3. Solanum *Alkaloids. Part III. The Alkaloids from* Solanum auriculatum.

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Alcoholic extraction of the dried berries of *S. auriculatum* leads to the isolation of a glycoalkaloid, m. p. 270° (decomp.), which on hydrolysis yields a mixture of sugars (see following paper) and an aglycone, m. p. 222—223°. The names *solauricine* and *solauricidine* are suggested for these respective compounds and evidence is adduced that solauricidine is neither identical with nor a dimorphic form of solasodine but is extremely closely related to it in both physical and chemical properties. No structural differences between solauricidine and solasodine have yet been found. The separation of alkaloid material from the juice of the green berries affords a product, m. p. 269—270° (decomp.), which on hydrolysis gives a mixture of bases consisting mainly of solasodine with a smaller amount of solauricidine. Both the latter bases occur in dimorphic forms, the respective pairs being indistinguishable.

The green berries of *Solanum auriculatum* were first investigated by Greshoff (*Ber.*, 1890, **23**, 3541; *Ber. deut. pharm. Ges.*, 1899, **9**, 214), who reported that they were rich in "solanine." More recently, Anderson and Briggs (J., 1937, 1036) isolated a colourless, crystalline glycoalkaloid, m. p. 272°, with colour reactions similar to those of solasonine. On hydrolysis with alcoholic hydrogen chloride, an aglycone was obtained, m. p. 216—219°, which raised the melting point of solasodine but depressed that of solanidine. Since it gave the same colour reactions as solasodine and afforded derivatives with the same melting point as those prepared from solasodine and admixture of respective pairs gave no depression, it was concluded that the aglycone was an isomorphic (more correctly dimorphic) form of solasodine.

This investigation has been continued and further evidence now indicates that the aglycones from *S. auriculatum* and solasodine are neither identical nor dimorphic forms, but are isomeric and extremely closely related in both physical and chemical properties, the only major difference so far observed being in their melting points. We suggest the names *solauricine* and *solauricidine* for the glucoside and aglycone respectively.

Analyses of solauricine and solauricidine as well as derivatives of the latter support formulæ $C_{45}H_{73}O_{16}N$ and $C_{27}H_{43}O_{2}N$ for these respective bases, which are the same as those suggested for solasonine and solasodine respectively (preceding paper). The melting point of the aglycone has been raised to 220—223°, which is considerably higher than that of the purest specimen of solasodine yet obtained, m. p. 200·5—202·5° (Part II). There is no doubt in our minds as to the purity of these specimens, whose homogeneity is also indicated by the crystallographic data (pp. 14, 15). From solasodine and solauricidine as well as the corresponding glycoalkaloids a number of derivatives have been prepared for comparison and the respective pairs almost without exception have melting points within a few degrees and give no depression on admixture. To avoid differences in melting point due to the rate of heating (cf. Briggs, *J. Amer. Chem. Soc.*, 1937, **59**, 1404), in most cases both the melting points of the respective pairs and the mixture have been determined at the same time in Mason's melting point apparatus (electrically heated copper block). Where a figure is not given in the following table, it indicates that the mixed melting point was taken separately, but in each case no depression was observed.

Derivative.	Solasonine, m. p.	Solauricine, m. p.	Mixed m. p.
Glycoalkaloid	276°	270°	272°
Picrate	197	185	184
Picrolonate	231	232	—
Aglycone	198	219	208—211
Hydrochloride	314·5—315	313—313·5	313·5—314
Hydrobromide	299	309	—
Hydriodide	288	285	286
Sulphate	293	?	—
Nitrate	269	266—267°	—
Aglycone			
Nitrite	260·5—262·5°	260—264°	—
Picrate	144	141	142°
Picrolonate	232	234	232
Tartrate	220	222	221
Oxalate	245—246	238	239
o-Nitrobenzoate	222	220	—
Acetyl derivative	195	197—203	—

(All the above compounds with the exception of the aglycones and their acetyl derivatives melt with decomposition.)

