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SYNTHESIS OF NEOHESPERIDOSE

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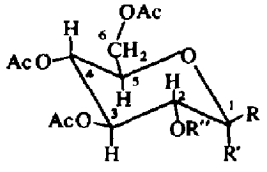
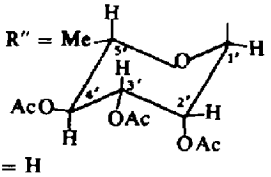
Abstract—β-Neohesperidose hepta-acetate has been synthesized directly from 1,3,4,6-tetra-O-acetyl-β-D-glucopyranose and an improved method of preparation from the anomeric 1,3,4,6-tetra-O-acetyl-α-D-glucopyranose is described. The free sugar was obtained by deacetylation of the hepta-acetate and crystallized in 67·1% yield as the β-monohydrate.

THE disaccharide, neohesperidose, occurs naturally as the glycosyl moiety of naringin and certain other flavonoid compounds and has been shown by Horowitz and Gentili[1] to be 2-O-α-L-rhamnopyranosyl-D-glucose. Reported syntheses[2,3] have involved the condensation of an acylated α-L-rhamnopyranosyl bromide with 1,3,4,6-tetra-O-acetyl-α-D-glucopyranose (I) to form a non-crystalline α-neohesperidose derivative which was deacylated and then acetylated to give the crystalline β-hepta-acetate (II). The yield of this compound is not reported by Horowitz *et al.*[2] but calculations indicate it to be 16·1% by the method of Kamiya, *et al.*[3] No report of the isolation of the free sugar in crystalline form appears to have been made.



I : R = R″ = H; R′ = OAc



II : R = OAc; R′ = H; R″ = Me

III: R = OAc; R′ = R″ = H

Independent investigations in these laboratories have confirmed the finding[3] that condensation is most readily accomplished by the method of Helferich and Zirner[4] involving reaction in the presence of mercuric cyanide and mercuric bromide in acetonitrile solution. Whereas the previous methods[2,3] have both employed the α-tetra-acetate (I) as one of the reactants, this paper describes the condensation of 2,3,4-tri-O-acetyl-α-L-rhamnopyranosyl bromide with the anomeric 1,3,4,6-tetra-O-acetyl-β-D-glucopyranose (III) to form the previously described neohesperidose hepta-acetate (II), m.p. 151–153°, directly and in good yield (66·6%).

However, whereas I is readily prepared directly from glucose, preparation of the anomeric β-tetra-acetate (III) involves a 5-stage synthesis from glucose via the β-penta-acetate, 3,4,6-tri-O-acetyl-2-O-trichloroacetyl-β-D-glucopyranosyl chloride, 3,4,6-tri-O-acetyl-β-D-glucopyranosyl chloride and 3,4,6-tri-O-acetyl-α-D-glucopyranosyl chloride. Although, with the exception of the trichloroacetyl derivative, all the intermediates can be prepared in excellent yield, the overall yield from glucose was at best only 10·0%. An alternative method for the preparation of β-neohesperidose hepta-acetate (II) in high yield was therefore sought.

This was accomplished by condensation of I with 2,3,4-tri-O-acetyl-α-L-rhamnopyranosyl bromide and conversion of the resultant α-neohesperidose hepta-acetate to the β-anomer (II) via the acetylated glycosyl bromide which, in conformity with theory,[5] is stabilized as the α-anomer in the D-glucose structure (cf. the conversion of α- to β-cellobiose octa-acetate[6]). By this method β-neohesperidose hepta-acetate (II) was prepared from I in a yield of 63·1% thus comparing favourably with the direct preparation from III.

These results provide chemical support that the crystalline product obtained by previous authors[2,3] is indeed the β-hepta-acetate (II), a conclusion presumably based hitherto on NMR and other physical evidence.[2]

Deacetylation of II yielded the free sugar which crystallized from aqueous ethanol as the β-monohydrate. Pure neohesperidose is completely tasteless in aqueous solution although in glycosidic form it imparts bitterness to some flavonoids and sweetness to others.[7]

EXPERIMENTAL

M.ps were determined by the Kofler method and are uncorrected. IR spectra were recorded on a Beckman IR 9 spectrophotometer by the KBr–disk method. NMR spectra were measured (by Mr. H. Seligmann, Institut für pharm. Arzneimittellehre, München) on a Varian A-60 spectrometer with $CDCl_3$ as solvent and TMS as internal standard (10·00 τ). Merck Kieselgel G was employed for TLC with 15% MeOH in benzene as irrigant and H_2SO_4 as spray reagent.

