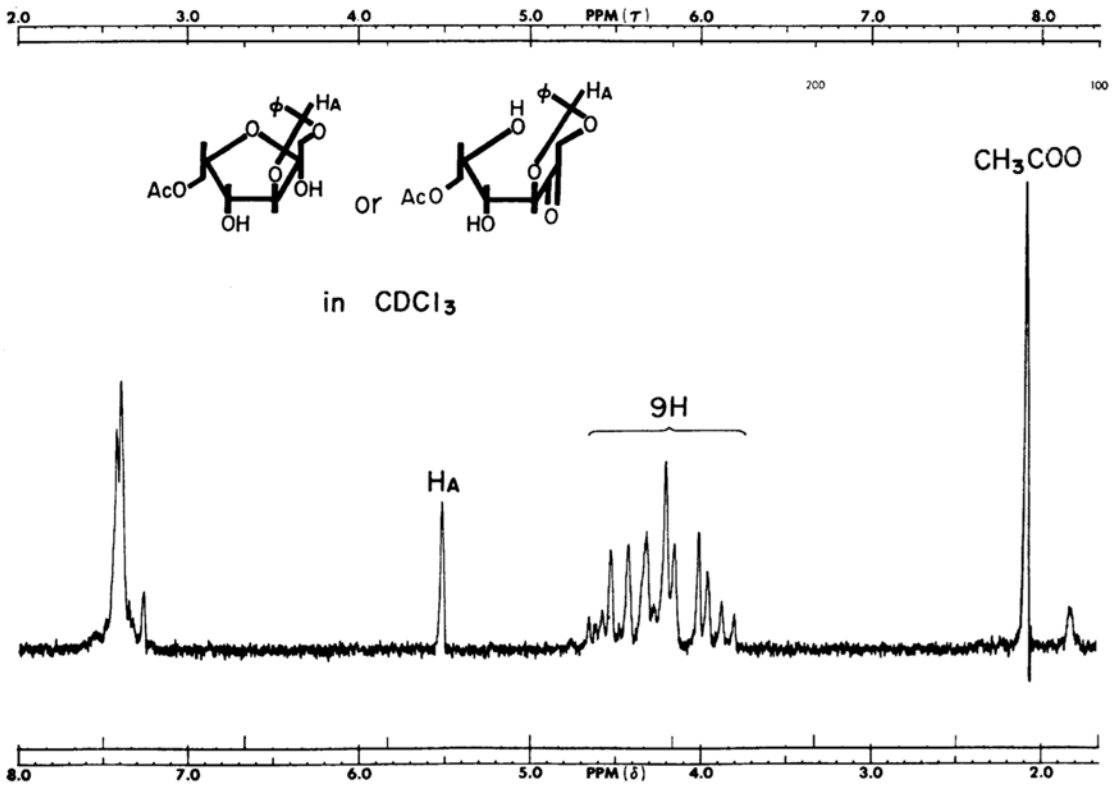

Fig. 1. PMR spectrum of IV in chloroform-d at 60 MHz.
H_A shows the signal due to a benzylic proton.

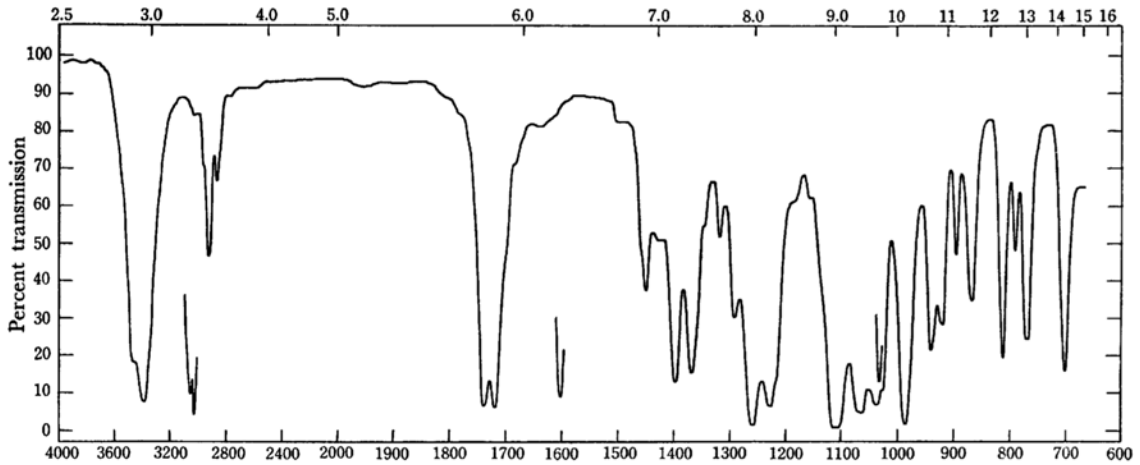

Fig. 2. IR spectrum of IV (KBr disk).

