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SOME CHEMICAL TRANSFORMATIONS OF 7-β-D-GLUCOPYRANOSYLTHEOPHYLLINE

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ABSTRACT

Selective chlorination of 7-β-D-glucopyranosyltheophylline with an excess of methanesulphonyl chloride in *N,N*-dimethylformamide gave 7-(6-chloro-6-deoxy-β-D-glucopyranosyl)theophylline. Likewise, selective tosylation of 7-β-D-glucopyranosyl- and 7-β-D-galactopyranosyl-theophylline gave, after acetylation *in situ*, the corresponding 7-(2,3,4-tri-*O*-acetyl-6-*O*-tosyl-β-D-hexopyranosyl)theophyllines. Treatment of the D-*gluco* 6′-toluene-*p*-sulphonate with excess of methanolic sodium methoxide gave the 3′,6′-anhydride, isolated as its acetate which was shown from ^{1}H-n.m.r. studies to be conformationally unstable in solution. Treatment of 7-(2,3,4-tri-*O*-acetyl-6-deoxy-6-iodo-β-D-glucopyranosyl)theophylline with silver fluoride in pyridine gave, after deacetylation, 7-(6-deoxy-β-D-*xylo*-hex-5-enopyranosyl)theophylline. Platinum-catalysed hydrogenation of this 5′-ene was stereoselective and gave mainly 7-(6-deoxy-β-D-glucopyranosyl)theophylline.

INTRODUCTION

In our previous paper[1], a convenient procedure for the preparation of theophylline nucleosides was described. Our next objective was the synthesis of unsaturated nucleoside derivatives, as some members of this class, including the naturally occurring, nucleoside antibiotics angustmycin A (**1**)[2,3] and blasticidin S[4], exhibit anti-tumour activity[5]. The unsaturated nucleosides so far synthesized are of two main structural types, namely, pentofuranosides possessing terminal 4′,5′-exocyclic double bonds analogous to angustmycin A (**1**), and pentofuranosides or hexopyranosides possessing non-terminal 2′,3′-endocyclic double bonds analogous to cytosinine (**2**), the nucleoside component of blasticidin S.

Our interest lay in synthetic nucleosides having an exocyclic double bond, the first of which (**4**) was prepared by Verheyden and Moffatt[6] by reaction of silver

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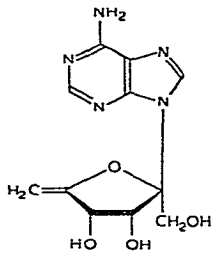

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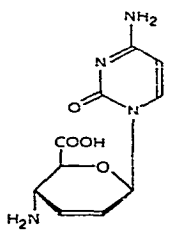

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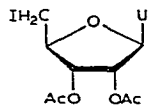

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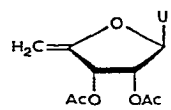

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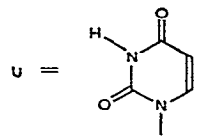
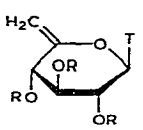


fluoride[8] with 2′,3′-di-*O*-acetyl-5′-deoxy-5′-iodouridine (**3**) in pyridine solution. Hough *et al.*[7] have prepared a range of exocyclic alkene derivatives of carbohydrates by means of this reaction[8], and we have extended these studies to nucleosides and now describe the synthesis of a terminally unsaturated, hexopyranosyltheophylline nucleoside (**5**).

RESULTS AND DISCUSSION

7-β-D-Glucopyranosyltheophylline (**7**), when treated with methanesulphonyl chloride in *N*,*N*-dimethylformamide for 19 h under the conditions described by Evans *et al.*[9] for methyl hexopyranosides, gave a good yield of the 6′-chloro-nucleoside (**8**). Acetylation of **8** gave the 2′,3′,4′-triacetate (**9**), whose ^{1}H-n.m.r. spectrum could be interpreted on a first-order basis (see Table I). The spectral assign-



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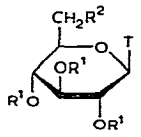
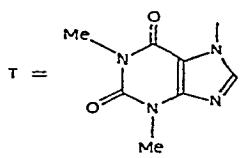
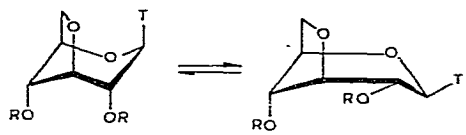
6 R = Ac