1,3,4,6-*Tetra*-O-*acetyl*-α-D-*glucopyranose* (I)

The compound was prepared from D-glucose (140·0 g) by the method of Helferich and Zirner.[4] After recrystallization of the crude product from $CHCl_3$–ether the yield was 76·0 g (28·1%), m.p. 98–99°; $[\alpha]_D^{25}$ +139·4° (*c* 3·8 in $CHCl_3$) (lit.[4] m.p. 98–100°; $[\alpha]_D^{20}$ +141·1°). The NMR spectrum showed signals at 3·74 (d, C-1 proton, $J_{1H_{eq},2H_{ax}}$ = 4 c/s), 4·84 (m, 2 protons), 5·86 (m, 4 protons), 7·39 (s, C-2 OH proton), 7·80 (s, C-1 OAc protons), 7·92 (s, C-3 and C-4 OAc protons) and 7·96 τ (s, C-6 OAc protons). (Found: C, 48·1; H, 5·6; OAc, 65·6. Calc. for $C_{14}H_{20}O_{10}$: C, 48·3; H, 5·7; OAc, 67·8%).

1,3,4,6-*Tetra*-O-*acetyl*-β-D-*glucopyranose* (III)

3,4,6-*Tri*-O-*acetyl*-2-O-*trichloroacetyl*-β-D-*glucopyranosyl chloride* was prepared from β-D-glucopyranose penta-acetate (130 g, 60·0% yield from D-glucose[6]) by the method of Lemieux and Howard.[8] The crude product was recrystallized once from CH_2Cl_2–ether, yield: 43·5 g (27·8%), m.p. 136–138° (lit.[8] m.p. 140–142°).

3,4,6-*Tri*-O-*acetyl*-β-D-*glucopyranosyl chloride* was prepared from the trichloroacetyl derivative (43·5 g) as described.[8] The crude product was refluxed for 10 min with benzene (200 ml), cooled and filtered to yield 28·3 g (94·2%). Although the m.p. was low (145–147°, lit.[8] 156–158°) only one spot was revealed by TLC and further recrystallization did not improve the subsequent yield of α-chloride.

3,4,6-*Tri*-O-*acetyl*-α-D-*glucopyranosyl chloride* was prepared from the β-anomer (28·3 g) by isomerization in acetone (2 l.) at room temp.[9] After 4 days the solvent was evaporated and the residue crystallized from AcOEt–hexane, yield: 24·0 g (84·8%), m.p. 92–94° (lit.[9] m.p. 93–94°).

Compound III was prepared from the α-chloride (24·0 g) as described.[9] Recrystallization of the crude product from benzene–ether afforded 19·4 g (75·4%), m.p. 136–137°; $[\alpha]_D^{25}$ +25·6° (*c* 3·8 in $CHCl_3$) (lit.[9] m.p. 137–138°; $[\alpha]_D$ +26°). The IR spectrum closely resembled that of I except in the 900–1200 cm^{-1} region where the latter showed additional medium-intensity bands. The NMR spectrum showed signals at 4·38 (d, C-1 proton, $J_{1H_{ax},2H_{ax}}$ = 8·5 c/s), 4·89 (m, 2 protons), 6·00 (m, 4 protons), 7·12 (s, C-2 OH proton), 7·82 (s, C-1 OAc protons), 7·92 (s, C-3 and C-4 OAc protons) and 7·96 τ (s, C-6 OAc protons). (Found: C, 47·9; H, 5·7; OAc, 66·3. Calc. for $C_{14}H_{20}O_{10}$: C, 48·3; H, 5·7; OAc, 67·8%).

Synthesis of β-*neohesperidose hepta-acetate* (II)

