304. Solanum *Alkaloids. Part VII.* The Stereochemical Relationship of Solasodine to Cholesterol.*

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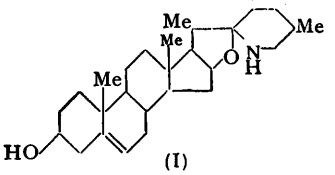
The preparation of crystalline *N*-acyl derivatives supports the formulation of solasodine as a secondary amine (Part V, *J.*, 1950, 3013). Hydrogenation of " α "- and " β "-solasodan at a platinum oxide catalyst affords " α "- and " β "-dihydrosolasodan, also obtained directly by hydrogenation of solaso-3 : 5-diene with the same catalyst. By applying the method of molecular-rotation differences for correlating the stereochemical configuration in the steroid series solasodine has been shown to have the same stereochemical configuration as cholesterol.

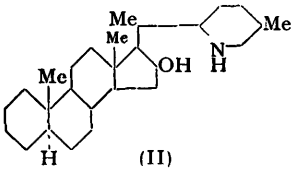
In Part V (*J.*, 1950, 3013) formula (I) was proposed for solasodine. *N*-Nitroso-derivatives were prepared from solasodine and some of its derivatives, indicating the presence of a secondary amino-group but no crystalline *N*-acyl derivative could be obtained. When the oxide ring had been broken by hydrogenolysis (cf. also Part VI *) *N*-acyl derivatives



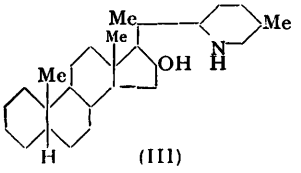
(I)

were readily obtained. This resistance of solasodine towards acylation was attributed to reduced basicity caused by the close association of the nitrogen atom with the oxide ring. By acetylation of solasodine, solasodanol, solaso-3 : 5-diene, and " α "- and " β "-solasodan with acetic anhydride–pyridine, *N*-acetyl derivatives have now been obtained, thus confirming the presence of the secondary amino-group in solasodine. *N*-Benzoyl derivatives, however, could not be prepared.

Hydrogenation of solaso-3 : 5-diene with a palladium–charcoal catalyst affords " α "- and " β "-solasodan as previously reported (Part VI, *loc. cit.*), but by chromatography on alumina the " β "-isomer has now been obtained with a considerably higher melting point. By catalytic hydrogenation of the " α "- and the " β "-isomer with a platinum oxide catalyst " α "- and " β "-dihydrosolasodan have been obtained, with suggested formulæ (II) and (III) respectively, characterised in the case of the " α "-isomer by a diacetyl derivative.



(II)



(III)

Direct hydrogenation of solaso-3 : 5-diene with a platinum oxide catalyst had earlier given the " α "-isomer (Part II, *J.*, 1942, 7) but it was then referred to as hexahydrosolasodiene or dihydro*chano*solasodan, both of which names should be discarded. Fractional crystallisation of the product of this reaction also affords the " β "-isomer in small yield.

Until now there have been too many discrepancies in the reported rotation of solasodine and its derivatives to apply the method of molecular-rotation differences, developed by Barton (Part I, *J.*, 1945, 813, to Part 16, *J. Amer. Chem. Soc.*, 1950, **72**, 1633; for a summary, see Barton and Klyne, *Chem. and Ind.*, 1948, 755), for correlating the stereochemical configuration with that of other steroids. By a systematic study of compounds in this series it has now been shown that solasodine has the same configuration as cholesterol and thus resembles solanidine (cf. Rochelmeyer, *Ber.*, 1938, **71**, 226, and Prelog

* Part VI, *J.*, 1950, 3020.

and Szpilfogel, *Helv. Chim. Acta*, 1944, **27**, 390). Asymmetric centres, additional to those occurring in cholesterol, are present in solasodine at $C_{(16)}$, $C_{(22)}$, and $C_{(25)}$, but no information on the configuration at these points is yet available. Table 1 records the observed molecular rotation and the value calculated from the equation: $[M]_D$ of the solasodine derivative $-[M]_D$ of solasodine (or other standard compound, *e.g.*, dihydrosolasodenol) = $[M]_D$ of the corresponding cholesterol derivative $-[M]_D$ of cholesterol. In the last four compounds the oxide ring has been opened and, for these, dihydrosolasodenol has been taken as a subsidiary standard.

