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Studies on Pillaromycin A. III.[1] The Structure of Pillarose

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Pillarose (I), $C_8H_{12}O_5$, gives positive Fehling's and iodoform reactions. Absorption of an isolated carbonyl is observed in the infrared and ultraviolet region.

I formed methyl pillarosides (VIIa, b) and mono-, diacetylpillaroses, and reacted with sodium borohydride to yield methyl dihydropillarosides (Xa, b). I consumed 2 moles of periodate. Periodate oxidation of I in acidic solution gave acetaldehyde, formic acid (and formaldehyde), succinaldehydic acid and carbon dioxide. From these degradation schemes and physico chemical properties of the above derivatives the structure, 2,3,6-trideoxy-2-glycoloylhexopyranos-4-ulose, was given to pillarose (I).

Pillarose (I), a new sugar obtained by acid hydrolysis of pillaromycin A[3] (II, PMA, $C_{28}H_{28}O_{11}$), was shown by elemental analysis and mass spectrometry, *m/e*: 188 (M^+) to have the molecular formula $C_8H_{12}O_5$.

Absorption of I at 1720 cm^{-1} in the infrared (IR) spectrum and at 280 mμ (ε=44.6) in the ultraviolet (UV) spectrum are attributed to the isolated carbonyl and not to the β-diketone configuration. I gave positive reaction with benzidine (violet-blue), Fehling's, Tollens', Barton's[4] reagents and positive iodoform reaction.

Acetylation of I gives as the main products two kinds of diacetates (VIa, VIb) $C_{12}H_{16}O_7$. Acid hydrolysis of PMA pentaacetate (III) affords the 8-O-monoacetylpillaroses (IVa, b) $C_{10}H_{14}O_6$ and PMN tetraacetate (V). Acetylation of IV a, b yields two kinds of diacetates identical with VIa and VIb. Futher, acetylation of the diacetate (VIa, b) does not proceed.

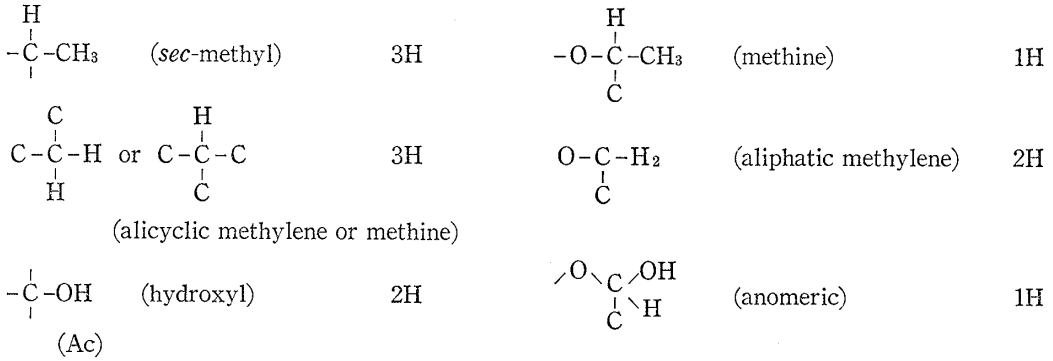
Table I. NMR Spectra of 1.8-O-Diacetylpillarose (VIa) (VIb)
(100 Mc in $CDCl_3$)

	H 1	H 8	H 5	OAc	OAc	H 2	H 3	Me 6
δ (ppm)	5.80	5.03	4.0	2.19	2.13	1.85	1.7—2.1	1.18
	d	s	q	s	s	m	m	d
VIa	1H	2H	1H	3H	3H	1H	2H	3H
J (cps)	6.5		6.5					6.5
δ	5.75	5.03	4.15	2.19	2.13	1.85	1.7—2.1	1.15
	d	s	q	s	s	m	m	d
VIb	1H	2H	1H	3H	3H	1H	2H	3H
J	3		6.5					6.5

s: singlet, d: doublet, q: quartette, m: multiplet

1) Part II: M. Asai, *Chem. Pharm. Bull.* (Tokyo), **18**, 1706 (1970).
2) Location: *Juso, Higashiyodogawa-ku, Osaka.*
3) *a*) In Part I: M. Asai, *Chem. Pharm. Bull.* (Tokyo), **18**, 1699 (1970); *b*) Mass spectrum of PMA pentaacetate (III), full acetylation product of PMA: *m/e*: 708 (M^+-42), monoacetylpillarose (IV): *m/e*: 188 (M^+-42), pillaromycinone (PMN) tetraacetate (V): *m/e*: 538 (M^+).
4) The reagent of Barton, Evans and Gardner (in Part I) is specific to β-diketone configuration and this contradication is resolved later.