(a) Compound III (1·10 g) was dissolved in a soln of $Hg(CN)_2$ (0·53 g) and $HgBr_2$ (0·75 g) in MeCN (10 ml)[4] and 2,3,4-tri-O-acetyl-α-L-rhamnopyranosyl bromide (1·45 g) was added. After 3 hr at room temp the solvent was evaporated and the residue treated with $CHCl_3$ (50 ml) and filtered. The filtrate was extracted with 1M KBr aq (3 × 10 ml) and water (2 × 20 ml). The $CHCl_3$ was evaporated and the residue crystallized from aqueous EtOH to give colourless needles of II, m.p. 152–153°, unchanged on admixture with the natural product prepared from naringin by ozonolysis and acetylation,[2] yield: 1·31 g (66·6%). Compound II had $[\alpha]_D^{25}$ +3·4° (*c* 4·2 in acetone). The IR spectrum had significant bands at 1752 (s), 1630 (w), 1432 (w), 1370 (s), 1225 (s), 1135 (m), 1080 (s), 1042 (s), 983 (w), 910 (w) and 604 (m) cm^{-1}. The NMR spectrum showed signals at 4·28 (d, C-1 proton, $J_{1H_{ax},2H_{ax}}$ = 8 c/s), 4·81 (m, 6 protons), 5·91 (m, 5 protons) and 8·81 τ (d, C-5′ Me protons, *J* = 6 c/s). In addition, 21 proton signals corresponding to 7 OAc groups were observed over the range 7·85–8·10 τ. (Found: C, 50·6; H, 5·7; OAc, 64·7. Calc. for $C_{26}H_{36}O_{17}$: C, 50·3; H, 5·8; OAc, 66·6%).

(b) Condensation took place under the same conditions as in (a) except that I (1·10 g) was used in place of III. After evaporation of the $CHCl_3$, the residue, which failed to crystallize, was dissolved in CH_2Cl_2 (2·5 ml) and treated with a soln of 40% HBr in glacial AcOH (10 ml) for 20 min at room temp. The soln was diluted with $CHCl_3$ (75 ml) and washed with iced water, sat $NaHCO_3$ aq and water until the washings were neutral to litmus. The $CHCl_3$ soln was dried ($CaCl_2$) and evaporated to dryness at 30°. The residue was treated with a soln of $Hg(OAc)_2$ (1·5 g) in glacial AcOH (20 ml) for 2 hr at room temp. The soln was diluted with $CHCl_3$ (100 ml), washed with water (3 × 50 ml) and evaporated to dryness. The residue crystallized from aqueous EtOH in colourless needles, identical by m.p., mixed m.p., $[\alpha]_D$, IR, NMR and TLC with the product obtained by method (a), yield: 1·24 g (63·1%).

β-*Neohesperidose monohydrate*

Compound II (1·0 g) in abs MeOH (10 ml) was treated with 1·2% MeONa (5 ml) at room temp. After 30 min the soln was adjusted to pH 7·0 with dil HCl aq, desalted (Pleuger Chromatodesalter), evaporated to near dryness at 30° and diluted with EtOH (8 ml). TLC and paper chromatography (in butanol–AcOH–water (20:5:11) and in benzene–butanol–pyridine–water (1:5:3:3) with aniline phthalate as spray reagent) revealed the presence of one compound only. Crystallization of β-neohesperidose monohydrate occurred after several weeks at room temp. Recrystallization from aqueous EtOH afforded colourless prisms (0·372 g, 67·1%), m.p. 191–192°; $[\alpha]_D^{22}$ −53·3° (7 min, *c* 3·0 in water) → −3·9° (6 hr, equil). Vacuum drying at 60° for 2 hr resulted in the loss of one molecule of water of crystallization. (Found: C, 44·4; H, 6·7. $C_{12}H_{22}O_{10}$ requires: C, 44·2; H, 6·7%).

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REFERENCES

[1] R. M. Horowitz and B. Gentili, *Tetrahedron* **19**, 773 (1963).
[2] R. M. Horowitz, B. Gentili and E. S. Hand, *I.U.P.A.C. International Symposium on the Chemistry of Natural Products* Abstracts 158. Kyoto (1964).
[3] S. Kamiya, S. Esaki and M. Hama, *Agr. Biol. Chem. Japan* **31**, 261 (1967).
[4] B. Helferich and J. Zirner, *Chem. Ber.* **95**, 2604 (1962).
[5] L. J. Haynes and F. H. Newth, *Adv. in Carbohydrate Chem.* **10**, 207 (1955).
[6] M. L. Wolfrom and A. Thompson, *Methods in Carbohydrate Chemistry* (Edited by R. L. Whistler and M. L. Wolfrom), Vol. II, p. 211. Acad. Press. N.Y. (1963).

[7] R. M. Horowitz, *Biochemistry of Phenolic Compounds* (Edited by J. B. Harborne) p. 545. Acad. Press, London (1964).
[8] R. U. Lemieux and J. Howard, *Methods in Carbohydrate Chemistry* (Edited by R. L. Whistler and M. L. Wolfrom), Vol. II, p. 400. Acad. Press, N.Y. (1963).
[9] R. U. Lemieux and G. Huber, *Canad. J. Chem.* **31**, 1040 (1953).