Synthesis of Two 3-(7'-Theophyllyl)glycals, 3-Deoxy-3-(7'-theophyllyl)-D-xylo-hex-1-enopyranose and Methyl 3-Deoxy-3-(7'-theophyllyl)-D-xylo-hex-1-enopyranuronate, and their Derivatives

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Two 3-(7'-theophyllyl)glycals, (IV) and (V), were synthesized by fusion of theophylline and the appropriate glycals in the presence of *p*-toluenesulfonic acid. The structure and stereochemistry of the glycals were determined mainly from NMR analysis of their dihydro and 1,6-anhydro derivatives.

Recently much attention has been paid to the synthesis of unsaturated nucleosides. Synthesis of 2-deoxynucleosides or 2,3-dehydro-2,3-deoxy-nucleosides by fusion of glycals with purine bases in the presence of an acid catalyst has been developed by Robins *et al.*¹⁾ They reported that fusion of tri-*O*-acetyl-D-glucal and theophylline in the presence of *p*-toluenesulfonic acid afforded the crystalline unsaturated nucleoside (I). The recent report of Robins *et al.*²⁾ also described the formation of isomeric mixture of glycals having a purine group at C-3 from the glucal and 2-methylthio-6-chloropurine without determination of its configuration at C-3. This paper deals with the selective formation of only one isomer of 3-(7'-theophyllyl)glycal derivatives from theophylline and galactal triacetate and its de-

rivative by the similar fusion, and determination of configuration of the products.

Theophylline and tri-*O*-acetyl-D-galactal (II) were fused *in vacuo* at 140°C for 1 hr in the presence of *p*-toluenesulfonic acid and the reaction mixture was extracted with ethyl acetate. The extract, on standing at room temp., precipitated 4,6-di-*O*-acetyl-3-deoxy-3-(7'-theophyllyl)-D-xylo-hex-1-enopyranose (IV) in 26% yield. Similar condensation of theophylline with the glycal diacetate derived from methyl galacturonate (III) gave the corresponding theophyllylglycal (V) in 20% yield.

NMR spectra of IV and V indicate the presence of a double bond in the molecule but long-range spin-spin couplings prevent unambiguous assignment of the structure. Accordingly, the structures of IV and V were deduced from the examination of the following derivatives. Catalytic hydrogenation of the glycal (IV) gave the 1,5-anhydrohexitol (VII), which was also obtained from the glycal (V) by catalytic hydrogenation to the dihydro derivative (VIII) followed by sodium borohydride reduction and acetylation; hence the position of attachment of the theophyllyl group in IV is same as that in V. The

1) M. J. Robins, W. A. Bowles and R. K. Robins, *J. Am. Chem. Soc.*, **86**, 1251 (1964); E. E. Leutzing W. A. Bowles, R. K. Robins, L. B. Townsend, *ibid.*, **90**, 127 (1968); W. A. Bowles and R. K. Robins, *ibid.*, **86**, 1252 (1964); E. E. Leutzing, R. K. Robins and L. B. Townsend, *Tetr. Lett.*, **1968**, 4475; K. Onodera and T. Yajima, *Carbohydr. Res.*, **13**, 97 (1970).

2) E. E. Leutzing, R. K. Robins and L. B. Townsend, *Tetr. Lett.*, **1970**, 3751.

TABLE I. ASSIGNMENT OF NMR SPECTRA OF VIII AND XI TAKEN IN CDCl₃

	δ in ppm		J in Hz
(VIII)	2	4.77	2, 3	7.0 ^{a)}
	3	5.76	3, 4	10.5 ^{a)}
	4	5.25	4, 5a	11.5 ^{a)}
	5a	2.73	4, 5e	5.0 ^{a)}
	5e	2.15	5a, 5e	11.5 ^{a)}
	6a	4.38	5a, 6a	11.5 ^{a)}
	6e	3.94	5a, 6e	5.0 ^{a)}
			5e, 6a	3.0 ^{a)}
			5e, 6e	2.0 ^{a)}
			6a, 6e	11.5 ^{a)}
(XI)	1	5.70	1, 2a	~0
	2a	2.61	1, 2e	~1.5
	2e	2.36	2a, 2e	13.0
	3	4.90	2a, 3	12.0 ^{a)}
	4	5.75	2e, 3	6.5 ^{a)}
	5	4.73	3, 4	10.0 ^{a)}
	6ex	3.84	4, 5	4.5 ^{a)}
	6en	4.26	5, 6ex	4.5 ^{a)}
			5, 6en	~0
			6ex, 6en	8.5