The nuclear magnetic resonance (NMR)[5] spectra of VI a and VIb are shown in Table I. From the data in Table I the protons in pillarose are assigned as follows.



Treatment of I with methanol containing hydrogen chloride affords methyl pillarosides (VIIa, b), which are also obtained by treatment of PMA (II) with methanol containing hydrogen chloride. VIIb exhibits a hydroxyl absorption at 3500 cm^{-1} and an isolated carbonyl absorption at 1715 cm^{-1} in the IR spectrum. The NMR spectrum of VIIb (Table II) shows the outbreak of a new OCH_3. It gives negative reaction with Barton's reagent and has the absorption at 280 mμ (ε=44.8) in the UV region. Benzoylation of VIIa, b gives methyl 8-O-monobenzoylpillarosides (IXa, b), as well as acetylation of VIIa,b gives methyl 8-O-monoacetylpillarosides (VIIIa, b). In the NMR spectra of VIIIb and IXb (Table II) the absorption of H_8 shifts by *ca.* 0.5 ppm to lower field than the absorption of H_8 in VIIb.

Table II. NMR Spectra of Methyl Pillaroside (VIIb), Methyl 8-O-Acetylpillaroside (VIIIb), Methyl 8-O-Benzoylpillaroside (IXb) (100 Mc in $CDCl_3$)

			H 1	H 8	H 5	OMe	OAc	H 2	H 3	Me
VIIb	δ (ppm)		4.64 d 1H	4.51 s 2H	4.13 q 1H	3.33 s 3H		1.80 m 1H	1.7—2.3 m 2H	1.01 d 3H
	J (cps)		3		6.5					6.5
VIIIb	δ (ppm)		4.72 d 1H	5.00 s 2H	4.15 q 1H	3.38 s 3H	2.19 s 3H	1.7—2.4 m 3H		1.18 d 3H
	J (cps)		3		6.5					6.5
IXb	δ (ppm)	7.35—8.2 5H	4.6 d 1H	5.21 s 2H	4.29 q 1H	3.32 s 3H		1.9 m 1H	1.7—2.3 m 2H	1.14 d 3H
	J (cps)		3		6.5					6.5

Reduction of the isolated carbonyl in VIIa, b with sodium borohydride affords methyl dihydropillarosides (Xa, b) and further acetylation of Xa, b yields two kinds of diacetates XIa, XIb, as the prominent acetylated compounds. Their NMR spectra (Table III, Fig. 1) show the new H_7 appearing in the lower field, and the H_8 (two protons, q) coupling with the H_7. Xa, b and XIa, b exhibit no absorption at 1720 cm^{-1} (isolated CO) in the IR spectra $CHCl_3$).

5) NMR spectra were measured on a Varian HA-100 or A-60A spectrometer. The chemical shifts were expressed in δ value from TMS (internal reference).

Table Ⅲ. NMR Spectra of Methyl Dihydropillaroside Diacetate (XIa, XIb) (100 Mc in $CDCl_3$)

		H 7	H 1	H_8 a	H_8 b	H 5	OCH_3	OAc	OAc	H 2	H 3	Me
XIa	δ (ppm)	5.14 oct	4.64 d	4.54 q	4.16 q	3.87 q	3.32 s	2.08 s	2.02 s	1.80 m	1.6—2.1 m	1.14 d
		1H	1H	1H	1H	1H	3H	3H	3H	1H	2H	3H
	J (cps)	2.5 8	3	2.5 12	8	6.5						6.5
XIb	δ (ppm)	5.19 oct.	4.62 d	4.33 q	3.92 q	3.89 q	3.30 s	2.08 s	2.02 s	1.80 m	1.6—2.0 m	1.19 d
		1H	1H	1H	1H	1H	3H	3H	3H	1H	2H	3H
	J (cps)	2.5 9	3	2.5 12	9	6.5						6.5