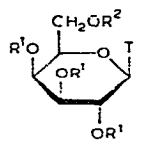


	R^1	R^2
7	H	OH
8	H	Cl
9	Ac	Cl
10	H	OTs
11	Ac	OTs
12	H	I
13	Ac	I
14	H	H
15	Ac	H

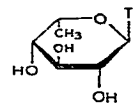




16 R = H
17 R = Ac



	R^1	R^2
18	H	H
19	Ac	Ts



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ments were verified by spin-decoupling by irradiation at the H-1′ doublet (τ 3.55, $J_{1',2'}$ 9.0 Hz) and at the H-5′ octet (τ 5.74). The coupling constants indicated that the $^4C_1$ conformation was preponderant in solution, as with all related compounds except the anhydro derivative **17**.

TABLE I

^{1}H-N.M.R. PARAMETERS[a]

Compound	**6**[b]	**9**[c]	**11**[d]	**15**[e]	**17**[b]	**19**[f]
H-1′	3.86d	3.55d	3.35d	3.52d	3.47d	3.36d
H-2′	4.17q	3.95t	3.73t	3.80t	4.53q	3.75t
H-3′	4.70t	4.30t	4.06t	4.24t	5.46q	4.22q
H-4′	4.34sx	4.57t	4.40t	4.72t	4.92q	4.06q
H-5′	—	5.74oc	~5.38	5.95oc	5.35cm	5.24bt
H-6′a	5.05bt	~6.3	~5.49	8.71d	~6.0cm	~5.48d
H-6′b	5.28bt	o		(3 × H-6′)		
H-8	2.13s	1.76s	1.49s	1.55s	2.04s	1.54s
OAc	7.84s	8.07s	8.03s	7.96s	7.74s	7.96s
	7.96s	8.13s	8.03s	8.02s	7.97s	8.04s
	8.10s	8.27s	8.15s	8.14s	—	8.16s
C_6H_4(OTs)	—	—	2.15d	—	—	2.18d
	—	—	2.87od	—	—	2.88od
CH_3(OTs)	—	—	7.85s	—	—	7.82s
NMe	6.41s	6.64s	6.54s	6.53s	6.41s	6.53s
	6.58s	6.72s	6.63s	6.60s	6.60s	6.61s
$J_{1',2'}$	9.0	9.0	9.0	9.0	4.5	9.0
$J_{2',3'}$	8.0	9.0	9.0	9.0	2.0	10.0
$J_{3',4'}$	8.0	9.0	9.0	9.0	5.5	3.5
$J_{4',5'}$	—	~9.5	~9.0	9.5	3.0	1.0
$J_{5',6'a}$	—	~3.0	—	6.0	—	~6.0
$J_{5',6'b}$	—	~5.5	—	—	—	
$J_{6'a,6'b}$	2.0	—	—	—	—	—
$J_{2',4'}$	—	—	—	—	~0.5	—
$J_{4',6'a}$	1.5	—	—	—	—	—
$J_{4',6'b}$	1.5	—	—	—	—	—

[a]First-order chemical shifts (τ values) and coupling constants (Hz) at 100 MHz. [b]In chloroform-*d* at ambient temperature. [c]In pyridine-d_5 at 90°; relative to HMDS (others relative to Me_4Si). [d]In pyridine-d_5 at ambient temperature. [e]In pyridine-d_5 at 50°. [f]In pyridine-d_5 at 60°. Key: b, broad; cm, complex multiplet; d, doublet; o, overlapped; oc, octet; q, quartet; s, singlet; sx, sextet; t, triplet.

In contrast, selective chlorination of 7-β-D-galactopyranosyltheophylline (**18**) for 2 days by the method described above gave an ~1:1 mixture of a product and the starting material. The lower reactivity at C-6′ in the *galacto* nucleoside **18** is attributed to unfavourable steric and polar interactions emanating from the axial HO-4′ in the transition state[9].