Whether the respective aglycones are dimorphic forms and the salts identical as the results in the above table would indicate has been tested experimentally in various ways.

Measurements of the optic axial angles of the crystals of the aglycones showed appreciable differences (solasodine, $2V = 74^\circ \pm 2^\circ$, the optic sign is positive in all cases discussed in this paper; solauricidine, $2V = 56^\circ \pm 2^\circ$; see later, however), and the optic axial angles of the corresponding hydrochlorides are indistinguishable, $2V = 85^\circ \pm 5^\circ$.

Dimorphism should disappear both in solution and in the vapour state. In solution, the specific rotations of the aglycones differ somewhat, solasodine — 80·4°, solauricidine — 89·9°, but those of the hydrochlorides are almost the same within experimental error (— 70·5° and — 68·2° respectively). When Halford's procedure (*J. Amer. Chem. Soc.*, 1931, **53**, 2640) for the identification of closely related compounds was applied to solasodine and solauricidine in boiling acetone solution, in only one out of five experiments was a rise of boiling point observed, and the hydrochlorides showed no effect on each other in boiling ethyl-alcoholic solution. In this case, owing to the high molecular weights of the substances involved and the lack of high solubility in the solvents concerned, any elevation of boiling point to be expected in the case of non-identical compounds would be small and possibly within the experimental error.

In the vapour state the evidence against dimorphism is conclusive. When solasodine and solauricidine are sublimed at low pressures, the melting points of the sublimed crystals are unaltered.

Should the aglycones be dimorphic, one form should be more stable than the other and the two interconvertible under appropriate conditions. In all our experiments, extending over some years and in which five independent workers have been involved, we have always obtained solauricidine, m. p. *ca.* 220°, on hydrolysis of the glycoalkaloid obtained by alcoholic extraction of the dried berries of *S. auriculatum* and during a similar period, often in the same room and using identical methods and solvents, we have always obtained solasodine, m. p. 198—200°, from *S. sodomæum* or *S. aviculare* (cf. Part I, this vol., p. 1) without any case of interconversion. Attempts to convert one form into the other by seeding during crystallisation have been unsuccessful, the product having an intermediate melting point depending on the amount of seeding crystals used. A similar result is obtained when the respective bases are kept above their melting points for some time and the melting points of the cooled solids redetermined, no appreciable change from the original melting points being observed.

Should the salts of the bases be identical, as some of the above evidence would indicate, then one and the same base should be obtained by the action of ammonia. When this has been done in ordinary preparative work and in experiments carried out under exactly similar conditions, the corresponding aglycones of different melting points have invariably been obtained.

Despite some evidence to the contrary the main weight of evidence definitely points to the conclusion that solauricidine is neither identical with nor a dimorphic form of solasodine. With this view, further experiments were undertaken in order to find the seat of such differences, but so far no structural differences have been discerned. The aglycone gives the analytical figures required for $C_{27}H_{45}O_3N$ when dried in the usual way and for $C_{27}H_{43}O_2N$ only after vigorous drying. Solauricidine contains one hydroxyl group on the C_3 atom in the *cis*-position to the angular methyl group on C_{10}, since it gives a precipitate with digitonin and forms an acetyl derivative, m. p. 197—203°, soluble in dilute acids, which no longer gives a precipitate with digitonin. The remaining oxygen is present attached to the nitrogen as a quaternary hydroxide or as the related carbinolamine, since the actions of methyl iodide and ethyl iodide both give the hydriodide, from which the aglycone is regenerated on treatment with dilute aqueous ammonia (see also Part II). Since the aglycone is a quaternary hydroxide, the salts would be expected to occur as anhydro-salts (cf. berberine and related alkaloids).