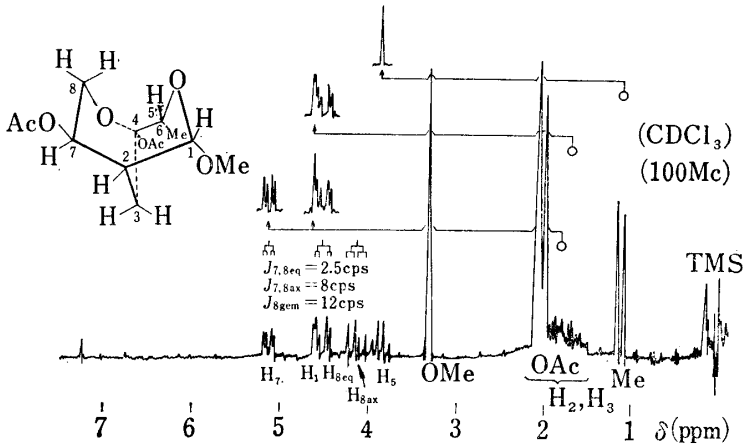


Fig. 1. NMR Spectrum of Methyl Dihydropillaroside Diacetate (XIa)

Oxidation of I in acidic solution with periodate yields equimolar amounts of acetaldehyde, carbon dioxide, formic acid (including minor amounts of formaldehyde) and succinaldehydic acid (identified with authentic sample).

As no clear difference of chemical shifts is observed between the pillarose moiety in PMA mono-*m*-bromobenzoate[6] (XII) and 1,8-O-diacetylpillarose (VI) and no distinguishable transformation seems to have occured, thus the spin decoupling studies on the compound (VI) may afford many informations on the chemical structure of pillarose moiety in PMA (II).

1) Field decoupling by irradiation in the region of the *sec*-methyl protons (1.18 ppm) of VIa shows the isolated *sec*-methyl function, namely, the collapse of the quartet at 4.0 ppm to a sharp singlet. The same change of field decoupling is observed in VIb. I and IV give acetaldehyde on the oxidation. I is also positive to iodoform test. These facts indicate the partial structure, CH_3–$\underset{\displaystyle H}{\underset{|}{C}}$–O– in pillarose.

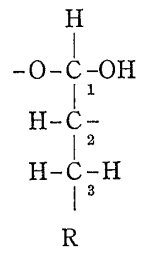
2) Field decoupling by irradiation in the region of the alicyclic protons (1.85 ppm) of VIa shows a change in anomeric proton region, the collapse of the doublet (J=6.5 cps) at 5.80 ppm to a singlet. The same change is observed on the anomeric proton (d, J=3 cps,

6) XII will be described in Part IV.

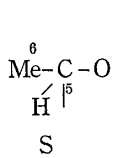
at 5.75 ppm) of VIb. I gives positive reactions to Fehling's and Tollens' reagents. These facts indicate that a hemiacetal configuration, –O–C(H)(OAc)–OH, is assigned to pillarose.

3) The signal of two protons observed as a singlet at 4.51 ppm in VIIb is found at 5.0 ppm in VIa and VIb, as well as at 5.0 ppm in VIIIb and at 5.21 ppm in IXb. From the above lower-field shift occurred by acylation the part structure $AcO–CH_2–C=$ is assigned. This methylene protons show a lowerfield shift as compared with those of ordinary methylene protons of $HO–CH_2–$ type. On the hydrogenation with sodium borohydride a newly occurring methine proton coupling with these methylene protons is observed. Together with the formation of formic acid and a small amount of formaldehyde on the periodate oxidation, the above part structure is extended to $HO\text{-}CH_2\text{-}CO$.