Treatment of 7-β-D-glucopyranosyltheophylline (**7**) with 1.1 mol. of tosyl chloride, in pyridine solution, gave the 6′-*O*-tosyl derivative **10**, isolated as its 2′,3′,4′-triacetate **11** after acetylation of the reaction mixture *in situ*. The triacetate was characterized by reaction with sodium iodide in refluxing butanone to give the

known[10,11] 7-(2,3,4-tri-*O*-acetyl-6-deoxy-6-iodo-β-D-glucopyranosyl)theophylline (**13**). Furthermore, reaction of **10** with strong base resulted in 3′,6′-anhydride formation, as described below. The 6′-iodide **13** was, however, more conveniently prepared by condensation of 2,3,4-tri-*O*-acetyl-6-deoxy-6-iodo-α-D-glucopyranosyl bromide and bis(theophyllin-7-yl)mercury[1].

Selective monotosylation of 7-β-D-galactopyranosyltheophylline (**18**), followed by acetylation *in situ*, gave 7-(2,3,4-tri-*O*-acetyl-6-*O*-tosyl-β-D-galactopyranosyl)-theophylline (**19**), and although the product was difficult to purify, its ^{1}H-n.m.r. spectrum (see Table I) supported the structure.

Treatment of 7-(6-*O*-tosyl-β-D-glucopyranosyl)theophylline (**10**), obtained by careful deacetylation of the triacetate **11**, with an excess of methanolic sodium methoxide gave the expected 3′,6′-anhydride **16**, which was isolated as its diacetate **17**. ^{1}H-N.m.r. spectroscopy (see Table I) of **17** at ambient temperature showed a long-range coupling between H-2′ and H-4′ ($J_{2',4'}$ ~0.5 Hz) characteristic of a "W-orientation" of these two nuclei. Such a coupling is considered to be diagnostic of the $^1C_4$ conformation, where both H-2′ and H-4′ are in equatorial positions. However, at ambient temperature, $J_{1',2'}$ is larger (4.5 Hz) than that expected (1–2.5 Hz) for the equatorial–equatorial coupling found in the $^1C_4$(D) conformation. Cooling the n.m.r. sample by stages to −70° caused a steady decrease in the value of $J_{1',2'}$ (to 1.5 Hz); $J_{2',3'}$ increased slightly from 2 to 3 Hz, whereas $J_{3',4'}$ remained constant at 5.5 Hz. Except for $J_{1',2'}$, the observed couplings at low temperatures are in accord with those of 3,6:3′,6′-dianhydro-α,α-trehalose tetrabenzoate, in which the pyranoid rings are in the $^1C_4$ conformation[12]. The results suggest that, at ambient temperature, the anhydride **17** exists to a considerable extent in the $B_{1,4}$ ($J_{1',2'}$ calc.: 7.5–8.5) or related skew conformation. This evidence can be reconciled with the steric interaction between the 3′,6′-anhydro bridge and the axial theophyllyl group at C-1 in the $^1C_4$ conformation.

Furthermore, applying the arguments advanced previously[1] regarding the reverse anomeric effect of purine substituents on the conformation of 6-membered pyranoside rings, the $B_{1,4}$ conformation with favourable dipole interactions could be expected to be a significant conformer (Fig. 1).

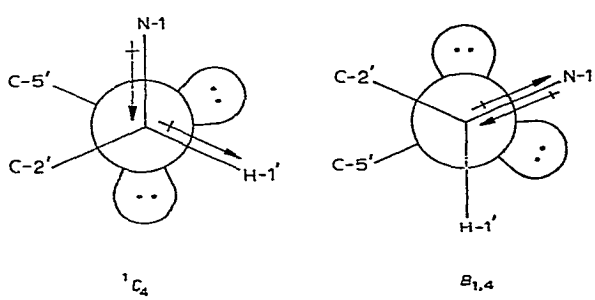

Fig. 1. Newman-projection diagrams viewed along the C-1′–O-5′ bond of the 3′,6′-anhydro derivative **17**.

Reaction of 7-(2,3,4-tri-*O*-acetyl-6-deoxy-6-iodo-β-D-glucopyranosyl)theophylline (**13**) with silver fluoride in pyridine gave a high yield of the unsaturated product **6**, deacetylation of which gave a 74% yield of 7-(6-deoxy-β-D-*xylo*-hex-5-enopyranosyl)theophylline (**5**).

