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ACETYL MIGRATION IN THE MONOACETATES OF METHYL 6-*O*-TRITYL-α-D-GLUCOPYRANOSIDE*

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ABSTRACT

Acetylation of methyl 6-*O*-trityl-α-D-glucopyranoside with one equivalent of acetic anhydride in pyridine yields, preferentially, the 4-acetate **8**. The 2- and 3-acetates can be converted under mild alkaline conditions into **8**, which is more stable towards acetyl migration.

INTRODUCTION

The culture filtrates of *Fusicoccum amygdali* Del. contain several substances related to fusicoccin[1–5] (**1**), the main phytotoxic product of the fungus. Among these substances, isofusicoccin (**2**) and allofusicoccin (**3**) are isomers of **1** which differ in the position of the acetyl group on the glucosidic residue[4]. At room temperature in 0.2M sodium hydrogen carbonate, **1**, **2**, and **3** are easily interconverted[4]. Similar observations have been made on **4**, **5**, and **6**, which differ from **1**, **2**, and **3**, respectively, by the lack of the acetyl group on the aglycone moiety[5]. The particularly easy migration of the *O*-acetyl group in these substances has prompted an investigation of the acetates of a simple 6-substituted glucoside, namely methyl 6-*O*-trityl-α-D-glucopyranoside. In this compound, the bulky aglycone group of fusicoccin is replaced by a methyl group and the *O*-*tert*-pentenyl residue by a trityl group. The latter substituent was chosen because of the selective reactivity of trityl chloride towards primary hydroxyl groups and the lack of interference in the analysis of p.m.r. spectra.

RESULTS

When methyl 6-*O*-trityl-α-D-glucopyranoside (**7**) was treated with one equivalent of acetic anhydride in pyridine, all the theoretically possible *O*-acetyl derivatives were obtained. After chromatographic fractionation, seven pure derivatives were isolated, namely three monoacetates (**8**, **9**, **10**), three diacetates (**11**, **12**, **13**), and the

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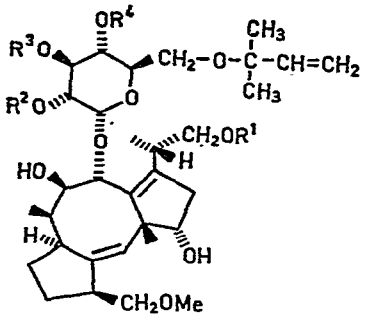
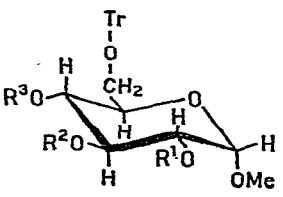


	R^1	R^2	R^3	R^4
1	Ac	H	Ac	H
2	Ac	H	H	Ac
3	Ac	Ac	H	H
4	H	H	Ac	H
5	H	H	H	Ac
6	H	Ac	H	H

triacetate (**14**), the major component being methyl 4-*O*-acetyl-6-*O*-trityl-α-D-gluco-pyranoside (**8**). The sites of acetylation were demonstrated by p.m.r. spectroscopy on the basis of the following widely accepted rules: (*a*) an acetyl group causes the signal for the geminal proton to shift to much lower field; (*b*) splittings in the range 8–14 Hz are indicative of vicinal *ax–ax* coupling, whereas those in the range 2–5 Hz are indicative of vicinal *eq–ax* or *eq–eq* couplings. Moreover, it has been assumed that most of the molecules of the products to be discussed have the *C1*(D) conformation[6].