(VIII), ordinary reaction conditions were required, such as heating on a boiling-water bath or using sodium acetate and acetic anhydride under heating. In the case of the acetylation on a boiling-water bath, the β-anomer of VIII (IX) was also isolated.

The structures of VIII and IX were confirmed by the methods described below. The PMR spectrum of VIII in chloroform-d revealed the presence of one axial (τ 7.79) and two equatorial (τ 7.95) acetoxyl groups.[9] Two one-proton signals due to H_4 and H_5 appeared as a quartet (τ 4.41) and a multiplet (τ 4.90) respectively in the AcO-$\underset{|}{\text{C}}$-$\underline{\text{H}}$ range. The coupling constants ($J_{3,4}\simeq$10 and $J_{4,5}\simeq$9Hz) suggested that the pyranose structures was in the 1C chair form. Thus, the structure

9) L. D. Hall, *Advan. Carbohyd. Chem.*, **19**, 51 (1964).

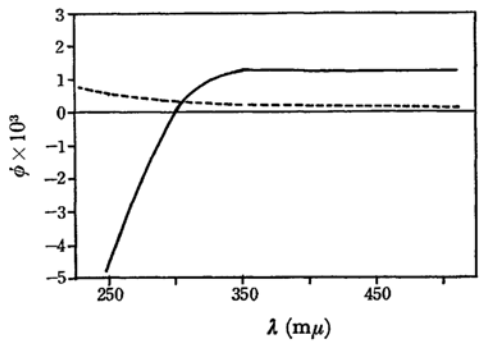

Fig. 3. ORD curves of IV and IX.
—— IV
--- IX

of VIII was determined to be 2,4,5-tri-*O*-acetyl-1,3-*O*-benzylidene-α-L-sorbopyranose.

The structure of IX should be compatible with either 2,4,5-tri-*O*-acetyl-1,3-*O*-benzylidene-β-L-sorbopyranose or 4,5,6-tri-*O*-acetyl-1,3-*O*-benzylidene-L-sorbose. However, the latter structure could de excluded because the ORD curve showed the absence of a carbonyl group[7] (Fig. 3). The positive value of the optical rotation and the fact that the PMR spectrum in chloroform-d was close to that of 1,2,3,4,5-penta-*O*-acetyl-β-L-sorbopyranose (X)[10] supported the former structure. The formation of IX was somewhat curious, for IX has an unstable *cis*-decalin type conformation in which its sugar moiety must also adopt the unlikely Cl chair form;[11] however, IX will be shown below to indeed possess this structure.

The easy acetylation of the tertiary hydroxyl group of V could not be attributed to the presence of the 1,3-*O*-benzylidene group, because the acetylation of the tertiary hydroxyl group of VII did not occur under similar reaction conditions. More especially, no acetylation of 1,3,4,6-di-*O*-benzylidene-β-L-sorbofuranose was obtained even on heating on a boiling-water bath. Therefore, the acetylation of the tertiary hydroxyl group of V must be caused by the closeness of the acetyl group at C_4 to the anomeric hydroxyl group. The closeness made possible the migration of the acetyl group from C_4 to C_2.

The existence of the long range coupling across 4 σ bonds between H_1 and H_3 also supported the structure of IX.[13] The coupling is usually observed in the 1,3-*O*-benzylidene-β-derivatives and suggests that the protons are in a zig-zag or W-letter arrangement (see Chart 2). The possibility of an epimerization on the C_3-configuration during the heating in pyridine was ruled out by the fact that the catalytic hydrogenation of IX in MeOH, followed by acetylation gave 1,3,4,5-tetra-*O*-acetyl-α-L-sorbopyranose (XII).[14]

In the hydrogenation of IX, methyl 1,3,4,5-tetra-*O*-acetyl-α-L-sorbopyranoside (XI)[15] was also isolated. This König-Knorr type glycosidation from IX to XI was also observed in the case of VI, which gave a fairly good yield of methyl 1,3,4,6-tetra-*O*-acetyl-α-L-sorbofuranoside (XIII).[16] However, the treatment of X under the same reaction conditions gave XI to a very limited extent. Accordingly, the existence of 1,3-*O*-benzylidene groups in VI and IX seems to enhance the rate of exchange of the acetoxyl group with the methoxyl group.