The ^{1}H-n.m.r. spectrum of **5** (see Table I) confirmed the structure, and revealed interesting features for the H-4′, H-6′a, and H-6′b resonances. The resonance for H-4′ occurred as a sextet at τ 4.34; the large coupling (8.0 Hz) was assigned to $J_{3',4'}$, because of the *trans*-diaxial disposition of H-3′ and H-4′ in the most favourable $^4C_1$ conformation, and the small couplings to the allylic splitting of the H-4′, H-6′a, and H-6′b resonances ($J_{4',6'a} \simeq J_{4',6'b} \simeq 1.5$ Hz). The vinyl protons were non-equivalent and gave narrow triplets at τ 5.05 and 5.28. The value of the geminal coupling of the vinyl protons was also small ($J_{6'a,6'b} \sim 2.0$ Hz), and indicative of sp^2-hybridised carbon as geminal couplings between protons on sp^3-hybridised carbon atoms are larger ($J \sim 10$–14 Hz).

The 6′-deoxy-hex-5′-ene **5** was tested[13] against Walker 256 rat tumour, but no activity was detected.

The 5′-ene **5** was recovered unchanged after treatment overnight with a large excess of diazomethane. Horton and co-workers[14] have reported similar unreactivity of unsaturated carbohydrates which were, however, affected by treatment with di-iodomethane in the presence of a zinc–copper couple to give cyclopropane derivatives[14]. The 5′-ene **5** did not react with aqueous sodium bisulphite, although Lehmann and Benson reported a quantitative yield of sodium (methyl 6-deoxy-α-D-glucopyranosid-6-yl)sulphonate from methyl 6-deoxy-α-D-*xylo*-hex-5-enopyranoside[15].

Hydrogenation of the 5′-ene **5** over Adams' catalyst gave a mixture of 6′-deoxy-D-*gluco*- and 6′-deoxy-L-*ido*-pyranosides, **14** and **20**, respectively, in the ratio of 2:5 (n.m.r.). The value of $J_{1',2'}$ 9 Hz for the anomeric proton in **14** and **20** suggested that both products exist mainly in the $^4C_1$ conformation in solution. Hence, in the hydrogenation, the major attack on the 5′-double bond was from below the plane of the pyranoid ring. Hough *et al.*[7] found that the glucoside ratio in related hydrogenations depended mainly on the catalyst employed.

An authentic sample of 7-(6-deoxy-β-D-glucopyranosyl)theophylline (**14**) was prepared by reduction of 7-(6-deoxy-6-iodo-β-D-glucopyranosyl)theophylline (**12**) with Raney nickel and hydrazine in refluxing methanol, and purified *via* its 2′,3′,4′-triacetate (**15**).

EXPERIMENTAL

General methods. — For procedures, see Ref. 1. Detection on t.l.c. was effected by spraying with 5% ethanolic sulphuric acid followed by heating for 1–2 min at 200°. Unsaturated nucleosides were detected with 1% ethanolic 1-naphthol and heating as described above.

7-(6-Chloro-6-deoxy-β-D-glucopyranosyl)theophylline (**8**) *and its triacetate* (**9**).—

To a solution of 7-β-D-glucopyranosyltheophylline[1] (**7**, 5 g) in anhydrous *N,N*-dimethylformamide (100 ml) maintained at 65° under anhydrous conditions, mesyl chloride (12 ml, 10 mol.) was added dropwise during 30 min. The mixture was kept at 65° for 19 h and then concentrated to a red syrup, which was treated with methanolic sodium methoxide to pH ~10.

After 2 h at room temperature, the mixture was neutralised with Amberlite IR-120(H^+) resin, filtered through Kieselguhr and silica gel, partially decolorised at the boiling point with activated charcoal, and then concentrated. Crystallisation of the yellow, syrupy residue from methanol (70 ml) gave **8** (4.3 g, 81%) which contained (t.l.c.) a trace of the starting material. Purification by elution from a short column of silica gel with dichloromethane–ethanol (9:1) gave **8** (2.6 g, 55%), m.p. 203–207° (dec.), $[\alpha]_D$ −22° (*c* 2, water), $\lambda_{max}^{H_2O}$ 273 nm (ε_{max} 12,000, pH 7) (Found: C, 43.1; H, 4.8; Cl, 10.1; N, 15.4. $C_{13}H_{17}ClN_4O_6$ calc.: C, 43.3; H, 4.8; Cl, 9.8; N, 15.5%).