	R^1	R^2	R^3
7	H	H	H
8	H	H	Ac
9	H	Ac	H
10	Ac	H	H
11	Ac	Ac	H
12	H	Ac	Ac
13	Ac	H	Ac
14	Ac	Ac	Ac

Each of the monoacetyl derivatives was isomerised at room temperature in the same biphasic medium (benzene–0.2M sodium hydrogen carbonate) previously used for the rearrangement of **1** and related compounds[4], and the rearrangements were monitored by t.l.c. After 20 h, **9** was partially converted into **8**, **10** was partially converted into **8** and **9**, whereas **8** was unaffected. After 30 h, each of the starting products gave **7**, besides the other two isomers. Three days later, all the reaction mixtures consisted of **7** and **8** only.

DISCUSSION

The results show that, under the described conditions, the preferred position for the acetoxyl group is at C-4, both for direct esterification (in spite of the reported,

enhanced sensitivity of position 2 to electrophilic attack[7]) and for transacetylation. A similar finding has been previously discussed for fusicoccin and its derivatives[4]. Related behaviour has also been observed for methyl 4,6-*O*-benzylidene-α-D-glucopyranoside[8]. The close analogy between the isomerization of fusicoccin and related compounds and that of the monoacetates of **7** excludes any marked influence by the nature of the aglycon and the 6-*O*-substituent.

It is known that the reactivity of a hydroxyl group towards acetylation is mainly dependent upon its "acidity" (expected to be enhanced by a neighbouring, electron-withdrawing group) or on its ability to form a hydrogen bond[9–11]. The latter factor must determine the preferential acetylation of the title compound at C-4. Dreiding models show that an intramolecular hydrogen bond can easily occur between HO-4 and O-6. This interpretation is supported by the relative polarity of the diacetates **11–13**, as inferred from their mobility in t.l.c. (silica gel). The 2,3-diacetate (**11**) has an R_F value higher than the 3,4- (**12**) or 2,4-diacetate (**13**), which have similar mobilities in several solvent systems (see Table I). If HO-4 in **11** is hydrogen bonded to O-6, the polarity of the compound will be decreased and its mobility on hydrated silica gel will be increased. In fact, all the derivatives containing a 4-*O*-acetyl group in the series of esters of the title compound, and in the series of fusicoccin derivatives, have much lower mobilities than those of the corresponding isomers (see Tables I and II).

The intermediate occurrence of an ortho acid ester has been generally postulated[12] in acetyl migration. The migration of the acetyl group from 2→3→4 can therefore be explained as follows. The anion of the 2,3-ortho acid ester, which can

TABLE I

R_F AND YIELDS OF THE PRODUCTS FROM ACETYLATION OF **7**

Compound	*Solvent* a	*Solvent* b	*Solvent* c	*Yield* (%)[a]
14	0.78	1.00	1.00	5.8
11	0.67	0.85	0.90	8.2
12	0.50	0.73	0.82	5.5
13	0.50	0.65	0.82	7.7
9	0.36	0.46	0.68	7.7
10	0.26	0.26	0.50	6.7
8	0.11	0.13	0.36	58.4
7	0.06	0.05	0.15	