TABLE 1.

Compound	M. p.	$[\alpha]_D$ *	$[M]_D$ (obs.)	$[M]_D$ (calc.) †	$[M]_D$ (obs.) − $[M]_D$ (calc.)
Solasodine	200—202°	−113·5° ± 2°	−469° ± 8°	−469°	Standard
Solasodanol	208—209	− 56·2 ± 3	−234 ± 12	−227	− 7°
Solaso-3 : 5-diene	177—178	−194·9 ± 1·5	−771 ± 6	−773	+ 2
Solasod-4-en-3-one ...	183—184	+ 8·2 ± 1·5	+ 33 ± 6	+ 20	+13
" α "-Solasodan	175—176	− 57·7 ± 3	−231 ± 12	−229	− 2
" β "-Solasodan	159—160	− 56·9 ± 3	−227 ± 12	−227	0
Dihydrosolasodenol ...	261—265	− 65·0 ± 3	−270 ± 12	−270	Standard
Dihydrosolasodanol ...	291—295	− 7·0 ± 4·5	− 29 ± 19	− 28	− 1
" α "-Dihydrosolasodan	184—186	− 8·3 ± 2·5	− 33 ± 10	− 30	− 3
" β "-Dihydrosolasodan	147·5—148·5	− 5·9 ± 3	− 24 ± 12	− 28	+ 4

* All rotations were observed in a 1-dm. micro-tube at room temp. (15—24°). All samples were heated to 120° overnight in a vacuum over magnesium perchlorate, with the exception of solasod-4-en-3-one which was dried at 105°. Chloroform was the solvent throughout, except for the relatively insoluble dihydrosolasodanol where chloroform–alcohol (95 : 5) was employed.

† The values taken for cholesterol and its derivatives are those recorded by Fieser and Fieser, " Natural Products Related to Phenanthrene," Reinhold Publ. Corp., 3rd Edn., pp. 95, 216, 252, 259.

The agreement between the observed and the calculated values is well within the experimental error in almost every case. Since there is no discrepancy in the observed and calculated values for the structures tentatively referred to as " α " and " β " isomers, the configuration assigned to them in Part V (*loc. cit.*) is thus confirmed. The " α "-isomers can therefore be referred to as derivatives of 5α-solasodan and the " β "-isomers as derivatives of 5β-solasodan.

The stereochemical relationship of solasodine with cholesterol has been confirmed with other acyl compounds by somewhat different procedures. *O*-Benzoylsolasodine and *O*-benzoylsolasodanol can be directly correlated by comparing the difference between the benzoyl derivative and the parent compound with the benzoyl derivative and its related parent compound in the cholesterol series as above, and the calculated figures recorded in Table 2 are based on this procedure.

In the case of the acetyl derivatives the procedure is complicated by acetylation of the amino-group. This may be overcome in two ways. First, a constant may be introduced to represent the effect of the *N*-acetyl grouping, *i.e.*, the value, $[M]_D$ of *N*-acetyl-5α-solasodan − $[M]_D$ of 5α-solasodan, is subtracted from the rotation of the solasodine derivative before the effect of acetylation of the 3-hydroxyl group is compared with that in the cholesterol series; *e.g.*, {$[M]_D$ of diacetylsolasodine − ($[M]_D$ of *N*-acetyl-5α-solasodan − $[M]_D$ of 5α-solasodan)} − $[M]_D$ of solasodine = $[M]_D$ of cholesteryl acetate − $[M]_D$ of cholesterol, *i.e.*, $[M]_D$ of diacetylsolasodine +38° − 231° + 469° = −188° + 149°, or $[M]_D$ of diacetylsolasodine = −315°.

In the second method, as an example, *N*-acetyl-5α-solasodan is taken as a standard corresponding to cholestane and the method of molecular rotation differences may be applied to changes in rings A and B: *e.g.* $[M]_D$ of diacetylsolasodine − $[M]_D$ of *N*-acetyl-5α-solasodan = $[M]_D$ of cholesteryl acetate − $[M]_D$ of cholestane, *i.e.*, $[M]_D$ of diacetylsolasodine +38° = −188° − 91° or $[M]_D$ of diacetylsolasodine = −317°, in good agreement with the first method. As the second method introduces a smaller number of factors, it has been used to calculate the values recorded in Table 2. A similar standard has to be introduced for the compounds where the oxide ring is broken.

