Solanum Alkaloids. Part XVII.[1] The Sugar Unit of Solamargine

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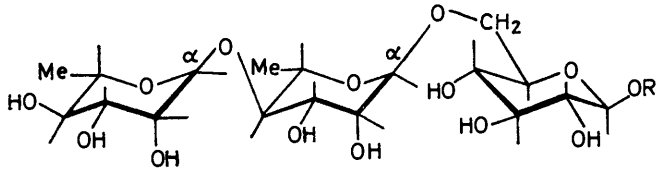
The sugar unit of solamargine (2; R = solasod-5-en-3β-yl) has been shown to be β-chacotriose {*O*-6-deoxy-α-L-mannopyranosyl-(1→2)-*O*-[6-deoxy-α-L-mannopyranosyl-(1→4)]-β-D-glucopyranose (2; R = H)}.

SOLAMARGINE, a glycosidic alkaloid from *Solanum marginatum*,[2] yields solasodine, glucose (1 mol. equiv.), and rhamnose (2 mol. equiv.) on hydrolysis. It exhibits no reducing properties; hence the sugars are joined through their potential aldehyde groups. Partial hydrolysis gives a solasodine β-glucoside,[2] showing that glucose is joined directly to the alkaloid. From the results of periodate oxidation the linear structure (1; R = solasod-5-en-3β-yl) was proposed for solamargine,[3] but subsequently Kuhn and his co-workers [4] showed that glucose was still present after periodate oxidation followed by hydrolysis, thereby eliminating a linear structure. Partial hydrolysis of solamargine also gives a solasodine rhamnoglucoside (β-solamargine),[4] which on periodate oxidation and hydrolysis again affords glucose. It appeared likely therefore that the sugar unit of solamargine was β-chacotriose (2; R = H), also obtained from α-chaconine (2; R = solanid-5-en-3β-yl).[5] The sugar portion has now been reinvestigated by the permethylation procedure of Kuhn and his co-workers [6] and shown to be β-chacotriose (2; R = H).



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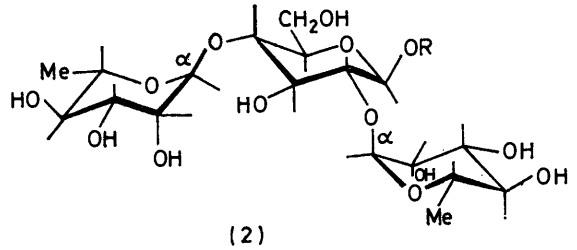

(2)

Methylation of solamargine with silver oxide and methyl iodide in dimethylformamide, followed by hydrolysis, gave a mixture of two methylated sugars which were separated by fractionation between chloroform and water. 2,3,4-Tri-*O*-methyl-L-rhamnose was obtained from the chloroform phase, and 3,6-di-*O*-methyl-D-glucose was identified in the aqueous phase by paper chromatography. Owing to the presence of trace impurities the latter sugar was not obtained homogeneous but its presence was confirmed as follows. Reduction of the sample followed by acetylation and g.l.c. comparison with authentic material showed the formation of 3,6-di-*O*-methyl-D-glucitol tetra-acetate. The product also contained a minor compound with the same retention time as methyl 3,6-di-*O*-methyl-α-D-glucoside diacetate, but this may be a coincidence since it is considered unlikely that methyl 3,6-di-*O*-methyl-α-D-glucoside would survive the acetylation procedure. A second portion of the sample was treated with methanolic hydrogen chloride and then acetylated. G.l.c. comparison with authentic samples showed the presence of diacetates of both methyl 3,6-di-*O*-methyl-α-D-glucoside and methyl 3,6-di-*O*-methyl-β-D-glucoside.