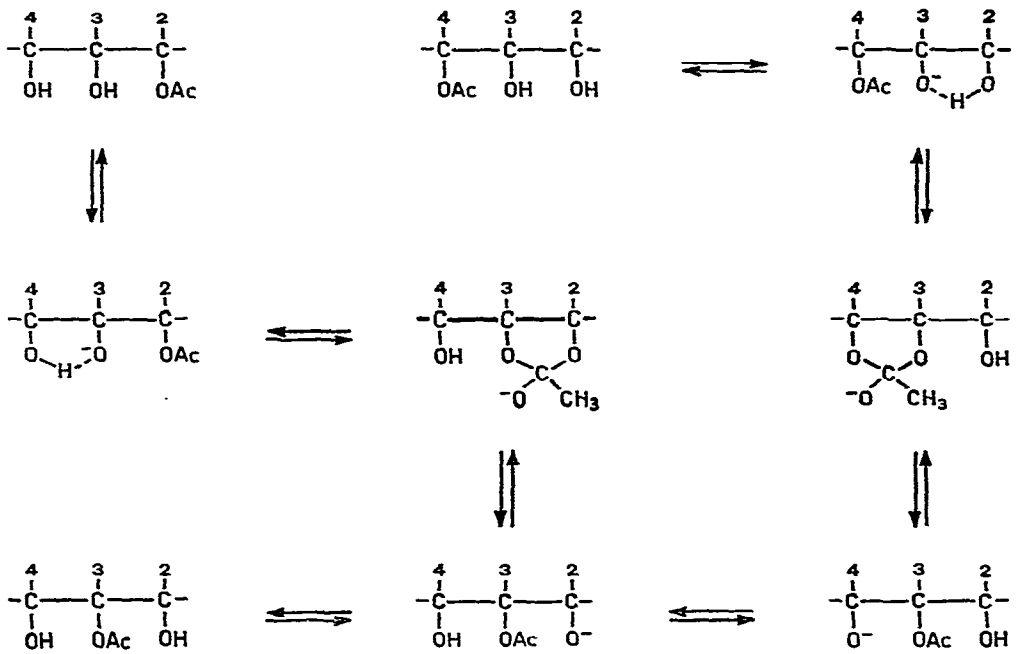
[a]Calculated on recovered, acetylated products (total recovery, 48%).

TABLE II

R_F OF FUSICOCCIN (**1**) AND ITS DERIVATIVES

Compound	**1**	**3**	**2**	**4**	**6**	**5**
R_F (solvent *d*)	0.62	0.56	0.42	0.15	0.15	0.09

arise in alkaline medium from the 2-acetate (**3**, **6**, or **10**), may open preferentially to give AcO-3 because the negative charge on O-2 in the transition state is stabilized by the electron-withdrawing effect of the anomeric carbon[7]. Further migration involves the anion of the 3,4-ortho acid ester, which may open preferentially to give AcO-4 because the negative charge on O-3 in the transition state is now stabilized by the hydrogen bond with HO-2. These considerations are summarized in the annexed scheme.



EXPERIMENTAL

General. — Optical rotations were measured with a Perkin–Elmer 141 polarimeter. I.r. spectra were recorded for dispersions in Nujol with an IR-9 Beckman spectrophotometer. U.v. spectra were recorded in CH_3CN with a DK-2 Beckman spectrophotometer; all trityl compounds gave λ_{max} 258 nm ($\varepsilon \sim 650$). Mass spectra were obtained with an MS-902 AEI spectrometer. P.m.r. spectra were recorded with a Varian HA-100 spectrometer; chemical shifts are on the δ scale, and splittings and coupling constants in Hz.

All melting points are uncorrected. Elemental analyses were performed by Mr. T. Bianco at the Research Laboratories of Richardson–Merrell S.p.A. (Naples, Italy).

Column chromatography was performed on Merck silica gel (0.05–0.2 mm) with a loading of 2–3%; thin-layer (0.25 mm) and preparative (2.0 mm) chromatograms were run on Merck silica gel F_{254}. Elution was performed with (*a*) 1:1 ethyl

acetate–hexane; (*b*) 6:1 chloroform–acetone; (*c*) 30:3:1 chloroform–acetone–methanol (*d*) 92:8 chloroform–propan-2-ol. Compounds were detected with 5% methanolic sulphuric acid at 110° for 15 min; trityl derivatives gave yellow-brown spots. *O*-Acetyl derivatives were converted into **7** on hydrolysis with methanolic sodium hydroxide, and into **14** on treatment with acetic anhydride and pyridine.