The above-described product analyses of the acetylations of III pointed out that IIIf is a predominant form in pyridine at low temperatures and that it transforms to IIIp with a rise in the temperature. The transformation from IIIf to IIIp was confirmed by the following PMR spectroscopic studies.

The PMR spectra of III in pyridine-d_5 are reported in Fig. 4. Two singlet signals (H_A) at τ 4.20 and 4.24, assignable to benzylic protons, appeared when measured at room temperature immediately after the dissolution of III in pyridine-d_5 (Fig. 4a). The third signal (H_B) at τ 4.09 assignable also to a benzylic proton which newly appeared when measured at 70°C (Fig. 4b), and its relative intensity increased synchronically with the decrease in the former two signals when the pyridine solution was heated at 100°C for 1 hr (Fig. 4c). An increase in the third signal was also obtained when the pyridine-d_5 solution was allowed to stand at room temperature for a long time (Fig. 4d).

The relative ratio of the signals (H_A) at τ 4.20 and 4.24 was constantly about 2 : 1 during the measurements. The one can reasonably be assigned to the benzylic proton of IIIf, and the other, to that of the keto-form of III (IIIk). The α-furanose form of III may be excluded, since a 1,3-*O*-acetal ring fused to an α-furanose can be expected to deform the furanose-ring conformation seriously.[16] On the other hand, the existence of IIIk is supported by the fact that IV adopts the keto-form IVk to

10) H. Paulsen, H. Köster and K. Heyns, *Chem. Ber.*, **100**, 2669 (1967).

11) Methyl 1,3,4,5-tetra-*O*-acetyl-β-L-sorbopyranoside was confirmed to exist as a conformer mixture of 1C and Cl chair forms.[12] The comparison of the PMR data of IX with those of the above pyranoside suggested that X may adopt mainly the Cl chair form.

12) K. Tokuyama, T. Maeda, K. Tori, S. Satoh and K. Kuriyama, paper presented at the 1st Symposium on Organic Structural Chemistry, Tokyo, Nov., 1968.

13) For example, see L. D. Hall, *Carbohyd. Res.*, **4**, 514 (1967).

14) Y. Khounine and A. Arragon, *Bull. Soc. Chim. France*, **1938**, 1404.

15) H. H. Schlubach and G. Graefe, *Ann.*, **532**, 211 (1937).

16) T. Maeda, K. Tori, S. Satoh and K. Tokuyama, This Bulletin, **41**, 2495 (1968).