A solution of **8** (1 g) in acetic anhydride (3 ml, 4 mol.) and pyridine (6 ml) was stored overnight at 0°. Dropwise addition of water precipitated the product, which was collected, washed with water, and dried to give **9** (1.28 g, 95%), m.p. 193–194°, $[\alpha]_D$ −12° (*c* 2, chloroform) (Found: C, 46.8; H, 5.0; N, 11.5. $C_{19}H_{23}ClN_4O_9$ calc.: C, 46.9; H, 4.8; N, 11.5%).

7-(6-O-Tosyl-β-D-glucopyranosyl)theophylline (**10**) *and its triacetate* (**11**). — 7-β-D-Glucopyranosyltheophylline[1] (**7**, 1 g) was dissolved in hot, anhydrous pyridine (15 ml), and the solution was cooled to below −10°. Tosyl chloride (0.61 g, 1.1 mol.) was added, and the mixture was shaken until dissolution was complete and then stored at −10° overnight. Acetic anhydride (2 ml) was added and the mixture was stored for 18 h at −10°. The solution was poured into ice–water (100 ml), and the resulting white precipitate (1.52 g, 84%) was collected, washed with water, dried, and recrystallized from dichloromethane (30 ml) and ethanol (100 ml) to give **11**, m.p. 216–220° (dec.), $[\alpha]_D$ +8° (*c* 1.7, chloroform) (Found: C, 50.3; H, 5.4; N, 8.8. $C_{26}H_{30}N_4O_{12}S$ calc.: C, 50.2; H, 4.9; N, 9.0%).

Treatment of **11** (3 g) with methanolic ammonia[1] gave **10** (1.93 g, 81%), m.p. 129–132° (from ethanol), $[\alpha]_D$ +24° (*c* 1.5, acetone) (Found: C, 48.7; H, 5.4; N, 10.0. $C_{20}H_{24}N_4O_9S \cdot C_2H_5OH$ calc.: C, 48.7; H, 5.5; N, 10.3%).

7-(2,3,4-Tri-O-acetyl-6-O-tosyl-β-D-galactopyranosyl)theophylline (**19**). — 7-β-D-Galactopyranosyltheophylline[1] (**18**, 1 g) was tosylated, and then acetylated as described above for **7**, to give **19** (1.33 g, 73%), m.p. 212–220° (dec.), $[\alpha]_D$ +2° (*c* 1, chloroform) (Found: C, 49.9; H, 4.9; N, 8.8. $C_{26}H_{30}N_4O_{12}S$ calc.: C, 50.2; H, 4.9; N, 9.0%).

7-(2,4-Di-O-acetyl-3,6-anhydro-β-D-glucopyranosyl)theophylline (**17**). — 7-(6-*O*-Tosyl-β-D-glucopyranosyl)theophylline (**10**, 1 g) was dissolved in a boiling solution of sodium methoxide (0.3 g of sodium, 15 ml of methanol). The solution was stored at room temperature for 2 h, then neutralized with glacial acetic acid, and concentrated, and the residual syrup was treated with acetic anhydride (4 ml) in pyridine (20 ml). After storage overnight at 0°, the reaction mixture was poured into ice–water (150 ml) and extracted with dichloromethane (4 × 50 ml). The extracts were washed with water,

dried ($MgSO_4$), and concentrated to a syrup, which was shaken with light petroleum to remove pyridine. Trituration of the residue with ethanol gave a white solid (0.55 g, 67%), which was recrystallized from ethanol to give **17**, m.p. 159–160°, $[\alpha]_D$ +43° (*c* 1, chloroform) (Found: C, 50.5; H, 5.1; N, 13.8. $C_{17}H_{20}N_4O_8$ calc.: C, 50.0; H, 4.9; N, 13.7%).