Analyses of the salts indicate, however, that (with the exception of the nitrite) actually in some cases further firmly bound water of crystallisation not removed on drying is present which masks any anhydro-salt formation (cf. ψ-strychnine). The action of nitrous acid yields a compound, $C_{27}H_{42}O_3N_2$, m. p. 260—264°, which, as in the case of solasodine, we regard as a quaternary nitrite, the only true anhydro-salt yet obtained in this series, since it regenerates solauricidine on treatment with dilute aqueous ammonia. Solauricidine is unsaturated, giving the usual tests for unsaturation, and catalytic hydrogenation with palladium–charcoal catalyst yields a hydro-derivative, m. p. 221·5—227·5°, which differs from dihydrosolasodine, m. p. 208·5—210·5°. The investigation of solauricidine is being continued.

Isolation of the alkaloid from the undried fruit of *S. auriculatum* by the more convenient and cheaper process described in Part II has given different results from those obtained by alcoholic extraction methods. The glycoalkaloid isolated by this process had m. p. 269—270° (decomp.), but was not rigidly purified. Hydrolysis with either 2% hydrochloric or sulphuric acid gave a crude amorphous material, m. p. 219°, but when crystallised from 80% alcohol, however, the substance melted at 184—186°. Only after a very lengthy series of crystallisations from different solvents, have two products been obtained, one, m. p. 198—200°, and the other (very small amount), m. p. 213—217°. These products are almost undoubtedly solasodine and solauricidine. When the hydrochloride obtained in the hydrolysis of the glycoalkaloid isolated above is rigidly purified and then converted into the free base, pure solasodine, m. p. 198—200°, is obtained after a single crystallisation. The hydrochloride, sulphate, nitrite and acetyl derivative of the material, m. p. 198—200°, all agree in melting point with the respective compounds of solasodine and give no depression on admixture with authentic specimens. Since, however, mixed melting points do not seem to be valid criteria of identification in this series, the free bases were submitted for measurement of their optic axial angles, with unexpected results. The purest specimens of solasodine, solauricidine (obtained by the alcoholic extraction method), and the product, m. p. 198—200°, isolated in the last instance, were all recrystallised from the same sample of methyl alcohol and then had m. p. 199—202°, 200—223°, and 199·5—202° respectively. The optic axial angles of the first two compounds, which had previously given values $2V = 74° \pm 2°$ and $55° \pm 2°$ respectively, as well as of the last material, now all had the same value within experimental error, $2V = 73°$, 73·5° and 73·5° respectively, *i.e.*, the value previously obtained only for solasodine. These and the earlier measurements were taken by Dr. F. J. Turner, Otago University, to whom we are greatly indebted. All three compounds were now recrystallised by Mr. N. E. Stace, M.Sc., a co-worker in Part II of this series, at Otago University again from methyl alcohol; the melting points then remained practically unchanged. However, the optic axial angles were again all the same but with a different value, $2V = 54°$, 58°, and 54° respectively, *i.e.*, the value previously obtained only for solauricidine. It is apparent, therefore, that both solasodine and solauricidine occur in dimorphic forms, the optical axial angles of each respective dimorphic form obtained from solasodine or solauricidine being indistinguishable. The only explanation which can be given for the conversion of one crystalline form into the other when crystallised from the same solvent is the presence of different nuclei in the atmosphere, an explanation which has been offered by Dewar, Morrison, and Read for a similar phenomenon with benzylidene-*dl*-piperitone (J., 1936, 1598).

EXPERIMENTAL.

Extraction of the Alkaloid with Alcohol.—The minced and dried green berries of *S. auriculatum* were continuously extracted with alcohol containing 1% of acetic acid in an all-metal extractor of the Soxhlet principle capable of treating 56 lb. of material, and the extract worked up as described in Part I. *Solauricine* was thus obtained in colourless plates, m. p. 269·5—270° (decomp.) after fifteen successive crystallisations from 75% ethyl alcohol or 80% dioxan–water (Found in dried material: C, 58·4; H, 8·2; N, 2·2, 2·2. $C_{45}H_{73}O_{16}N,2H_2O$ requires C, 58·8; H, 8·4; N, 1·5%).

The colour reactions of solauricine are the same as those of solasonine (Part II). The picrate and the picrolonate were prepared by heating the components in alcoholic solution and recrystallised from 80% alcohol.