Methyl 6-O-trityl-α-D-glucopyranoside (**7**). — A modification of the Helferich and Becker[14] procedure was used. To a solution of methyl α-D-glucopyranoside[13] (15 g) in dry pyridine (80 ml), trityl chloride (22.5 g, recrystallized from light petroleum immediately before use) was added with vigorous stirring until dissolution was complete. After 48 h at room temperature, the clear, yellow reaction mixture was poured into ice–water, and the amorphous precipitate was collected and dissolved in ether (200 ml). The solution was washed successively with saturated, aqueous potassium hydrogen sulphate (3 × 50 ml), saturated, aqueous sodium hydrogen carbonate (3 × 50 ml), and water. Concentration of the dried (Na_2SO_4) ethereal solution yielded a syrupy product, which was crystallized twice from methanol to give **7** (33 g, 70%), m.p. 133–135°, $[\alpha]_D^{22}$ +51.5° (*c* 1.5, chloroform); lit.[14] m.p. 128–130°, $[\alpha]_D^{15}$ +72.8° (pyridine).

Partial acetylation of **7**. — A solution of dry **7** (24 g) in anhydrous pyridine (40 ml) was treated dropwise, with continuous stirring at −15°, with a mixture of acetic anhydride (6 ml) and pyridine (40 ml) during 2 h. The mixture was stored for 20 h at −20° and for 3 h at room temperature, and was then poured into ice–water. The resulting, amorphous solid was separated, and a solution in ether (200 ml) was washed successively with saturated, aqueous potassium hydrogen sulphate (3 × 50 ml), saturated, aqueous sodium hydrogen carbonate (3 × 50 ml), and water, dried (Na_2SO_4), and concentrated. The syrupy residue contained nine components (t.l.c.; solvents *a*, *b*, and *c*).

The mixture was partially fractionated by elution from a column (125 × 4 cm) of silica gel with ethyl acetate–hexane (1:1). The following fractions were collected: *A*, triphenylmethanol (20 mg), m.p. 164–166° (from methanol), *m/e* 260 (M^+); *B*, **14** (trace); *C*, **11**; *D*, a mixture of **11**, **12**, and **13**; *E*, a mixture of **12**, **13**, **9**, and **10**; *F*, a mixture of **9** and **10**; *G*, **8**; *H*, a mixture of **8** and **7**.

Fractions *D*, *E*, *F*, and *H* were rechromatographed, but a complete separation of the various components was achieved only by p.l.c. Compounds **12** and **13** were separated by using solvent *b*, and **9** and **10** by solvent *c*; R_F values and yields are shown in Table I.

Characterization of the acetylated compounds. — *Methyl 4-O-acetyl-6-O-trityl-α-D-glucopyranoside* (**8**). Compound **8** reduced periodate, and had m.p. 100–102° (from chloroform–carbon tetrachloride), $[\alpha]_D^{22}$ +63° (*c* 1.13, chloroform): ν_{max} 1730 (C=O, acetate), 1600 and 1500 (C=C, arene), 1250 (C–O–C, acetate), 1155 (C–O–C, ether), and 1040 cm^{-1} (C–OH *sec.*). P.m.r. data (C_6D_6): δ 4.67 (*d*, *J* 3.5 Hz, H-1), 5.13 (*dd*, *J* 9.0 and 10 Hz, H-4). These assignments were confirmed by decoupling experiments. Thus, H-1 but not H-4 was decoupled by irradiation at δ 3.58, and H-4 was decoupled by irradiation at δ 3.93. Thus, the acetyl group must be at C-4.

Anal. Calc. for $C_{28}H_{30}O_7$: C, 70.26; H, 6.32. Found: C, 70.67; H, 6.60; mol. wt. (mass spectrometry), 478.

Methyl 3-O-acetyl-6-O-trityl-α-D-glucopyranoside (**9**). Compound **9**, which did not reduce periodate, was obtained as an amorphous solid (m.p. 85–95°) by precipitation with carbon tetrachloride from solution in ethyl acetate. It had $[\alpha]_D^{22}$ +74° (*c* 1.1, chloroform); ν_{max} 1740 (C=O, acetate), 1600 and 1500 (C=C, arene), 1270 (C–O–C, acetate), 1155 (C–O–C, ether), and 1060 cm^{-1} (C–OH *sec.*). P.m.r. data (acetone-d_6+D_2O): δ 5.11 (*dd*, *J* 9 and 10 Hz, H-3), 4.77 (*d*, *J* 3.5 Hz, H-1). INDOR experiments showed that both these signals have transitions in common with those of a proton having signals that are partially overlapped by that for OMe, and confirmed the assignments.