Most of the values obtained are in fair agreement with the calculated values and thus confirm the previous results. The main exception is *N*-acetylsolaso-3 : 5-diene but this

may be ascribed to the " vicinal action " described by Barton and Cox (*Nature*, 1947, **159**, 470) (the compound was purified until it had a constant melting point and rotation).

TABLE 2.

Compound	M. p.	$[\alpha]_D$ *	$[M]_D$ (obs.)	$[M]_D$ (calc.)	$[M]_D$ (obs.) − $[M]_D$ (calc.)
N-Acetyl-5α-solasodan	156—157·5°	− 8·7° ± 4°	− 38° ± 17°	−38°	Standard
N-Acetylsolaso-3 : 5-diene	178—180	−100 ± 2·5	−438 ± 11	−582° ± 17°	+144°
Diacetylsolasodine	165—166·5	− 56 ± 2	−279 ± 10	−317 ± 17	+ 38
Diacetylsolasodanol	186—187	− 13·2 ± 3	− 66 ± 15	− 69 ± 17	+ 3
Diacetyldihydro-5α-solasodan	75—77	+ 39·7 ± 1	+193 ± 5	+193	Standard
Triacetyldihydro-solasodenol	169·5—170·5	− 21·2 ± 4	−115 ± 22	− 86 ± 5	− 29
Triacetyldihydro-solasodanol	156·5—157·5	+ 31·8 ± 2	+173 ± 10	+162 ± 5	+ 11
O-Benzoylsolasodine	220—221	− 80·1 ± 2	−414 ± 10	−394 ± 8	− 20
O-Benzoylsolasodanol	209—211	− 47·2 ± 3	−245 ± 16	−229 ± 12	− 16
Tribenzoyldihydro-solasodenol	228—229	+ 22·5 ± 2	+164 ± 15	—	—

* The rotations and drying of samples were carried out as described for Table 1, except that diacetyldihydro-5α-solasodan was dried at room temperature for 24 hours.

The $[M]_D$ calculated from the rotation recorded for solani-3 : 5-diene (Soltys, *Ber.*, 1933, **66**, 764) (−350°) is also not in agreement with the calculated value (−411°) and thus indicates some " vicinal action " or a compound of doubtful purity.

[*Added, January 14th*, 1952.] On treatment of *N*-nitrosolasodine with boiling aqueous acetic acid, nitrogen is eliminated (cf. Oddo, *Gazzetta*, 1911, **41**, 434; Oddo and Caronna, *Ber.*, 1936, **69**, 283), and on chromatography of the product diosgenin has been isolated in small yield. Since the structure and configuration of diosgenin is known from its conversion into cholesterol (Marker and Turner, *J. Amer. Chem. Soc.*, 1941, **63**, 767), the structure and configuration of solasodine are now also confirmed. The main product of the above reaction is an isomer of diosgenin formed probably by a Demjanow rearrangement during the transformation, details of which will be submitted later.

EXPERIMENTAL

M. p.s were determined in evacuated tubes.

Solasodine.—The final purification of solasodine was carried out by chromatography on alumina, with light petroleum–benzene (3 : 1). Crystallisation of the fraction, m. p. 198—201°, from methyl alcohol afforded hexagonal plates, m. p. 200—202°, $[\alpha]_D^{22}$ −113·5° ± 2° (*c*, 5·03).

Diacetylsolasodine.—A mixture of solasodine (500 mg.), pyridine (5 c.c.), and acetic anhydride (1 c.c., 9 mols.) was heated under reflux for 2 hours and, after cooling, poured on ice plus aqueous ammonia. Successive crystallisation of the precipitated *diacetate* (yield, almost quantitative) from methyl alcohol and ethyl acetate afforded colourless plates, insoluble in dilute acetic acid (Found : C, 75·0; H, 9·4; N, 2·7. $C_{31}H_{47}O_4N$ requires C, 74·8; H, 9·5; N, 2·8%), $[\alpha]_D^{26}$ −56·3° ± 3·5° (*c*, 3·41), −56·2° ± 2° (*c*, 4·90).