The pure solauricine was then hydrolysed by heating with 2% hydrochloric or sulphuric acid in the water-bath for 3 hours, the hydrochloride or sulphate of solauricidine separating from the hot solution in a crystalline condition. In some cases the salts were further purified by several recrystallisations from 80% alcohol, but in most cases the crude salts were converted into the free *base* by treatment in aqueous suspension with excess of ammonia at 100° for some hours, with substantially the same results. The material thus formed had m. p. 218—220° and after repeated crystallisation from 80% alcohol and methyl alcohol it formed colourless hexagonal plates, m. p. 220—223° (Found in dried material: C, 74·6, 74·9; H, 10·4, 10·3; N, 3·3. $C_{27}H_{43}O_2N,H_2O$ requires C, 75·1; H, 10·5; N, 3·2%. Found for a different sample more vigorously dried: C, 77·7; H, 10·3. $C_{27}H_{43}O_2N$ requires C, 78·45; H, 10·4%). $[\alpha]_D^{250°} - 89·8°$ ($l = 1$ dcm., $c = 0·2560$ in methyl alcohol). The colour reactions are the same as those recorded for solasodine (Part II).

The salts were all formed by addition of the components in alcoholic solution; they were recrystallised from 80% alcohol and dried for analysis. The melting points are recorded on p. 13.

Solauricidine hydrochloride (Found : C, 66·9; H, 10·0; N, 3·95. $C_{27}H_{43}O_2N,HCl,2H_2O$ requires C, 66·8; H, 9·9; N, 2·9%). $[\alpha]_D^{250^\circ}$ − 68·2° ($l = 2$ dcm., $c = 0·4248$ in methyl alcohol).

Solauricidine sulphate (Found: C, 61·95; H, 9·5; N, 2·8. $C_{27}H_{43}O_2N,H_2SO_4,\frac{1}{2}H_2O$ requires C, 62·3; H, 8·8; N, 2·7%).

Solauricidine hydriodide (Found : C, 60·0; H, 8·2; N, 2·5. $C_{27}H_{43}O_2N,HI$ requires C, 59·9; H, 8·1; N, 2·6%).

Solauricidine picrate (Found: C, 60·2; H, 7·1; N, 8·8. $C_{27}H_{43}O_2N,C_6H_3O_7N_3,H_2O$ requires C, 59·9; H, 7·4; N, 8·5%).

Solauricidine nitrite (Found : C, 72·8; H, 9·5. $C_{27}H_{42}O_3N_2$ requires C, 73·3; H, 9·5%). On treatment in aqueous suspension with ammonia, the nitrite (prepared as described in Part II) regenerated solauricidine, m. p. 218—221·5°.

Digitonin (13·5 mg.), dissolved in warm water (2 c.c.), was added to a solution of solauricidine (4·5 mg.) in warm alcohol (2 c.c.); an insoluble digitonide (15·5 mg.) separated on standing.

The acetyl derivative, obtained quantitatively as described in Part II for solasodine, after repeated crystallisation from ethyl acetate and ethyl acetate–alcohol formed needles, m. p. 197—203°. It dissolved immediately in dilute acetic acid and did not give a precipitate with digitonin.

The action of methyl or ethyl iodide on solauricidine in xylene solution afforded in both cases solauricidine hydriodide, m. p. 285° (decomp.) (cf. Part II), undepressed by an authentic specimen. It regenerated solauricidine on treatment with dilute aqueous ammonia.

Hydrogenation of Solauricidine.—A solution of solauricidine (300 mg.) in glacial acetic acid (6 c.c.) was hydrogenated at 45 lb. pressure in the presence of a palladium–charcoal catalyst (300 mg.) for 24 hours. The catalyst was removed, and the filtrate diluted with an equal volume of water and treated with excess of ammonia at 100° for 6 hours. The colourless product (265 mg.), after two recrystallisations from alcohol containing a drop of concentrated aqueous ammonia, formed thin plates, m. p. 221·5—227·5°, giving a negative test with antimony trichloride in chloroform solution. This material was unfortunately lost during a subsequent recrystallisation—the experiment has not yet been repeated, as the hydrogenation was carried out on the last quantity of solauricidine at our disposal.