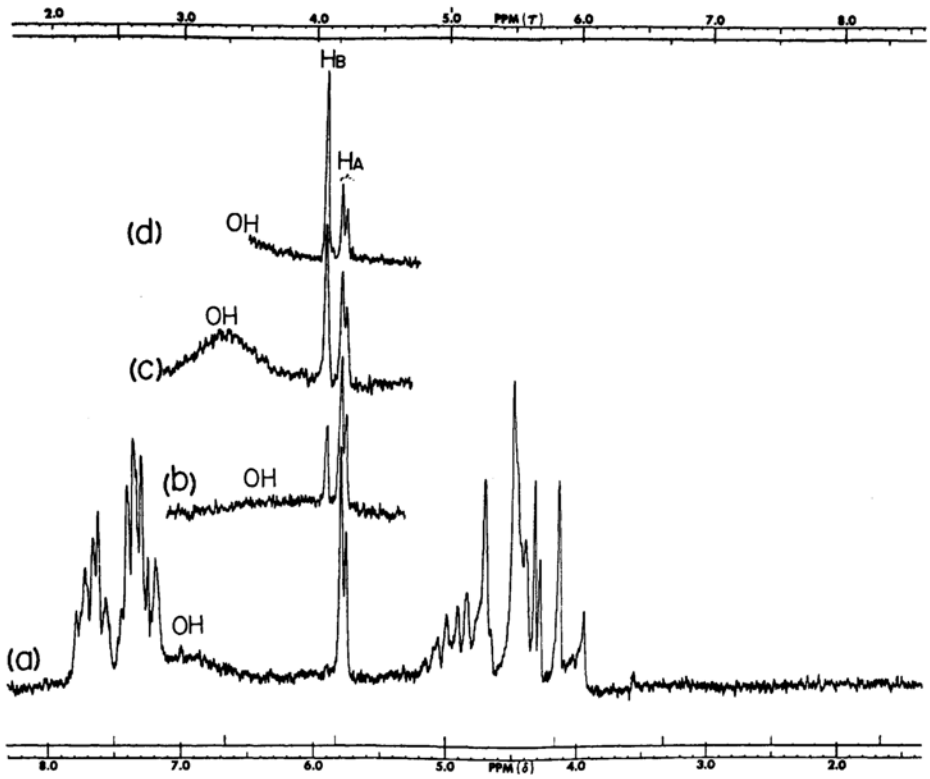

Fig. 4. PMR spectra of III in pyridine-d_5 at 60 MHz.
(a) Measured at room temperature immediately after dissolution of III
(b) Measured at 70°C
(c) Measured at room temperature after heating the solution at 100°C for 1 hr
(d) When the solution was allowed to stay at room temperature for 12 hr

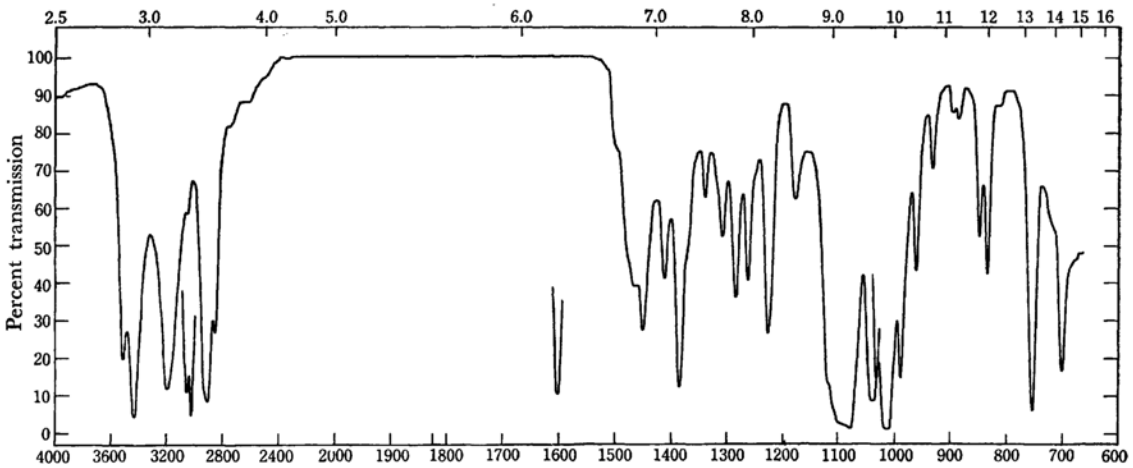

Fig. 5. IR spectrum of III (IIIf) (KBr disk).

some extent. However, as the absorption band due to the carbonyl group was hardly detected in the attenuated total reflection IR (ATR) spectrum of the pyridine solution of III, it was concluded that IIIk was a minor component compared to IIIf. Therefore, we could assign the signal at τ 4.20 to that of IIIf, and the one at τ 4.24, to IIIk. The third signal (H_B) at τ 4.09 was assigned to the benzylic proton of IIIp, since the acetylation of the pyridine solution, which showed a strong intensity of this signal, gave VII as the major product.