O-*Benzoylsolasodine.*—Solasodine (600 mg.) in pyridine (10 c.c.) and benzoyl chloride (0·75 c.c., 4 mols.) were heated under reflux for ½ hour and set aside for 1 day. The precipitate which separated was unchanged solasodine (166 mg.). The filtrate was poured on ice + aqueous ammonia and the product treated with ammonia in acetone. The material recovered on dilution with water, after repeated crystallisation from methyl alcohol and acetone, afforded glistening, colourless, hexagonal plates (Found : C, 78·3; H, 8·9; N, 2·5. Calc. for $C_{34}H_{47}O_3N$: C, 78·9; H, 9·15; N, 2·7%), $[\alpha]_D^{24}$ −80·1° ± 2° (*c*, 5·20), soluble in warm dilute acetic acid. Rochelmeyer (*Arch. Pharm.*, 1939, **277**, 329) records m. p. 216—217° for a benzoyl derivative of solasodine. The benzoyl derivative failed to give a precipitate with digitonin.

Diacetylsolasodanol.—The sample of solasodanol had m. p. 208—209°, $[\alpha]_D^{23}$ −56·2° ± 3° (*c*, 4·97). *Diacetylsolasodanol* was prepared as was acetylsolasodine, from solasodanol (340 mg.), pyridine (8 c.c.), and acetic anhydride (1·4 c.c., 18 mols.). After successive crystallisations from aqueous alcohol, aqueous methyl alcohol, and acetone it separated in colourless plates, insoluble

in dilute acetic acid (Found: C, 74·4; H, 9·8. $C_{31}H_{49}O_4N$ requires C, 74·5; H, 9·9%), $[\alpha]_D^{24}$ −13·2° ± 3° (*c*, 4·16).

Benzoylsolasodanol.—*Benzoylsolasodanol*, prepared similarly to benzoylsolasodine, from solasodanol (200 mg.), pyridine (5 c.c.), and benzoyl chloride (0·5 c.c., 9 mols.), after successive crystallisation from aqueous alcohol, aqueous methyl alcohol, and aqueous acetone, formed hexagonal plates, soluble in warm dilute acetic acid (Found: C, 79·1; H, 9·7; N, 2·4. $C_{34}H_{49}O_3N$ requires C, 78·6; H, 9·5; N, 2·7%), $[\alpha]_D^{22}$ −47·2° ± 3° (*c*, 4·385). It failed to give a precipitate with digitonin.

Dihydrosolasodanol.—A sample of dihydrosolasodanol, purified by Dr. G. A. Nicholls by chromatography on alumina with benzene as the initial solvent and benzene–acetone (1 : 1) for elution, had m. p. 291—295°, $[\alpha]_D^{21}$ −65° ± 2° (*c*, 4·97). The triacetyl derivative, prepared from dihydrosolasodanol (320 mg.), pyridine (4 c.c.), and acetic anhydride (0·5 c.c., 7 mols.) as in the above cases, after repeated crystallisation from aqueous ethyl and methyl alcohol formed plates up to 2 cm. in length, m. p. 156·5—157·5°, slightly higher than that recorded in Part V (*loc. cit.*). It had $[\alpha]_D^{26}$ +31·8° ± 2° (*c*, 6·13) and was insoluble in dilute acetic acid.

Solaso-3 : 5-diene.—The sample of solaso-3 : 5-diene (cf. Part II, *loc. cit.*), after repeated crystallisation from alcohol, methyl alcohol, and acetone, had $[\alpha]_D^{24}$ −194·9° ± 1·5° (*c*, 4·975).

N-*Acetylsolaso-3 : 5-diene.*—This *derivative*, prepared by refluxing solaso-3 : 5-diene (240 mg.), pyridine (5 c.c.), and acetic anhydride (0·5 c.c., 9 mols.) for 2 hours, after repeated crystallisation from acetone and aqueous acetone formed hexagonal plates of constant rotation, $[\alpha]_D^{19}$ 100° ± 2·5° (*c*, 4·27) (Found: C, 79·7; H, 9·8; N, 3·2. $C_{29}H_{43}O_2N$ requires C, 79·6; H, 9·9; N, 3·2%).