Anal. Calc. for $C_{28}H_{30}O_7 \cdot 1.5H_2O$: C, 66.53; H, 6.53. Found: C, 66.01; H, 6.60; mol. wt. (mass spectrometry), 478.

Methyl 2-O-acetyl-6-O-trityl-α-D-glucopyranoside (**10**). Compound **10**, which reduced periodate, was obtained as a chromatographically homogeneous, amorphous solid (m.p. 130–150°) after treatment with carbon tetrachloride of the substance eluted from the preparative plates. It had $[\alpha]_D^{22}$ +47° (*c* 0.86, chloroform); ν_{max} 1745 (C=O, acetate), 1600 and 1500 (C=C, arene), 1265 (C–O–C, acetate), 1155 (C–O–C, ether), and 1055 cm^{-1} (C–OH *sec.*). P.m.r. data (CD_3OD): δ 4.55 (*dd*, $J_{2,1}$ 3.5, $J_{2,3}$ 10 Hz, H-2). Since **10** is a monoacetate of **7** which is different from **8** and **9**, it must be the 2-acetate.

Anal: Calc. for $C_{28}H_{30}O_7 \cdot 1.5H_2O$: C, 66.53; H, 6.53. Found: C, 66.01; H, 6.40; mol. wt. (mass spectrometry), 478.

Methyl 2,4-di-O-acetyl-6-O-trityl-α-D-glucopyranoside (**13**). The analytical sample had m.p. 179–181° (from ethanol), $[\alpha]_D^{22}$ +88° (*c* 1.55, chloroform); ν_{max} 1730 (C=O, acetate), 1590 and 1480 (C=C, arene), 1265 (C–O–C, acetate), 1160 (C–O–C, ether), and 1060 cm^{-1} (C–OH *sec.*). P.m.r. data (acetone-d_6): δ 5.0–4.85 (*m*, 2 H), 4.80–4.65 (*q*, 1 H), 3.94 (*dd*, *J* 9 and 10 Hz, H-3), 3.84 (*m*, H-5), 3.12 (*d*, H-6,6′).

On irradiation of H-6,6′, the *m* for H-5 at 3.84 collapsed to a *d* (*J* 10 Hz). Irradiation at 3.84 caused the two lines centred at 3.12 to collapse to an *s*, and also identified H-4 as responsible for some of the lines in the range 5.0–4.85. It follows that the *dd* at 3.94 is due to the H-3, and that the two acetylated positions must be C-2 and C-4.

Anal. Calc. for $C_{30}H_{32}O_8 \cdot H_2O$: C, 66.91; H, 6.32. Found: C, 67.08; H, 6.27; mol. wt. (mass spectrometry), 520.

Methyl 2,3-di-O-acetyl-6-O-trityl-α-D-glucopyranoside (**11**). The analytical sample had m.p. 159–162° (from ethanol), $[\alpha]_D^{22}$ +69° (*c* 1.45, chloroform), in accordance with literature values[15]; ν_{max} 1750 (C=O, acetate), 1600 and 1500 (C=C, arene), 1265 (C–O–C, acetate), 1165 (C–O–C, ether), and 1060 cm^{-1} (C–OH *sec.*). P.m.r. data (C_6D_6): δ 5.00 (H-2), 4.95 (H-1), 5.55 (*dd*, $J_{3,2} = J_{3,4} = 10$ Hz, H-3). The last signal was decoupled into a *d* (*J* 10 Hz) on irradiation at the frequency of the H-2 signal.