*7-(6-Deoxy-β-*D*-xylo-hex-5-enopyranosyl)theophylline* (**5**) *and its triacetate* (**6**). — A solution of 7-(2,3,4-tri-*O*-acetyl-6-deoxy-6-iodo-β-D-glucopyranosyl)theophylline[1] (**13**, 12 g) in anhydrous pyridine (60 ml) was stirred with anhydrous silver fluoride (12 g) in the dark. T.l.c. indicated a considerable proportion of unsaturated product to be present after 15 min. The quantity of silver fluoride employed represented a considerable excess (4.5 mol.), but the commercial material is an ochre powder of uncertain composition, probably containing silver subfluoride (Ag_2F) and silver oxide. Detection of **5** was particularly easy using a modification of the Molisch test[17]; **5** gave an apple-green spot (soon darkening), whereas **13** gave a mauve spot (more persistent)

After 45 min, the reaction mixture was poured into water (400 ml), filtered, and extracted with dichloromethane (5 × 80 ml). The extract was washed with water (2 × 100 ml), dried ($MgSO_4$), and concentrated to a reddish pyridine solution, which was shaken with light petroleum (3 × 300 ml) to remove the pyridine. A solution of the residual syrup in dichloromethane (200 ml) was washed with water (2 × 50 ml), dried ($MgSO_4$), and concentrated to dryness. Deacetylation of the residue with methanolic ammonia[1] (60 ml) and recrystallisation of the product (5.1 g, 74%) from methanol (300 ml) gave colourless platelets of **5**, m.p. 215–220° (dec.), $[\alpha]_D$ −85° (*c* 1.15, water), $\lambda_{max}^{H_2O}$ 276 nm (ε_{max} 9,230, pH 7) (Found: C, 48.0; H, 5.0; N, 17.4. $C_{13}H_{16}N_4O_6$ calc.: C, 48.1; H, 5.0; N, 17.3%.

Conventional treatment of **5** (1 g) with acetic anhydride (2 ml) and pyridine (10 ml), with crystallisation of the product from ethanol and light petroleum, gave an ethanolate (1.22 g, 82%). Recrystallisation from propan-2-ol gave **6** as an hemipropan-2-olate, m.p. 130–142°, $[\alpha]_D$ −70° (*c* 1, chloroform) (Found: C, 50.8; H, 5.5; N, 11.8. $C_{19}H_{22}N_4O_9 \cdot 0.5C_3H_8O$ calc.: C, 51.25; H, 5.4; N, 11.65%). The i.r. and ^{1}H-n.m.r. spectra confirmed the presence of alcohol of crystallisation in the ethanolate and propan-2-olate.

*Hydrogenation of 7-(6-deoxy-β-*D*-xylo-hex-5-enopyranosyl)theophylline* (**5**). — A solution of **5** (1 g) in methanol (150 ml) was hydrogenated (31 p.s.i.) over Adams' catalyst (0.09 g) for 20 h. The mixture was then filtered through Kieselguhr and concentrated. ^{1}H-N.m.r. spectroscopy of the syrupy residue in pyridine-d_6 indicated 6-deoxy products in the ratio of 5:2 (integrated areas of the signals for the anomeric protons at τ 3.5 and 3.3, respectively).

Trituration of the syrupy mixture with dichloromethane gave a white solid, the i.r. spectrum of which was similar to that of 7-(6-deoxy-β-D-glucopyranosyl)theophylline (**14**). Recrystallisation from ethyl acetate gave **14**, m.p. 251–254°, $[\alpha]_D$ −26° (*c* 1, water); lit.[16] m.p. 254°, $[\alpha]_D$ −23° (water).

*7-(6-Deoxy-β-*D*-glucopyranosyl)theophylline* (**14**) *and its triacetate* (**15**). — A mixture of 7-(6-deoxy-6-iodo-β-D-glucopyranosyl)theophylline[1] (**12**, 1.03 g), methanol

(50 ml), anhydrous sodium acetate (0.38 g), and Raney nickel (5 ml) was boiled under reflux, and hydrazine hydrate (1 ml) was added dropwise (effervescence, evolution of ammonia).

After 1 h, the reaction mixture was filtered through Kieselguhr and concentrated, and the syrupy residue was conventionally acetylated with acetic anhydride (2 ml). Crystallisation of the product (0.72 g, 70%) from methanol gave **15**, m.p. 234–236°, $[\alpha]_D$ −6° (*c* 1.1, chloroform); lit.[16] m.p. 230°, $[\alpha]_D$ 0° (1,1,2,2-tetrachloroethane).

Deacetylation of **15** (0.23 g) with methanolic ammonia[1] (15 ml) gave **14** (0.14 g, 85%), and recrystallisation from ethyl acetate gave needles, m.p. 248–253°, $[\alpha]_D$ −23° (*c* 1, water); lit.[16] m.p. 254°, $[\alpha]_D$ −23° (water).

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