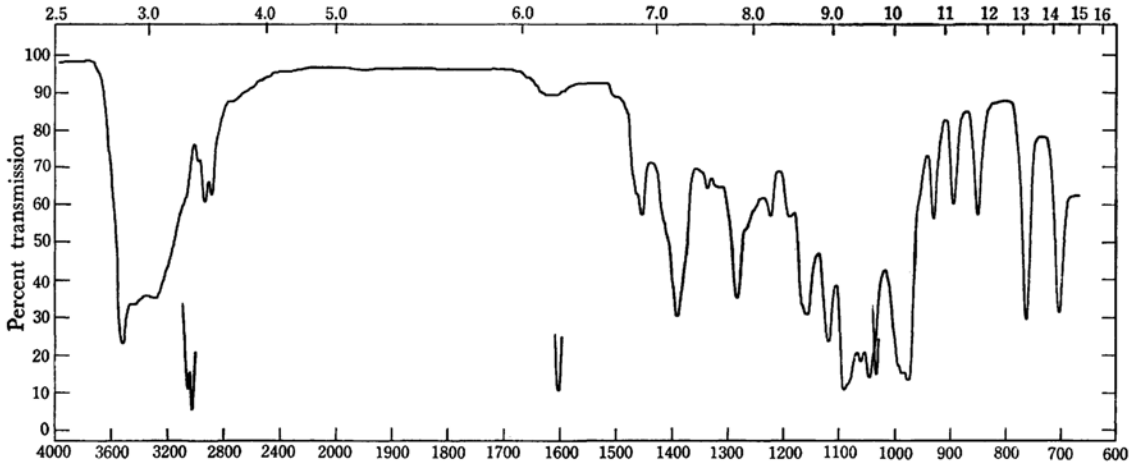

Fig. 6. IR spectrum of III (mainly IIIp) (KBr disk).

As has previously been reported, III adopts IIIf in a crystalline state. Further, the above-mentioned facts establish that III exists in solution as a mixture of IIIf, IIIk, and IIIp. As IIIp is the dominant form in pyridine we attempted to isolate it. Crystals of IIIf usually appeared upon the concentration of the pyridine solution, which showed a high concentration of IIIp. On the other hand, an amorphous powder was obtained on the addition of petroleum ether to the concentrated pyridine solution before any crystals started to appear. This powder had a low melting point, a negative optical rotation (which suggested the presence of IIIp), and it obviously differed from IIIf in its IR spectrum (see Figs. 5 and 6). The recrystallization of this powder from methanol gave IIIf, and the acetylation gave VII as the major product. Therefore, this powder is considered to contain considerable amount of IIIp. These data also supported the idea that IIIf is dominant in a crystalline state.

In conclusion, III usually crystallizes as IIIf and equilibrates among IIIf, IIIk, and IIIp in solution. It is obscure why IIIf of the unstable *cis*-decalin type can exist exceptionally in the case of benzylidene derivatives of L-sorbose (I). The presence of IV of the keto-form in a crystalline state is also surprising. We hope that these interesting fused-ring systems will be elucidated by thermodynamic treatments.

Experimental

All the melting points were recorded on a Kofler microstage apparatus and have been corrected.

The optical rotations were determined in chloroform containing 1% ethanol unless otherwise stated, and the concentrations were recorded in percentages. The ORD curves were obtained on a Nippon-Bunko ORD/UV 5 spectrometer.

The PMR spectra were measured on a Varian A-60A spectrometer equipped with a variable temperature probe using 5% solutions of samples and with TMS as the internal standard. The results obtained from first-order approximation are listed in Table 1.

Thin-layer chromatography (TLC) and preparative TLC (PTC) were carried out on a silica-gel plate in the

TABLE 1. CHEMICAL SHIFTS (τ) AND COUPLING CONSTANTS (J, Hz) IN $CDCl_3$[a]

Compd.	H_1, $H_{1'}$	H_3	H_4	H_5	H_6	$H_{6'}$	Benzylic H	CH_3COO	Other H
IV	5.3 — 6.2[b]						4.48	7.90	OH 5.3—6.2[b]
VIII	4.88, 6.23	6.30	4.41	4.90	5.98	6.44	4.42	7.79, 7.95 (6H)	
	$J_{1,1'}=12.0$	$J_{3,4}=10.0$	$J_{4,5}=9.0$	$J_{5,6}=6.3$	$J_{5,6'}=10.7$				
					$J_{6,6'}=11.3$				
XI	5.43, 5.77	5.54	4.90	5.24	5.76	5.97	4.44	7.91 (6H), 7.97	
	$J_{1,1'}=12.0$	$J_{3,4}\simeq 2$	$J_{4,5}\simeq 3$	$J_{5,6}\simeq 2$	$J_{5,6'}\simeq 2$				
	$J_{1,3}\leqq 1.0$		$J_{4,6'}\leqq 1.0$		$J_{6,6'}\simeq 13.0$				
X	5.33, 5.52	4.53	4.82	5.12	5.68	6.09	—	7.90 (15H)	
	$J_{1,1'}=12.0$	$J_{3,4}\simeq 5$	$J_{4,5}\simeq 4$	$J_{5,6}\simeq 3$	$J_{5,6'}\simeq 2.5$				
			$J_{4,6'}\leqq 1.0$		$J_{6,6'}=13.0$				