Anal. Calc. for $C_{30}H_{32}O_8$: C, 69.23; H, 6.15. Found: C, 69.09; H, 6.31; mol. wt. (mass spectrometry), 520.

Methyl 3,4-di-O-acetyl-6-O-trityl-α-D-glucopyranoside (**12**). The analytical sample had m.p. 71–74° (from methanol–water), $[\alpha]_D^{22}$ +121° (*c* 0.63, chloroform); ν_{max} 1755 (C=O, acetate), 1600 and 1595 (C=C, arene), 1265 (C–O–C, acetate), 1160 (C–O–C, ether), and 1055 cm^{-1} (C–OH *sec.*). P.m.r. data (C_6D_6): δ 1.53 and 1.78 (2 *s*), 4.54 (*d*, *J* 3.5 Hz, H-1). The last signal collapsed to an *s* by irradiation at 3.57; therefore HO-2 is not acetylated, and the six lines in the range 5.60–5.15 are due to H-3 and H-4, thus identifying the compound as the 3,4-diacetate.

Anal. Calc. for $C_{30}H_{32}O_8$: C, 69.23; H, 6.15. Found: C, 68.80; H, 6.35; mol. wt. (mass spectrometry), 520.

Methyl 2,3,4-tri-O-acetyl-6-O-trityl-α-D-glucopyranoside (**14**). — The mobility of **14** on t.l.c., the m.p., and the mass spectrum were identical to those of an authentic sample[15] obtained by complete acetylation of **7**.

Isomerization of the monoacetates of **7**. — Samples (10 mg) of **8**, **9**, and **10** were separately dissolved in 5 ml of benzene. Each solution was shaken at room temperature with 1 ml of 0.2M sodium hydrogen carbonate. The reactions were monitored up to 3 days by t.l.c. of samples withdrawn from the benzene phase.

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REFERENCES

1 A. Ballio, M. Brufani, C. G. Casinovi, S. Cerrini, W. Fedeli, R. Pellicciari, B. Santurbano, and A. Vaciago, *Experientia*, 24 (1968) 631.
2 A. Ballio, A. Carilli, B. Santurbano, and L. Tuttobello, *Ann. Ist. Super. Sanità*, 4 (1968) 317.
3 A. Ballio, C. G. Casinovi, G. Randazzo, and C. Rossi, *Experientia*, 26 (1970) 349.
4 A. Ballio, C. G. Casinovi, M. Framondino, G. Grandolini, F. Menichini, G. Randazzo, and C. Rossi, *Experientia*, 28 (1972) 126.
5 A. Ballio, C. G. Casinovi, M. Framondino, G. Grandolini, G. Randazzo, and C. Rossi, *Experientia*, 28 (1972) 1150.
6 E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, *Conformational Analysis*, Wiley, New York, 1965.
7 See, for example, J. M. Sugihara, *Advan. Carbohyd. Chem.*, 8 (1953) 1.
8 R. W. Jeanloz and D. A. Jeanloz, *J. Amer. Chem. Soc.*, 79 (1957) 2579.
9 K. W. Buck, A. B. Foster, A. R. Perry, and J. M. Webber, *J. Chem. Soc.*, (1963) 4171.
10 K. W. Buck, J. M. Duxbury, A. B. Foster, A. R. Perry, and J. M. Webber, *Carbohyd. Res.*, 2 (1966) 122.
11 S. J. Angyal, M. E. Tate, and S. D. Gero, *J. Chem. Soc.*, (1961) 4116.
12 E. Pacsu, *Advan. Carbohyd. Chem.*, 1 (1945) 77.
13 J. E. Cadotte, F. Smith, and D. Spriestersbach, *J. Amer. Chem. Soc.*, 74 (1952) 1501.
14 B. Helferich and J. Becker, *Ann.*, 440 (1924) 1.
15 H. Bredereck, *Ber.*, 68 (1935) 777.