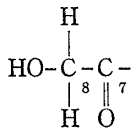
From the above observations I should be constructed from the part structures R, S, T and U (U_1 or U_2). Pillarose gave equimolar amounts of $HCO\text{-}CH_2\text{-}CH_2\text{-}COOH$, CO_2, CH_3COH and HCOOH (HCOH) on the periodate oxidation. All eight carbons in pillarose were found in the oxidative degradation products and were elucidated without duplication by the part structures. The observation that diacetylpillarose (VI) is not acetylated excludes the hemiketal structure, U_1. The number of oxygens in the combined structure of R, S, T and U_2 is six, which is in excess of one from pillarose (I, $C_8H_{12}O_5$), the duplication of the oxygen must comes from the ether oxygen in R and S. Combination of R and S as shown in the part structure W makes the number of oxygen to five. The five oxygens in pillarose are well accounted for by the part structures W, T and U_2. In all combinations, the possible ones which satisfy the unsaturation number (three) of pillarose must be X, Y and Z.



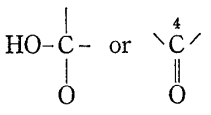
R



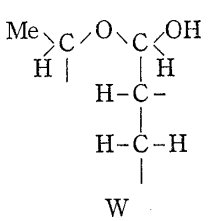
S



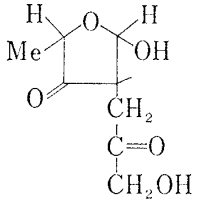
T



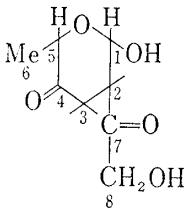
U_1 U U_2



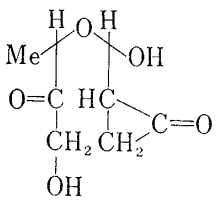
W



X



Y



Z

The NMR spectrum and spin decoupling of XIa were reinvestigated. On the hydrogenation with sodium borohydride of VIIa, b, the two protons (H_8) appearing as a singlet at 5.03 ppm split to a pair of quartettes (ABX type), one (J=2.5 cps, 12 cps) at 4.54 ppm and the other (J=8 cps, 12 cps) at 4.16 ppm. The geminal coupling constant (J=12 cps) of H_8 protons suggests a new cyclic structure. When the new H_7 proton at 5.14 ppm is irradiated, the ABX type of the H_8 protons altered to AB type. The octette of the H_7 proton (J=2.5 cps, 8 cps and 1 cps) observed at 5.14 ppm suggests the presence of one proton on the other neighboring carbon. Field decoupling by irradiation at 1.8 ppm results the collapse of the doublet (J=3 cps anomeric proton) at 4.64 ppm to a singlet. The fact suggests the presence of

C_2-methine proton adjacent to C_1. When the doublet (CH_3) at 1.13 ppm was irradiated the quartette (J=6.5 cps) of H_5 proton at 3.87 ppm collapsed to a singlet. The chemical shift of H_5 proton in XIa lies at *ca.* 0.2—0.4 ppm higher field than those of H_5 protons in VI, VII, VIII, IX, thus indicating the following ketal formation. Consequently the following part structure is assigned to XI. The absorption near 1720 cm^{-1} in the IR spectra of I and VII is characteristic to the six-members ring ketone or the aliphatic isolated ketone rather than the five-members ring ketone. I, IV, VII and VI consumed 2, 1, 1 and 0 mole periodate respectively. From these facts, among the above described structures (X, Y and Z), the structure Y may be probable to pillarose (I). And to methyl dihydropillaroside (X) the structure Q is assigned.