a) Aromatic protons appeared at τ 2.5—2.8 as multiplets
b) Unresolved

same manner as has been previously described.[2] The solvent systems used were chloroform-acetone (9 : 1, v/v, solvent A), ether-petroleum ether (5 : 1, v/v, solvent B; 3 : 1, v/v, solvent C, 2 : 1, v/v; solvent D), and benzene-ether (2 : 1, v/v, solvent E).

General Procedure of Acetylation. A compound (1 part in weight) was treated with a mixture of pyridine and acetic anhydride (1 : 1 v/v; 10 parts in volume) at the cited temperature. The reaction mixture was then poured onto crushed ice, neutralized with sodium hydrogencarbonate, and extracted with chloroform. The chloroform was washed with water, 1N HCl and water, and then dried and evaporated. The acetate thus obtained was purified by recrystallization and/or by PTC.

Acetylation of III. a) III (1.00 g) was acetylated at −30°C for 2 hr. The recrystallization of the product from ethanol gave IV as needles (301 mg). V (60 mg)[2] was separated from the mother liquor (351 mg) by repeated PTC with solvents A and B.

IV: mp 153—155°C, $[\alpha]_D^{25}$ +16.5° (*c* 0.956). Found: C, 58.14; H, 5.86%; mol wt, 314. Calcd for $C_{15}H_{18}O_7$: C, 58.06; H, 5.85%; mol wt, 310. ORD: $[\phi]_{400}$ +172°; $[\phi]_{300}$ +298°; $[\phi]_{232}$ +616.

b) III (500 mg) was acetylated for 5 hr at room temperature and then for 1 hr at around 70°C. VI[2] was mainly obtained, it was purified by recrystallization from ethanol-water. The yield was 536 mg.

c) A solution of III (583 mg) in pyridine (6 m*l*) was heated on a boiling-water bath for 13.5 hr and then kept overnight at room temperature. Acetic anhydride (6 m*l*) was added to the solution. After having been kept at room temperature for 15.5 hr, the solution was worked up by the general procedure. A crystalline syrup (871 mg) was obtained. The recrystallization of the syrup from ether gave VII (126 mg). From the mother liquor, VI (212 mg) and VII (175 mg) were separated by PTC with solvent A. The total yield of VII was 311 mg.

d) III (1.00 g) was preliminarily heated in a way similar to the above and then acetylated at around 0°C for 4 hr. A syrup (1.20 g) was obtained. The recrystallization of the syrup from ether gave VII (697 mg). From the mother liquor, V (140 mg) was separated by PTC with solvent D.

Acetylation of VII. a) VII (600 mg) was acetylated on a boiling-water bath for 3 hr. The products were separated into VIII (131 mg) and IX (200 mg) by PTC with solvent D.

VIII (84 mg) was obtained as needles by further recrystallization from ether. It had mp 203.5—205°C, $[\alpha]_D^{23}$ −38.7° (*c* 0.988). Found: C, 57.58; H, 5.76%; mol wt, 394. Calcd for $C_{19}H_{22}O_9$: C, 57.86; H, 5.62%; mol wt, 394.

IX was a very hygroscopic syrup, $[\alpha]_D^{23}$ +14.7° (*c* 0.911). Found: C, 56.51; H, 5.65%; mol wt, 412. Calcd for $C_{19}H_{22}O_9$: C, 57.86; H, 5.62%; mol wt, 394. ORD: $[\phi]_{400}$ +1273°, $[\phi]_{350}$ +1307°, $[\phi]_{300}$ +89°, $[\phi]_{250}$ −4670°.

b) A solution of VII (30 mg) in acetic anhydride (3.0 m*l*) was heated at 70°C in the presence of sodium acetate (0.30 g). After 4.5 hr, the mixture was cooled to room temperature and kept overnight. Then the solution was worked up by the usual procedure. The recrystallization of crude crystals from ether (34 mg) gave VIII (21 mg). The lack of any formation of IX was confirmed by TLC.

Acetylations of IV, V and VII. These acetylations were carried out a) below 0°C and b) at 100°C for 3 hr. The reactions were checked by TLC with solvents A and D. The results are listed in Table 2.