Application of Halford's Procedure for the Identification of Solauricidine.—The b. p. of acetone was determined in the usual apparatus and again after the addition of excess of solasodine to form a saturated solution. Solauricidine was then added, and the boiling point redetermined, 10—15 minutes usually being allowed for the attainment of equilibrium. The experiment was then repeated in the reverse order of addition. In four out of five separate experiments the b. p. did not vary by 0·01°, but in one case a rise of 0·08° was observed. When the procedure was applied to the hydrochlorides in boiling ethyl alcohol, in two experiments where the additions were reversed the b. p. did not alter by 0·001°.

Extraction of the Alkaloid by Dilute Acetic Acid.—The improved process for the isolation of the alkaloid from the juice of the green berries as described in Part II yielded in this case a crystalline glycoalkaloid, m. p. 269—270° (decomp.). This was assumed to be solauricine and was hydrolysed directly with either 2% hydrochloric or sulphuric acid, yielding the insoluble hydrochloride or sulphate respectively of the aglycone. The sulphate, without further purification, was treated in aqueous suspension with excess of ammonia at 100° for 4 hours and yielded the crude aglycone, m. p. 219—220°, as expected. On crystallisation from 80% alcohol (charcoal), however, the m. p. dropped to 184—186°. The m. p. was only slowly raised by recrystallisation but after a very lengthy series of crystallisations from 80% alcohol, 80% methyl alcohol, 80% dioxan and finally from methyl alcohol two products were obtained, one, m. p. 199·5—202°, unchanged on further crystallisation, and the other, m. p. 213—217°, in much smaller yield. Probably the purification is retarded also by the presence of solasodiene and the corresponding compound from solauricidine formed as by-products (see Part II).

If the crude hydrochloride obtained by hydrolysis of the glycoalkaloid is purified by repeated crystallisation from 80% alcohol to m. p. 316° (decomp.) and then converted into the aglycone, solasodine, m. p. 198—200°, is obtained without difficulty.

The purified hydrochloride, sulphate, nitrite and the acetyl derivative of this material, m. p. 198—200°, all had the same m. p.'s as those prepared from authentic solasodine and respective pairs showed no depression.

The following crystallographic measurements were made in 1938 by Dr. F. J. Turner, using a microscope fitted with a universal stage.

Solasodine (*ex S. aviculare*; see Part I) :

$2V$ = 70°, 74°, 76° (mean 74° ± 2°). Optical sign positive. Six-sided crystals with γ perpendicular to the plane of flattening (Fig. 1). θ = 107° ± 3°.

Solauricidine :

$2V$ = 54°, 56°, 58°, 58° (mean 56° ± 2°). Optical sign positive. Small, ill-defined, platy crystals with γ approximately perpendicular to the plane of flattening.

The following measurements were made by Dr. F. J. Turner in 1940 on the purest specimens available, which were all crystallised from the same sample of methyl alcohol before measurement.

Solasodine (*ex S. sodomæum*), m. p. 199—202° :

$2V$ = 73°, 73°, 74°, 72°, 74° (mean 73° ± 1°). Optical sign positive; all homogeneous crystals (Fig. 1). $\theta = 112° \pm 1°$, $\phi = 124° \pm 1°$.

Solauricidine (*ex S. auriculatum*), m. p. 220—223° (obtained from the original alcoholic extraction process) :

$2V$ = 74°, 78°, 65°, 78°, 72°, 70°, 68°, 75°, 72°, 77°, 80° (mean 73·5°) Optical sign positive. Refractive indices : α 1·53 ~ 1·54, β 1·55 ~ 1·56.

Some of the crystals were clear and homogeneous, but many had central, apparently fibrous cores, surrounded by a clear border zone (Fig. 2).