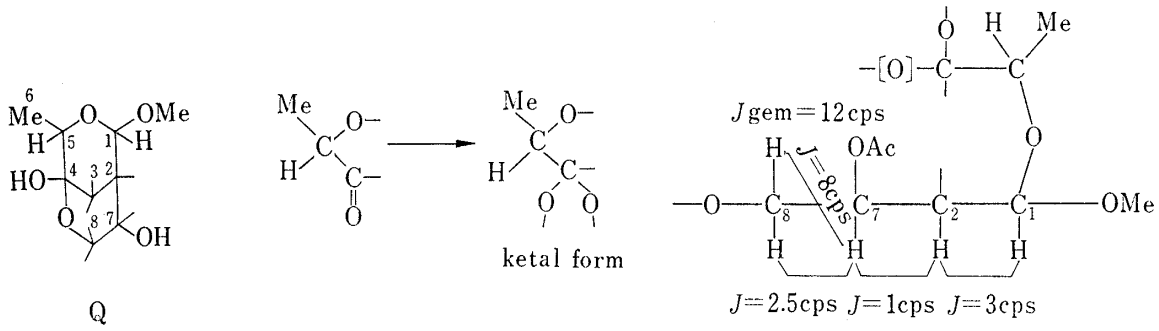


Chart 1

Experimental[7]

Pillarose (I)——PMA (II) (50 g) was hydrolyzed at 75° for 3 hr in 50% acetic acid (AcOH, 1.5 liter). The hydrolysate was diluted with water (3 liter) and then extracted with ethyl acetate (EtOAc, 0.4 liter ×3).

The aqueous layer was passed through a charcoal column (30 g; 2.1×35) and made neutral with Amberlite IR-4B (OH) (1.5 liter) and concentrated to a syrupy residue (20 g). The syrup (500 mg) was chromatographed on cellulose powder [Tōyō Roshi, 100—200 mesh, column 2.2×130 cm solvent, EtOAc: Acetone (3:1)]. The eluate positive to benzidine reagent was collected and evaporated *in vacuo* to give a syrup. *Anal.* Calcd. for $C_8H_{12}O_5$: C, 51.06; H, 6.38. Found: C, 50.74; H, 6.62, $[\alpha]_D^{22}$ −16.7° (c=1.0, in H_2O). IR ν_{max}^{Liq} cm^{-1}: 3600—3200, 1720, 1100, 1045, 990. Mass Spectrum *m/e*: 188 (M^+), 170, 131, 128, 113, 110, 99, 85.

8-O-Acetylpillarose (IV) (The Acid Hydrolysis of PMA Pentaacetate)——PMA pentaacetate (III) (1 g) dissolved in 50% AcOH (30 ml) was allowed to stand for 3 hr at 75°. The reaction mixture was diluted with water (60 ml) and then extracted with EtOAc (30 ml×3). The EtOAc extract was washed with water and dried. After removal of the solvent, recrystallization of the residue from EtOAc afforded crystals (500 mg, mp 241°, Found: C, 62.65; H, 4.72), which were identified with PMN tetraacetate (V) by means of IR, NMR and mass spectrum.

The aqueous layer was treated with active charcoal and made neutral with Amberlite IR-4B (30 ml) and then evaporated to syrupy residue (200 mg) (IVa, b). The syrup was chromatographed on cellulose powder [Tōyō Roshi, 100—200 mesh, column 1.5×120 cm, solvent, EtOAc–$CHCl_3$ (1:3)]. The eluate positive to benzidine reagent was collected and evaporated *in vacuo* to give the syrupy IVa, b. *Anal.* Calcd. for $C_{10}H_{14}O_6$: C, 52.17; H, 6.08. Found: C, 51.95; H, 6.35. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1745, 1725. NMR (100 Mc in $CDCl_3$): 2.19 (3H, s, OAc). Mass Spectrum *m/e*: 188 (M^+-42), 170, 155, 131, 128, 113, 110, 99, 85.

1,8-O-Diacetylpillarose (VIa, VIb)——Pillarose (100 mg) in pyridine (0.7 ml) was acetylated with acetic anhydride (0.35 ml) for 18 hr at room temperature and the reaction mixture was poured in ice-water, then extracted with EtOAc. After washing with water, the EtOAc solution was concentrated *in vacuo* to give crude acetylated products (80 mg). The crude products in 0.5 ml of EtOAc was further purified by the thin-layer chromatography (TLC) [silica gel (Merk), (30 g, 20×20 cm), solvent, EtOAc: $CHCl_3$ (1:3)]. The fraction, positive to potassium permanganate ($KMnO_4$) reaction, having the *Rf* value of 0.5—0.53 was collected and evaporated *in vacuo*. Cooling of the syrup gives crystalline (diacetate VIa) and syrup (VIb).