^{a)} Confirmed by spin decoupling technique.

structure and stereochemistry of VIII was deduced as shown in Table I from the analysis of its NMR spectrum by using a spin-spin decoupling technique. The NMR data indicate that the substituents at C-2, C-3 and C-4 are ax, eq, and eq, respectively. That the theophyllyl group is attached at C-4 and not at C-3 is evident from the observation that chemical shifts of the signal corresponding to H-4 (5.15 ppm) and H-2 (4.67 ppm) in the NMR spectrum of the deacetylated compound (X) are in the similar regions to that of the acetate (VIII), but the signal corresponding to H-3 disappeared from the 5~6 ppm region, indicating the presence of the acetoxyl group at C-3 in the acetate (VIII). That the theophyllyl group is attached at 7'-position was established from its UV spectrum.³⁾ Hydrolysis of the diacetate (IV) with barium

methoxide in methanol afforded the diol (VI) which was convertible to the acetate (IV) by acetylation. Catalytic hydrogenation of (VI) gave the dihydro compound (IX), which was acetylated to the diacetate (VII). Treatment of (IV) or (VI) with hydrogen chloride in methanol led to the formation of the 1,6-anhydro derivative (XII) from which the monoacetate (XI) was obtained by acetylation. The structure and stereochemistry of the 1,6-anhydro compound (XI) was deduced similarly to the case of VIII as shown in Table I.

Careful analysis of NMR spectra of the crude condensates of the glycols and theophylline disclosed the formation of 2,3-unsaturated nucleosides as well as the theophyllylglycols as shown in Table II. Contrary to the case of glucal,²⁾ selective formation of the D-xylo derivatives, IV and V, from the D-galactal derivatives indicates that the reaction would proceed by a direct S_N2 displacement of the acetyl group at C-3 in the galactal derivatives.

3) J. M. Gulland, E. R. Holiday and T. F. Macrae, *J. Chem. Soc.*, 1934, 1639.

FIG. 1.

TABLE II. COMPOSITION OF THE PRODUCTS IN THE CONDENSATES

The composition was calculated from the signal areas of aromatic proton of the products in the NMR spectra of the condensates after removal of unreacted theophylline

Starting glycol	Yield of condensate	Theophyllylglycol	2, 3-Unsaturated nucleoside
(II)	86%	(IV) <i>ca.</i> 44%	two isomers { (XIIIa) <i>ca.</i> 11% ^{a)} (XIIIb) <i>ca.</i> 8%
(III)	82%	(V) <i>ca.</i> 37%	two isomers { (XIVa) <i>ca.</i> 9% ^{a)} (XIVb) <i>ca.</i> 5%

^{a)} Obtained as crystals, see Experimental.

EXPERIMENTAL

All melting points are uncorrected. The spectra were recorded on the following instruments: IR spectra, JASCO IR-G and IR-E; UV spectra, Hitachi EPS-3T; ORD, JASCO ORD/UV-5 and Yanagimoto ORD-185; NMR spectra, JEOL 4H-100 (spin-spin couplings accompanied by an asterisk were confirmed by the spin-decoupling technique); mass spectra, Hitachi

RMS-4. Tlc was carried out on silica gel (Merck) using benzene-ethyl acetate as the solvent.

Methyl 3,4-di-O-acetyl-D-lyxo-hex-1-enopyranuronate (III). To aq. acetic acid (50%, 20 ml) was added at -5°C with vigorous stirring zinc dust (2.0 g) and then a solution of cupric sulfate (hydrate, 0.2 g) in water (8 ml). After 15 min to this mixture was added at below -5°C with stirring a solution of methyl

2, 3, 4-tri-*O*-acetyl-1- α -bromo-1-deoxy-D-galacturonate⁴⁾ (2.20 g) in acetic acid (8 ml) slowly in a period of 1 hr. After stirring at 0°C for further 5 hr, the mixture was extracted with methylene chloride 5 times and the extracts were combined, washed with aq. sodium bicarbonate, dried over calcium chloride and evaporated to dryness. Tlc separations of the residual syrup (1.51 g) gave a pure product which was crystallized from hexane-ethanol as prisms, mp 41.5~42.5°C. *Anal.* Found: C, 51.19; H, 5.51. Calcd. for C₁₁H₁₄O₇: C, 51.16; H, 5.47%.