Table 2. Acetylation products

Starting material	Reaction conditions	
	a)	b)
IV	V, VI	VI
V	VI	VI
VII	recovered	VIII, IX

Formation of XI from IX. A solution of IX (168 mg) in methanol (20 m*l*) was hydrogenated in the presence of 5% Pd-C (840 mg) at atmospheric pressure. After 1 hr, the catalyst was removed by filtration and washed with methanol. The combined solution of the filtrate and the washings were evaporated to give a syrup (77 mg). The syrup was acetylated without further purification. The product was separated into XII (31 mg) and XI (30 mg) by PTC with solvent C. A mixture of XII, methyl iodide (5 m*l*), and silver oxide (0.5 g) was refluxed for 4 hr and then kept overnight at room temperature. The precipitates were removed by filtration. The filtrate was concentrated to give XI (23 mg).

Preparation of X. 1,3,4,5-Tetra-*O*-acetyl-α-L-sorbopyranosyl chloride (3.59 g)[17] was treated with anhydrous acetic acid (100 m*l*) in the presence of mercuric acetate (5 g) at room temperature. After 70 min, the reaction mixture was poured into ice water and extracted with chloroform. The extract was subsequently washed with water, a 5% sodium hydrogencarbonate solution, and water. The solution was dried over $MgSO_4$ and then evaporated to give a syrup (4.6 g). X (0.26 g, R_f 0.38—0.45) was isolated by PTC with solvent E. The recrystallization of crude X from ether gave needles (97 mg); mp 108—109.5°C, $[\alpha]_D^{23}$ +71.6° (*c* 0.705) (lit.[15] mp 113.8°C, $[\alpha]_D$ +74.4°).

Preparation of XIII from VI. VI (767 mg) was hydrogenated by the same procedure as was used for IX. The acetylation of a crude product gave a syrup (432 mg) from which XIII (88 mg) was isolated by repeated PTC with solvents A and D.

Treatment of X under Hydrogenation Conditions. A solution of X (10.5 mg) in methanol was treated in a manner similar to that used for IX. Hardly any hydrogen up-take could be observed. The thin-layer chromatogram showed the existence of a trace of XI along with the unreacted X.

The Equilibrium of III in Pyridine. *a) Isolation of IIIp.* (i) A solution of crystals of IIIf (100 mg) in pyridine (0.2 m*l*) was allowed to stand at room temperature. After 6 days, the solution was poured into petroleum ether (10 m*l*). A precipitated syrup was separated by decantation and washed with petroleum ether. The addition of ether to the syrup gave an amorphous powder (67 mg) which consisted mainly of **IIIp.** It had mp 151—182°C, $[\alpha]_D^{23}$ −26.7°→−24.1°

17) K. Tokuyama and M. Katsuhara, This Bulletin, **39**, 2728 (1966).

(24 hr) (*c* 0.640, methanol). Found: C, 58.41; H, 5.99%. Calcd for $C_{13}H_{16}O_6$: C, 58.20; H, 6.01%. The acetylation of the powder (10 mg) at 0°C for 6 hr gave VII (9.6 mg).

(ii) A solution of crystals of IIIf (1 part) in pyridine (10 parts) was heated at 100°C for 15 hr and then kept at room temperature for 35 hr. The solution was concentrated to a brown syrup containing a small amount of pyridine. The syrup was washed with petroleum ether and then dissolved in methanol. Insoluble crystals of IIIf were removed by filtration. The filtrate was evaporated to give a syrup. Ether was added to the syrup and the powder thus precipitated, which contained IIIf and IIIp, was removed by filtration. The filtrate was evaporated to give a powder. The recrystallization of the powder from ether gave the powder of IIIp of a considerable purity. It had mp 150—158°C.

b) *Transformation of IIIp to IIIf.* (i) A solution of IIIf (21.5 mg) in pyridine (0.4 m*l*) was heated at 100°C for 13.5 hr and then kept at room temperature for 30.5 hr. The solution was evaporated under reduced pressure. Crystals of IIIf (21.4 mg) were thus obtained.

(ii) A solution of IIIp (7 mg), prepared by the above procedure (a-ii), in methanol was allowed to stand overnight at room temperature; then it was concentrated. Crystals of IIIf (6 mg) were obtained.

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