Although there is some discrepancy in recorded data, the solasodine glucoside obtained from solamargine [m.p. 251—253° (decomp.), $[\alpha]_D^{20}$ −122 ± 4° (MeOH); nitroso-derivative, m.p. 233.5—234° (decomp.)] [2] could be identical with a synthetic 3-*O*-β-D-glucosylsolasodine (γ-solamargine) [m.p. 256—259° (decomp.), $[\alpha]_D$ −87° (MeOH); nitroso-derivative, m.p. 243—245° (decomp.)] prepared by Bite and Rettegi.[7] Comparison of molecular rotation differences (see ref. 8) between solamargine and its hydrolysis products with corresponding compounds derived from related alkaloids (Table) supports the earlier suggestion that the glucose unit of the trisaccharide unit of solamargine is joined to solasodine by a β-linkage.[3]

Molecular rotation differences

Compound	$[\alpha]_D$(°)	$[M]_D$	$\Delta[M]_D$
Solasodine	−113[2]	−467	
			−41
Solasodine 3β-D-glucoside	−87[7]	−508	
			−213
β-Solamargine	−100[4]	−721	
			−189
Solamargine	−105[2]	−910	
Δ^5-Tomatidenol	−37.9[8]	−157	
			−102
Δ^5-Tomatidenol 3β-D-glucoside	−45[8]	−259	
			−362
γ-Solamargine	−86.1[8]	−621	
			−124
β-Solamargine	−85.6[8]	−745	
Solanidine	−9.8[5]	−39	
			−185
γ-Chaconine	−40[5]	−224	
			−216
β-Chaconine	−61[5]	−430	
			−295
α-Chaconine	−85[5]	−725	

With the revised structure (2; R = solasod-5-en-3β-yl) for solamargine the earlier results [3] of periodate

[1] Part XVI, L. H. Briggs, R. C. Cambie, and J. L. Hoare, *J. Chem. Soc.*, 1963, 2848.
[2] L. H. Briggs, E. G. Brooker, W. E. Harvey, and A. L. Odell, *J. Chem. Soc.*, 1952, 3587.
[3] L. H. Briggs and E. G. Brooker, *J. Chem. Soc.*, 1953, 2833.
[4] R. Kuhn, I. Löw, and H. Trischmann, *Ber.*, 1955, **88**, 289.
[5] R. Kuhn, I. Löw, and H. Trischmann, *Ber.*, 1955, **88**, 1690.
[6] R. Kuhn, I. Löw, and H. Trischmann, *Ber.*, 1955, **88**, 1492.
[7] P. Bite and T. Rettegi, *Magyar Kém. Folyóirat*, 1966, **72**, 512 (*Chem. Abs.*, 1967, **66**, 38,204); *Acta Chim. Acad. Sci. Hung.*, 1967, **52**, 99 (*Chem. Abs.*, 1967, **67**, 54,397).
[8] P. M. Boll, *Acta Chem. Scand.*, 1963, **17**, 1852.

oxidation are now anomalous. However, as was the case with solasonine,[1] repetition of the oxidation in the dark with 5 mol. equiv. of periodate afforded the expected results, solamargine consuming *ca.* 4 mol. equiv. of periodate and liberating *ca.* 2 mol. equiv. of formic acid in 24 h.

In earlier attempts to obtain mono- or di-glycosidic derivatives of solasodine an examination was made of the ripe fruit of *S. marginatum* after natural fermentation.[9] Work-up afforded a new alkaloid, $C_{39}H_{63}NO_{11}$, m.p. 261° (decomp.), $[\alpha]_D^{20}$ −89°, which afforded solasodine, glucose, and rhamnose on hydrolysis. However, direct comparison showed that the compound was not identical with β-solamargine, m.p. 245—247°, $[\alpha]_D$ −100°, obtained from partial hydrolysis of solamargine by the method of Kuhn and his co-workers.[4] Two solasodine rhamnoglucosides are possible from solamargine, *viz.* that where the rhamnose is joined to the 2-position of glucose and that where it is joined to the 4-position. Although periodate oxidation of the alkaloid, m.p. 261°, followed by hydrolysis revealed no glucose in the product, this evidence is not sufficient to distinguish between the two possibilities.