The optic orientations of the central and the border zone do not coincide, but in both zones the axial angle = 74° ± 2°. This may simply be a result of the way in which the substance was crystallised, perhaps twinning or probably large crystals have grown around nuclei consisting of tufts of fibres that had first crystallised.

FIG. 1.

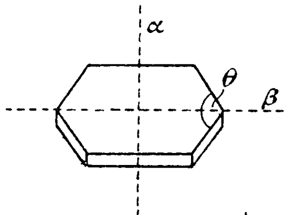
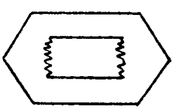


FIG. 2.



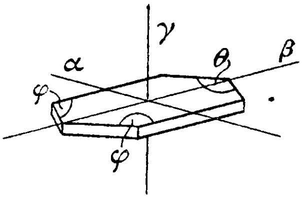
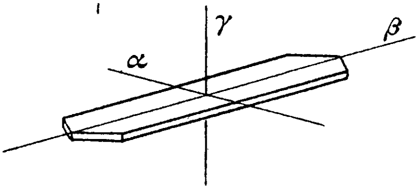


FIG. 3.

FIG. 4.



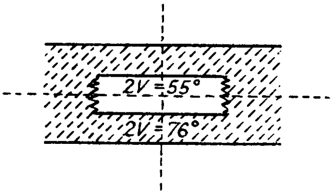


FIG. 5.

Solasodine (*ex S. auriculatum*), m. p. 199·5—202° :

$2V$ = 74°, 70°, 73°, 68°, 74°, 70°, 75°, 73°, 75°, 75°, 75°, 74°, 73°, 78°, 74°, 74° (mean 73·5°). Optical sign positive. Clear homogeneous crystals. Refractive indices : α 1·53 ~ 1·54, β 1·55 ~ 1·56.

The specimens of solasodine (*ex S. auriculatum*) and solauricidine are all closely similar in crystal habit, crystallographic angles, optic orientation, and, in so far as they have been measured, in refractive index. The crystals are tabular in habit, being flattened perpendicularly to the acute bisectrix (γ) and somewhat elongated (sometimes much elongated) parallel to β (Figs. 3 and 4). $\phi = 125° \pm 3$—4°, $\theta = 110° \pm 3$—4°.

Many crystals show traces of cleavage parallel or subparallel to the plane $\beta\gamma$ or at least parallel to β.

All three samples were then recrystallised from methyl alcohol by Mr. N. E. Stace, M.Sc., at Otago University and resubmitted for crystallographic measurement, with the following results.

Solasodine (*ex S. sodomæum*) :

$2V$ = 54°, 55°, 53°, 54° (mean 54°). Optical sign positive. Crystal angles the same as before crystallisation. Small clear crystals, readily measured.

Solauricidine (*ex S. auriculatum*) :

$2V$ = 59°, 59°, 54°, 52°, 62°, 60°, 59°, 58° (mean 58°). Optical sign positive.

Solasodine (*ex S. auriculatum*) :

$2V$ = 54°, 55°, 54°, 56°, 54°, 55°, 54° (mean 54°). Optical sign positive. Clear, tabular, homogeneous crystals. One crystal had $2V$ = 76°, and another had a central zone, $2V$ = 55°, surrounded by an outer zone, $2V$ = 76°, the two being in the same optic orientation (Fig. 5). In the latter crystal there appears to be a parallel growth of two separate identities.

The hydrochloride of solauricidine gave the following values, indistinguishable from those of solasodine hydrochloride (see Part I) :

$2V$ = 78°, 80°, 80°, 88°, 90° (mean 85° ± 5°). Optical sign positive. Six-sided tabular crystals with γ inclined at 60—70° (approximate value only) to the plane of flattening and slightly elongated parallel to β in most cases. The hydrochloride has the same orientation and habits as solasodine hydrochloride, *ex S. sodomæum* or *ex S. aviculare.*

All the above optic axial angles were measured on separate crystals.

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