Conversion of the unsaturated uronate (III) into tri-O-acetylgalactal (II). To a methanol solution (4 ml) of the uronate (62 mg) was added at room temp. sodium borohydride (107 mg) in small portions and after 30 min the mixture was acidified by addition of acetic acid (10 drops), evaporated to dryness, and treated with pyridine (4 ml) and acetic anhydride (2 ml) at room temp. After standing for 12 hr, the reaction mixture was diluted with methylene chloride, washed with aq. sodium bicarbonate, dried and evaporated. Tlc purification of the residue afforded a syrup (41 mg), NMR spectrum of which was completely identical with that of authentic tri-*O*-acetylgalactal (II).⁵⁾

Condensation of tri-O-acetylgalactal (II) and theophylline. Tri-*O*-acetylgalactal (4.30 g) and pulverized theophylline (dried at 110°C for 24 hr; 3.0 g) were mixed thoroughly and the mixture was fused at 140°C for 15 min. After addition of *p*-toluenesulfonic acid (20 mg) the mixture was continued heating at 140°C for further 1 hr under reduced pressure. The resulting cake was extracted with ethyl acetate. The residue was almost pure theophylline (0.76 g). The extract, on standing, precipitated crystals (1.64 g, 26%), which was recrystallized from ethyl acetate to give 4,6-di-*O*-acetyl-3-deoxy-3-(7'-theophyllyl)-D-xylo-hex-1-enopyranose (IV) as prisms, mp 174~175°C (sintered at 166°C). $\lambda_{\text{max}}^{\text{MeOH}}$ m μ (ϵ): 274 (8270); ORD (MeOH): $[\phi]_{386}^{\text{trough}}$ -4900°, $[\phi]_{360}^{\text{peak}}$ +3100°; NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 7.72 (1H, s, arom.), 6.87 (dd, $J=1.5^*$ and 6.5^* Hz, H-1), 5.40 (br. s, H-4), 5.25 (br. d, $J=5.0^*$, H-3), 4.97 (ddd, $J=1.5^*$, 5.0^* and 6.5^* , H-2), 4.3~3.9 (3H, m, H-5, 6 and 6'), 3.54 and 3.36 (N-Me), 2.13 and 2.03 (OAc). *Anal.* Found: C, 51.70; H, 4.96; N, 14.30.

4) E. L. Pippen and R. M. McCready, *J. Org. Chem.*, **16**, 262 (1951).

5) A. Rosenthal and D. Read, *Can. J. Chem.*, **35**, 788 (1957).

Calcd. for C₁₇H₂₀O₇N₄: C, 52.04; H, 5.14; N, 14.28%.

Tlc separations of the residue obtained from the mother liquor gave one of the anomers of 7'-(2,3-didehydro-2,3-dideoxy-D-*threo*-hexopyranosyl) theophylline (XIIIa), which was crystallized from ethanol as needles, mp 163°C. $\lambda_{\text{max}}^{\text{MeOH}}$ m μ (ϵ): 274 (8950); NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 7.69 (1H, s, arom.), 6.90 (dd, $J=1.5^*$ and 3.0^* Hz, H-1), 6.55 (ddd, $J=1.5^*$, 5.0^* and 10.0^* , H-3), 6.35 (dd, $J=3.0^*$ and 10.0^* , H-2), 5.18 (dd, $J=2.5^*$ and 5.0^* , H-4), 4.4~3.9 (3H), 3.60 and 3.43 (N-Me), 2.12 and 1.97 (OAc). *Anal.* Found: C, 52.13; H, 4.98; N, 13.90. Calcd. for C₁₇H₂₀O₇N₄: C, 52.04; H, 5.14; N, 14.28%. Another isomer (XIIIb) was obtained as a syrup.