7) All melting points were uncorrected.

VIa: mp 45—50°. *Anal.* Calcd. for $C_{12}H_{16}O_7$: C, 52.94; H, 5.92. Found: C, 52.94; H, 6.54. $[\alpha]_D^{23}$ −15° (c=1, MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1750, 1700, 1370, 1040, 1015, 990. NMR (100 Mc in $CDCl_3$) shows in Table I. Mass Spectrum *m/e*: 230 (M^+-42), 188, 170, 155, 136, 128, 113, 110, 99, 85. VIb: $[\alpha]_D^{22}$ −65° (c=1, MeOH). NMR (100 Mc in $CDCl_3$) shows in Table I.

Methyl Pillaroside (VIIb)——Pillarose (I, 2 g) was treated with 5% HCl–methanol (60 ml) for 1 hr at room temperature and the reaction mixture was poured in ice–water. After removing the HCl with Amberlite IR-45 (OH), the aqueous solution was concentrated and was passed through charcoal column (2 g). Fractions of eluate positive to $KMnO_4$ reaction and to benzidine reagent were collected and concentrated *in vacuo* to give a crude syrup (VIIa, b), which was further purified by the preparative TLC on silica gel [solvent, EtOAc:$CHCl_3$ (1:1)]. The main fraction positive to $KMnO_4$ reaction having the *Rf* value of 0.35 was collected and evaporated *in vacuo* to give the oil of VIIb. *Anal.* Calcd. for $C_9H_{14}O_5$: C, 53.66; H, 6.94. Found: C, 53.21; H, 7.25. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550, 3500, 1715, 1100, 1050, 1000, 985. NMR (100 Mc in $CDCl_3$) shows in Table II. Mass Spectrum *m/e*: 160, 145, 142, 113, 110, 85.

Methyl 8-O-Acetylpillaroside (VIIIb)——Methyl pillaroside (100 mg) in pyridine (0.7 ml) was treated with acetic anhydride (0.35 ml) for 1 hr at room temperature and the reaction mixture was poured to ice–water, then extracted with EtOAc. After washing with water the EtOAc solution was concentrated *in vacuo* to give crude acetylated products (80 mg) (VIIIa, b). It was further purified by the preparative TLC on silica gel [solvent, EtOAc:$CHCl_3$ (1:2)]. The main fraction, positive to $KMnO_4$ reaction, having the *Rf* value of 0.35 was collected and evaporated *in vacuo* to give the oil of VIIIb. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1752, 1725. NMR (100 Mc, in $CDCl_3$) shows in Table II.

Methyl 8-O-Benzoylpillaroside (IXa, IXb)——Methyl pillaroside (430 mg) in pyridine (5.15 ml) was acylated with benzoic anhydride (2.15 g) under ice–cooling. After being kept standing at room temperature for 2 hr, the reaction mixture was poured to ice–water and then extracted with EtOAc. After washing with water, aq. 2% sodium bicarbonate ($NaHCO_3$) solution and water, the EtOAc solution was evaporated *in vacuo* to give a crude syrup (IXa, b). The syrup was further purified by the preparative TLC on silica gel [solvent, $CHCl_3$:EtOAc (6:1)]. The fraction, positive to $KMnO_4$ reaction, having the *Rf* value of 0.8—0.85 was eluted with EtOAc. Evaporation and cooling of eluate gives crystals (IXb). From the mother liquor syrupy IXa was obtained. IXa. $[\alpha]_D^{23}$ −34.3° (c=0.5, $CHCl_3$). IXb. mp 103—105°. *Anal.* Calcd. for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92. Found: C, 62.94; H, 6.24. $[\alpha]_D^{23}$ −98.8° (c=0.5, in $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 1740, 1725, 1280, 1130, 1050, 1015, 985, 715. NMR (100 Mc, in $CDCl_3$) shows in Table II.