No benzoyl derivative could be prepared.

5α-*Solasodan and* 5β-*Solasodan.*—Hydrogenation of solaso-3 : 5-diene in methyl-alcoholic acetic acid as described in Part V (*loc. cit.*) afforded a crude product, m. p. 145—150°, separated readily by crystallisation with methyl alcohol (charcoal) into two main fractions, m. p. 169—175° and m. p. 139—153°. The former was relatively pure and 5α-solasodan was the only product obtained after chromatography (light petroleum; alumina). After crystallisation from acetone it formed shiny flakes, m. p. 175—176°, $[\alpha]_D^{24}$ −58·1° ± 3° (*c*, 5·33), −57·7° ± 2·5° (*c*, 5·19).

The second fraction was refluxed with light petroleum and filtered from an insoluble portion, identified after crystallisation as solasodanol, showing that the original solaso-3 : 5-diene contained some unchanged solasodine. The light petroleum solution was chromatographed on alumina but separation was not clean, the m. p. of the fractions varying from 140—145° to 155—158°. The fraction with the highest m. p., after repeated crystallisation from acetone, formed large needles of " β "-solasodan (5β-solasodan), of constant m. p. 159—160° (Found: C, 80·8; H, 11·1. $C_{27}H_{45}ON$ requires C, 81·1; H, 11·35%), $[\alpha]_D^{23}$ −56·9° ± 3° (*c*, 5·04). At no stage were crystals of the " β "-solasodan, m. p. 132—134°, as recorded in Part V (*loc. cit.*), obtained, and the m. p.s of all the low-melting fractions could be raised above 150° by crystallisation from acetone.

N-*Acetyl-5α-solasodan.*—This *derivative*, prepared by refluxing 5α-solasodan (132 mg.), pyridine (2 c.c.), and acetic anhydride (0·4 c.c., 14 mols.) for 1½ hours, after successive crystallisation from aqueous alcohol, aqueous methyl alcohol, and aqueous acetone, formed hexagonal plates (Found: C, 78·4; H, 10·4; N, 3·1. $C_{29}H_{47}O_2N$ requires C, 78·9; H, 10·7; N, 3·2%), $[\alpha]_D^{24}$ −8·7° ± 4° (*c*, 2·42).

5α-Solasodan could not be benzoylated by the usual method.

N-*Nitroso-5α-solasodan.*—To an ice-cold solution of 5α-solasodan (100 mg.) in glacial acetic acid (1 c.c.) and water (3 c.c.) was added, dropwise and with stirring, a cold solution of sodium nitrite (84 mg., 5 mols.) in water (1 c.c.). The precipitate (quantitative yield), which commenced to form at the first drop, after being kept in the refrigerator overnight, was crystallised successively from 75%, 90%, and 95% alcohol and then formed rods, m. p. 227·5—229° (Found: C, 75·4; H, 10·2; N, 6·3. $C_{27}H_{44}O_2N_2$ requires C, 75·65; H, 10·35; N, 6·5%).

N-*Acetyl-5β-solasodan.*—This *derivative*, prepared by refluxing 5β-solasodan (104 mg.), pyridine (1 c.c.) and acetic anhydride (0·5 c.c., 20 mols.) for 2 hours, after repeated crystallisation from aqueous alcohol and aqueous acetone, formed glistening, hexagonal flakes, m. p. 150·5—151·5° (Found: C, 79·3; H, 10·6; N, 3·1%).

N-*Nitroso-5β-solasodan.*—This *compound*, prepared from 5β-solasodan (95 mg.) in glacial acetic acid (0·25 c.c., 19 mols.) and water (2 c.c.) by a solution of sodium nitrite (90 mg., 5 mols.) in water (1 c.c.), separated after repeated crystallisation from aqueous alcohol and aqueous acetone in colourless needles, m. p. 174—176° (Found: C, 75·95; H, 10·3; N, 6·3%).