EXPERIMENTAL

Descending paper chromatography was carried out on Whatman no. 1 paper, by equilibration for 12 h, with one of the following solvent systems: A, butan-1-ol–pyridine–water (3 : 1 : 1.5; upper phase with 1 vol. of pyridine); B, ethyl acetate–acetic acid–water (3 : 1 : 3); C, butan-1-ol–ethanol–water (4 : 1 : 5). G.l.c. was carried out on an F and M model 402 High Efficiency gas chromatograph (flame ionization detector; helium as carrier gas). The column (115 cm × 3.8 mm) was 10% (w/w) LAC-4R-886 polyester wax supported on acid-washed Chromosorb W, 100—120 mesh.

Per-O-methylsolamargine Methiodide.—Solamargine [10] (3.5 g; dried at 100° over $MgClO_4$ *in vacuo* for 5 days) and methyl iodide (30 ml) in dimethylformamide (75 ml) were treated with portions of silver oxide (2.5 g; dried at 20° over P_2O_5 *in vacuo*) while nitrogen was bubbled through the cooled (0—5 °C) solution. The mixture was then shaken in an atmosphere of nitrogen for 70 h with periods of cooling in ice. The solids were removed and washed with dimethylformamide (40 ml) and then chloroform (50 ml). A precipitate which formed in the filtrate was dissolved by shaking with potassium cyanide (20 g) in water (350 ml). The chloroform layer was separated, the aqueous layer was extracted with chloroform, and the combined extracts were washed with water. Removal of solvent from the dried extracts gave a brown *gum* which coalesced at *ca.* 145° (Found, for sample dried at 100 °C to constant weight: OMe, 23.6. $C_{55}H_{94}INO_{15}$ requires 8 OMe, 21.9%).

Hydrolysis of Per-O-methylsolamargine Methiodide.—Per-*O*-methylsolamargine methiodide (3.65 g) and methanolic 5% hydrochloric acid (150 ml) were heated under reflux for 6 h. Water (50 ml) was added to the cooled mixture and most of the methanol was removed by distillation *in vacuo*. More water (50 ml) was added and the precipitated solids were removed from the cooled mixture. The filtrate was then heated under reflux with concentrated hydrochloric acid (10 ml) for 2 h. The cooled solution was extracted with chloroform (6 × 50 ml) and the combined extracts were washed with water until neutral.

2,3,4-Tri-O-methyl-L-rhamnose.—Solvent was removed from the combined extracts (above) to give a brown gum which showed one spot (dark brown with aniline hydrogen phthalate) on paper chromatography in solvent C corresponding to that of 2,3,4-tri-*O*-methyl-L-rhamnose. The R_G value (relative to 2,3,4,6-tetra-*O*-methylglucose) was 1.01 (lit.,[11] 1.01), identical with that of an authentic sample.

The gum was chromatographed on a charcoal–Celite column. Elution with aqueous 2.5% pentan-2-one gave 2,3,4-tri-*O*-methylrhamnose as a clear viscous oil, $[\alpha]_D^{20}$ +25° (*c* 1.0 in H_2O) with no mutarotation (lit.,[6] $[\alpha]_D^{24}$ +27.5°; no mutarotation). The anilide, prepared by the method of Kuhn *et al.*,[6] was purified by sublimation to give flakes, m.p. and mixed m.p. 124—125°.

3,6-Di-O-methyl-D-glucose.—The aqueous layer from hydrolysis of per-*O*-methylsolamargine methiodide was neutralized with silver carbonate and the silver salts were removed and washed with methanol. The filtrate was concentrated *in vacuo* to give a brown gum which showed one major spot in solvents A, B, and C, corresponding to 3,6-di-*O*-methyl-D-glucose. The R_G value was 0.51 (lit.,[11] 0.51), identical with that of an authentic sample. Very faint spots corresponding to 2,3,4-tri-*O*-methylrhamnose, R_G 1.01, 3,4-di-*O*-methylrhamnose, R_G 0.86 (lit.,[11] 0.88), and 4-*O*-methylrhamnose, R_G 0.60 (lit.,[11] 0.57) were also present.