Condensation of methyl 3,4-di-O-acetyl-D-lyxo-hex-1-enopyranuronate (III) and theophylline. The uronate (1.17 g) and theophylline (1.0 g) were fused in the presence of *p*-toluenesulfonic acid (5 mg) for 2 hr in the similar manner as described above to give recovered theophylline (0.41 g) and the products from which two crystalline substances were separated by means of tlc. Methyl 4-*O*-acetyl-3-deoxy-3-(7'-theophyllyl)-D-xylo-hex-1-enopyranuronate (V) was obtained by crystallization from ethyl acetate as prisms (0.34 g, 20%), mp 187~187.5°C. $\lambda_{\text{max}}^{\text{MeOH}}$ m μ (ϵ): 274 (8170); ORD (MeOH): $[\phi]_{386}^{\text{trough}}$ -4500°, $[\phi]_{360}^{\text{peak}}$ +3100°; NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 7.73 (1H, s, arom.), 6.96 (dd, $J=1.5^*$ and 6.5^* Hz, H-1), 5.60 (q, $J=2.0^*$, H-4), 5.28 (br. d, $J=5.0^*$, H-3), 5.97 (ddd, $J=2.0^*$, 5.0^* and 6.5^* , H-2), 4.81 (br. t, $J=2.0^*$, H-5), 3.23 (O-Me), 3.60 and 3.40 (N-Me), 2.13 (OAc). *Anal.* Found: C, 50.40; H, 4.69; N, 14.72. Calcd. for C₁₆H₁₈O₇N₄: C, 50.79; H, 4.80; N, 14.81%.

One of the anomers of the 2,3-unsaturated glycoside (XIVa) was crystallized from ethanol as needles (85 mg), mp 230°C. $\lambda_{\text{max}}^{\text{MeOH}}$ m μ (ϵ): 274 (7700); NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 7.70 (1H, s, arom.), 7.05 (dd, $J=2.0$ and 3.0 Hz, H-1), 6.57 (ddd, $J=2.0$, 5.0 and 10.5 , H-3), 6.32 (dd, $J=3.0$ and 10.5 , H-2), 5.00 (dd, $J=3.0$ and 5.0 , H-4), 4.53 (d, $J=3.0$, H-5), 3.77 (O-Me), 3.59 and 3.40 (N-Me), 2.09 (OAc). *Anal.* Found: C, 50.88; H, 4.57; N, 14.56. Calcd. for C₁₆H₁₈O₇N₄: C, 50.79; H, 4.80; N, 14.81%. Another anomer was obtained as a syrup.

3-Deoxy-3-(7'-theophyllyl)-D-xylo-hex-1-enopyranose (VI). A solution of the diacetate (IV) (686 mg) in abs. methanol (10 ml) containing barium methoxide (1 N, 0.9 ml) was refluxed for 30 min. After being cooled

to room temp. the resulting precipitate was collected and crystallized from water to give needles (403 mg), mp 242~244°C. *Anal.* Found: C, 47.31; H, 4.84; N, 16.99. Calcd. for $C_{13}H_{16}O_5N_4 \cdot H_2O$: C, 47.85; H, 5.56; N, 17.17%.

Acetylation of VI (11.9 mg) with pyridine and acetic anhydride afforded the crystalline diacetate (IV) which was identified by NMR spectral comparisons.

4, 6-Di-O-acetyl-1, 5-anhydro-2, 3-dideoxy-3-(7'-theophyll-yl)-D-xyllo-hexitol (VII).

From IV. The glycol diacetate (IV) (106 mg) was hydrogenated at room temp. in ethyl acetate (2 ml) in the presence of 10% palladium on charcoal (100 mg) for 48 hr to afford, after purification by tlc, the anhydrohexitol (VII) as an amorphous solid. NMR $\delta_{Me_4Si}^{CDCl_3}$: 7.70 (1H, s, arom.), 5.63 (dd, $J=5.0^*$ and 9.0^* Hz, H-4), 5.15 (dt, $J=5.0^*$ and 10.0^* , H-3), 4.62 (dd, $J=7.5$ and 10.0 , H-6), 3.57 and 3.40 (N-Me), 2.11 and 1.93 (OAc).

From VIII. To the uronate (VIII) (23 mg) in methanol (1 ml) was added sodium borohydride (34 mg) in small portions during 30 min with stirring.

The mixture was acidified with acetic acid (3 drops) and evaporated under reduced pressure to dryness. The residue was acetylated with pyridine (0.4 ml) and acetic anhydride (0.2 ml) to give, after purification by tlc, the anhydrohexitol diacetate (VII) as an amorphous solid (15 mg). NMR and IR spectra as well as *R_f* values of tlc of this compound were identical with those of VII obtained from V.