Dihydro-5α-solasodan.—5α-Solasodan (110 mg.), in a mixture of glacial acetic acid (10 c.c.)

and acetone (20 c.c.), was hydrogenated in the presence of platinum oxide (75 mg.) at 35 lb./in.^{2} for 40 hours. After removal of the catalyst, the volume was reduced to a few c.c. by vacuum-distillation, and the final solution heated at 100° with excess of ammonia for 20 minutes. The insoluble product, after crystallisation from acetone, formed a mixture of rectangular plates and flattened needles, m. p. 186—188°, undepressed by an authentic sample prepared by hydrogenation of solaso-3 : 5-diene and separated by chromatography on alumina from a light petroleum solution. We are indebted to Dr. G. A. Nicholls for this preparation. Its rotation was $[\alpha]_D^{22}$ $-8{\cdot}3° \pm 2{\cdot}5°$ (*c*, 5·26).

Diacetyldihydro-5α-solasodan.—Prepared by refluxing dihydro-5α-solasodan (250 mg.), pyridine (5 c.c.), and acetic anhydride (0·6 c.c., 9 mols.) for 2 hours, the *diacetyl* derivative formed colourless flakes after repeated crystallisation from aqueous acetone (Found, in material dried at room temp.: C, 74·5, 74·4; H, 10·3, 10·1; N, 3·2. $C_{31}H_{51}O_3N,H_2O$ requires C, 73·95; H, 10·5; N, 2·8%), $[\alpha]_D^{18}$ $+39{\cdot}7° \pm 1°$ (*c*, 5·47).

Dihydro-5β-solasodan.—5β-Solasodan (70 mg.), in 1 : 2 glacial acetic acid–acetone was hydrogenated in the presence of platinum oxide (70 mg.) at 46 lbs. for 35 hours. After working up of the product as for the 5α-isomer and repeated crystallisation from acetone, the *dihydro*-compound formed plates (Found: C, 81·1, 81·2; H, 11·8, 11·9; N, 3·6. $C_{27}H_{47}ON$ requires C, 80·7; H, 11·8; N, 3·5%), $[\alpha]_D^{20}$ $-5{\cdot}9° \pm 3°$ (*c*, 4·96), m. p. 160·5—161·5°, undepressed by a sample prepared by Dr. G. A. Nicholls by the hydrogenation of solaso-3 : 5-diene with a platinum oxide catalyst (cf. Part II, *loc. cit.*) In the latter case, the 5β-isomer, being somewhat more soluble than the 5α-isomer, was separated by fractionally crystallising the reaction product from acetone.

Dihydrosolasodenol.—A sample of dihydrosolasodenol (Part VI, *loc. cit.*), after purification by chromatography on alumina in acetone–benzene (1 : 9), had $[\alpha]_D^{21}$ $-65° \pm 3°$ (*c*, 4·97). Its triacetyl derivative (Part VI, *loc. cit.*) had $[\alpha]_D^{22}$ $-21{\cdot}2° \pm 4°$ (*c*, 2·44).

Tribenzoyldihydrosolasodenol.—This *derivative* was prepared by refluxing dihydrosolasodenol (300 mg.), pyridine (5 c.c.), and benzoyl chloride (1 c.c., 12 mols.) for 30 minutes. The amorphous mauve material finally obtained, after repeated crystallisation from alcohol and aqueous acetone, formed colourless rods, insoluble in dilute acetic acid (Found: C, 78·9; H, 7·9; N, 1·6. $C_{48}H_{57}O_5N$ requires C, 79·2; H, 7·9; N, 1·9%), $[\alpha]_D^{23}$ $+22{\cdot}8° \pm 2°$ (*c*, 5·18), $+22{\cdot}3° \pm 2°$ (*c*, 5·51).

Solasod-4-en-3-one.—A sample prepared by Mr. E. G. Brooker (Part II, *loc. cit.*) and crystallised from acetone formed needles, m. p. 183—184°, $[\alpha]_D^{15}$ $+8{\cdot}2° \pm 1{\cdot}5°$ (*c*, 5·03).

The analyses are by Dr. T. S. Ma and Mr. A. D. Campbell, Otago University, Dunedin. We are indebted to the Chemical Society, the Australian and New Zealand Association for the Advancement of Science, the Royal Society of New Zealand, and the Research Fund Committee of the University of New Zealand for continued grants.

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