Methyl Dihydropillaroside (X), Methyl Dihydropillaroside Diacetate (XIa, XIb)——To a 0.5 g of methyl pillaroside in 15 ml of water a 0.1 g of sodium borohydride in 10 ml of water was added dropwise in 40 min under stirring. The reaction mixture was acidified with AcOH and was passed through columns of Amberlite IR-120 (H; 10 ml) and Amberlite IR-45 (OH; 20 ml) and then concentrated *in vacuo* to give a syrup. The syrup (270 mg) in pyridine (1.5 ml) was acetylated with acetic anhydride (0.75 ml) for 5 hr and the reaction mixture was poured to ice–water then extracted with EtOAc. EtOAc extract was washed with water and concentrated to give a syrup (200 mg). The syrup was purified by column chromatography on silica gel (1.1×45 cm) [solvent, $CHCl_3$:EtOAc (2:1)]. Fraction having the *Rf* value of 0.45 on TLC gives XIb and the other having the *Rf* value of 0.55 on TLC gives XIa. XIa $[\alpha]_D^{23}$ −54° (c=0.5, in $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1750, 1125, 1050, 1040, 980. NMR (100 Mc, in $CDCl_3$) shows in Table III. XIb. *Anal.* Calcd. for $C_{13}H_{20}O_7$: C, 54.16; H, 6.99. Found: C, 53.89; H, 7.26. $[\alpha]_D^{23}$ −121° (c=0.3, in $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1750, 1125, 1050, 1040, 980. NMR (100 Mc, in $CDCl_3$) is shown in Table III.

Oxidation of Pillarose and Its Derivatives with Periodate——A: 190 mg (1 mmole) of pillarose was oxidized with 640 mg (3 mmole) of sodium periodate in 300 ml of 0.5% sulfuric acid at 40° for 2 hr. The volatile oxidation products were introduced to the 2,4-dinitrophenylhydrazone (2,4-DNPH) (mp 164°) showing the identical IR spectrum with that of acetaldehyde.

From the mother liquor a small amount of 2,4-DNPH of formaldehyde was detected by the paper partition chromatography.[8]

145 mg of barium carbonate was also recovered from volatile fraction.

The reaction mixture was divided into two portions and from each portion formic acid and succinaldehydic acid was detected as follows: a) One portion of the reaction mixture was neutralized with N NaOH and evaporated to dryness. The dried matter was dipped with 20 ml of ethanol (EtOH) for 12 hr and the extract was concentrated to dryness. The residue in 1 ml of water was desalted with Amberlite IR-120 (H type, 1 ml). The acidic fraction (0.3 ml) was introduced into ammonium salt and was applied to a PPC using 95% EtOH/ammonia (100/1) as developing agent and ammonical silver nitrate ($AgNO_3$) as detecting agent. Spot on the paper which has the *Rf* value of 0.21 (yellow spot) was recognized as that of formic acid. b) To the other portion of the reaction mixture, 500 mg of strontium carbonate was added under stirring, then excess IO_4 ion precipitated out. The filtrate was concentrated to 2 ml, and 40 ml of EtOH was added to the concentrate. After removing the precipitate the filtrate was concentrated to dryness. To the residue dissolved in 5 ml of water, a 50 mg of 2,4-dinitrophenylhydrazine in 10 ml of 6N

8) J. Gasparic and M. Vecera, *J. Chromatog.*, **1**, xviii (1958).

HCl was added. The solution was kept standing for 30 min. The reaction mixture was extracted with EtOAc. After washing with water the EtOAc (layer) was treated with aq. 2% $NaHCO_3$. The aqueous layer was acidified and re-extracted with EtOAc. After washing with water the EtOAc was concentrated to give crystalline 2,4-DNPH of succinaldehydic acid (100 mg). mp 200° (Literature[9] 204°). *Anal.* Calcd. for $C_{10}H_{10}O_6N_4$: C, 42.56; H, 3.57; N, 19.85. Found: C, 42.38; H, 3.67; N, 19.55.

B: The consumption of periodate was estimated by the usual method and shown below:

	Periodate consumption (mole)	HCOOH	CH_3CHO	HCHO	CO_2
Pillarose	2	+	+	±	+
Methyl pillaroside	1	+	−	±	−
8-O-Acetylpillarose	1	−	+		−
1,8-O-Diacetylpillarose	0	−	±		−

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