The gum was deionized by chromatography on a mixed bed of Duolite A-4 (OH^- form) and Amberlite IR 120 (H^+ form) ion-exchange resins to give 3,6-di-*O*-methyl-D-glucose as a clear oil which could not be crystallized.

Glucitol Acetates.—A portion of the oil (0.25 ml) containing 3,6-di-*O*-methyl-D-glucose was treated with sodium borohydride (*ca.* 15 mg) at 20 °C for 1 h and the mixture was then evaporated to dryness. Acetic anhydride (0.25 ml) containing 2% of concentrated sulphuric acid was added and the mixture was warmed on a steam bath for 1.5 h. The mixture was worked up in the usual manner and the resulting chloroform solution concentrated to *ca.* 0.5 ml. Comparative g.l.c. at 200 °C with an authentic sample showed a strong peak corresponding to 3,6-di-*O*-methyl-D-glucitol tetra-acetate. A further peak corresponded with that of an authentic sample of methyl 3,6-di-*O*-methyl-α-D-glucose diacetate.

Acetylated Methyl Glycosides.—A portion of the oil (0.5 ml) containing 3,6-di-*O*-methyl-D-glucose was dissolved in methanol (1 ml) containing dry hydrogen chloride (5%) and heated in a sealed tube at 65—70 °C for 3.5 h. The solution was neutralized with concentrated ammonium hydroxide (3 drops) and evaporated to dryness. The residue was treated with acetic anhydride (0.5 ml) in pyridine and heated on a steam-bath for 30 min. The mixture was worked up in the usual manner to give a chloroform solution which was concentrated to 0.5 ml. Comparative g.l.c. at 190 °C with authentic samples showed the presence of methyl 3,6-di-*O*-methyl-α-D-glucoside diacetate and methyl 3,6-di-*O*-methyl-β-D-glucoside diacetate.

Solasodine Rhamnoglucoside.—The isolation of the glycoside from the fermented ripe berries of *S. marginatum* has been described previously.[9] The product had m.p. 261°

[9] L. H. Briggs, *Tagungsber. Deut. Akad. Landwirtschaftswiss., Berlin*, 1961, No. 27, p. 37.

[10] L. H. Briggs and E. G. Brooker, *J. Chem. Soc.*, 1958, 1419.

[11] E. L. Hirst, L. Hough, and J. K. N. Jones, *J. Chem. Soc.*, 1949, 928.

(decomp.), $[\alpha]_D^{22}$ −89° (Found: C, 65.3; H, 8.6; N, 1.8. Calc. for $C_{39}H_{63}NO_{11}$: C, 64.9; H, 8.8; N, 1.9%); picrate, m.p. 178° (decomp.) (Found: C, 57.2; H, 6.8; N, 5.8; Calc. for $C_{39}H_{63}NO_{11},C_6H_3N_3O_7$: C, 56.8; H, 7.0; N, 5.9%); picrolonate, m.p. 209—210° (decomp.) (Found: C, 59.8; H, 7.0; N, 7.1. Calc. for $C_{39}H_{63}NO_{11},C_{10}H_8N_4O_5$: C, 59.7; H, 7.3; N, 7.1%). Hydrolysis of the glycoside in the usual way gave solasodine; paper chromatography in solvent A showed the presence of glucose and rhamnose.

The rhamnoglucoside (20 mg) was kept at 20 °C with 0.1M-sodium periodate (9 ml) and 0.1M-acetic acid (4 ml) for 24 h. The mixture was worked up by the method of Kuhn and his co-workers [4] to give a residue which was shown to contain glucose by paper chromatography in solvent A.

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