Methyl 3-O-acetyl-2, 6-anhydro-4, 5-dideoxy-4-(7'-theophyll-yl)-L-xyllo-hexonate (VIII). The uronate (V) (59 mg) was hydrogenated in ethyl acetate (10 ml) in the presence of 10% palladium charcoal (60 mg) at room temp. for 17 hr. The mixture was filtered and evaporated to dryness. The residue was crystallized from ethanol to give small needles, mp 146°C. NMR spectrum is shown in Table I; MS *m/e*: 380 (M^+). *Anal.* Found: C, 50.85; H, 5.49; N, 14.92. Calcd. for $C_{16}H_{20}O_7N_4$: C, 50.52; H, 5.30; N, 14.73%.

1,5-Anhydro-2,3-dideoxy-3-(7'-theophyll-yl)-D-xyllo-hexitol (IX). Compound VI (208 mg) was hydrogenated at room temp. in methanol (5 ml) in the presence of 10% palladium on charcoal (210 mg) for 120 hr to give needles (143 mg), mp 244°C. MS *m/e*: 310 (M^+). *Anal.* Found: C, 50.21; H, 5.41; N, 18.02. Calcd.

for $C_{13}H_{16}O_5N_4$: C, 50.31; H, 5.85; N, 18.06%.

The diol (IX) (28 mg) was acetylated with acetic anhydride (0.2 ml) and pyridine (0.4 ml) to give an amorphous solid which was identified as the diacetate (VII) by comparison of NMR and IR spectra.

Methyl 2, 6-anhydro-4, 5-dideoxy-4-(7'-theophyll-yl)-L-xyllo-hexonate (X). To a solution of the acetate (VIII) (59 mg) in abs. methanol (3.0 ml) was added sodium methoxide (1 N in methanol, 0.5 ml) and the mixture was refluxed for 5 hr. After cooling the solution separated crystals which were collected and recrystallized from ethanol yielding needles, mp 228°C (in sealed tube). NMR $\delta_{Me_4Si}^{CDCl_3}$: 7.73 (1H, s, arom.), 5.15 (dt, $J=5.0$ and 10.0 Hz, H-4), 4.67 (d, $J=5.0$, H-2), 4.4~3.5 (3H, m, H-3, 6ax, and 6eq), 3.90 (O-Me), 3.58 and 3.40 (N-Me), 2.5~1.8 (2H, H-5ax and 5eq); MS *m/e*: 338 (M^+). *Anal.* Found: C, 50.09; H, 5.35; N, 17.06. Calcd. for $C_{14}H_{18}O_6N_4$: C, 49.70; H, 5.36; N, 16.56%.

Acetylation of X (6.3 mg) with pyridine (0.2 ml) and acetic anhydride (0.1 ml) at room temp. for 15 hr afforded, after tlc separations, a syrup (6 mg), NMR spectrum of which was completely identical with that of VIII.

1, 6-Anhydro-2, 3-dideoxy-3-(7'-theophyll-yl)-D-xyllo-hexopyranose (XII).

From IV. To a solution of the diacetate (IV) (200 mg) in methylene chloride (4 ml) and abs. methanol (4 ml) was added methanol saturated with hydrogen chloride (6 drops) and the mixture was allowed to stand at room temp. for 72 hr, when the mixture precipitated crystals (107 mg), mp 349~352°C (in sealed tube). MS *m/e*: 308 (M^+). *Anal.* Found: C, 48.95; H, 5.13; N, 17.35. Calcd. for $C_{13}H_{16}O_5N_4 \cdot 1/2 H_2O$: C, 49.27; H, 5.40; N, 17.66%.

From VI. The diol (VI) (67 mg) was dissolved in abs. methanol (2 ml) and treated with methanol saturated with hydrogen chloride (2 drops). The mixture was heated for 1 hr on a water-bath and precipitated crystalline solid was collected (57 mg), mp 349~352°C.

From XI. Addition of sodium methoxide (1 N in methanol, 0.2 ml) into a solution of 1,6-anhydro acetate (XI) (46 mg) in abs. methanol (1 ml) caused immediate precipitation of crystals, mp 349°C (33 mg).

4-O-Acetyl-1,6-anhydro-2,3-dideoxy-3-(7'-theophyllyl)-D-xylo-hexopyranose (XI). A suspension of (XII) (46 mg) in pyridine (1 ml) and acetic anhydride (0.5 ml) was stirred at room temp. for 1 hr to result a clear solution, which was allowed to stand for further 12 hr. Methylene chloride was added and the mixture was worked up as usual to give, after tlc purifications, as an amorphous solid (46 mg). NMR spectrum is shown in Table I.