337. *Alkaloids from* Solanum Pseudocapsicum, *L.*

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THIS paper is an outcome of the participation of one of us in the South African meeting of the British Association in 1929, when Professor J. M. Watt of Johannesburg drew his attention to the poisonous properties of the " winter cherry," introduced into South Africa, and now wild there. M. Breyer-Brandwyk in Professor Watt's laboratory obtained from

this plant an amorphous alkaloid (*Bull. Sci. Pharmacol.*, 1929, **36**, 542) which has a depressant effect on the heart (Watt, Heimann, and Epstein, *Quart. J. Pharm.*, 1932, **5**, 649). We are greatly indebted to Professor Watt for a supply of the leaves, collected near Johannesburg; from these one of us with E. Schlittler obtained a crystalline alkaloid, for which the name *solanocapsine* is now suggested, together with an amorphous base, which may be called *solanocapsidine*. Dr. Schlittler's preliminary observations have been generously placed at our disposal and are here incorporated. Whether, like other *Solanum* species, *S. pseudocapsicum* contains a gluco-alkaloid, remains doubtful; none could be isolated, although after treatment with 2*N*-hydrochloric acid on the water-bath the solution of the crude alkaloid gave reactions for carbohydrates (Molisch) and for pentoses; no sugar derivative could be obtained. It is conceivable that these two bases (and particularly solanocapsine) are secondary products, formed during isolation, and are not present as such in the plant. Solanocapsine has the formula $C_{25}H_{42}O_2N_2$ or $C_{26}H_{44}O_2N_2$; we have related our analyses to the higher homologue. A formula with more hydrogen, *e.g.*, $C_{25}H_{44}O_2N_2$, is less likely on theoretical as well as on analytical grounds, for it does not allow of the requisite number of rings (see below). Solanocapsine was used for a number of mild degradations, but insufficient material was available for selenium dehydrogenation, which was carried out on the amorphous and more abundant solanocapsidine. The latter has a very similar formula, probably $C_{26}H_{42}O_4N_2$, and, assuming a similarity of structure in the two alkaloids, we have applied the results of the selenium dehydrogenation to solanocapsine, which enables us to suggest an outline of its constitution. There are still many gaps, which may be filled when more material becomes available.

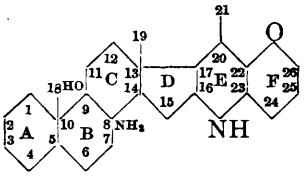
Solanocapsine reacts with two equivalents of nitrous acid; an imino-group acquires a nitroso-group, and an amino- is converted into a hydroxyl group, probably the one originally present is eliminated as water, and the resulting substance has acquired a double bond. Solanocapsine shows three active hydrogens at room temperature and four at 95°, the fourth being one of those in the amino-group. Since the imino-group accounts for one and the amino-group for one (or two) of the three (or four) active hydrogens, there is also present one hydroxyl group. On heating with acetic anhydride, solanocapsine yields a neutral *diacetyl* derivative, in which the hydroxyl is not acetylated, and since this group is moreover readily eliminated with a hydrogen atom and formation of a double bond (not present in the original alkaloid), we conclude that the hydroxyl group is tertiary. This elimination of water, resulting in apo*solanocapsine*, is easily brought about by boiling alkali; nitrous acid converts *apo*solanocapsine into the same nitroso-compound as is formed from solanocapsine.

The function of the second oxygen atom could not be determined; no evidence of a carbonyl or alkoxy-group could be obtained and hence we conclude that this oxygen atom is a member of a heterocyclic ring. Solanocapsine very readily condenses with acetone and the resulting *compound*, which is still basic, shows only one active hydrogen atom, whether at room temperature or at 95°; this hydrogen atom therefore belongs to the imino-group. Acetylation of the acetone compound results in *monoacetyl solanocapsine*, in which the acetyl is attached to the imino-group; acetone is split off by the acetic acid formed during isolation of the product.

The double bond of the readily purified nitroso-compound has been utilised as a point of attack by permanganate. Apart from a neutral oxidation product which still seems to contain all the original carbon atoms, there was obtained an amphoteric acid, $C_{15}H_{24}O{\cdot}NH(CO_2H)_2$. Since the amino-nitrogen is no longer present in the nitroso-compound, the single nitrogen of the oxidation product must be the imino-nitrogen (freed from its nitroso-group) and since the acid contains three active hydrogen atoms, accounted for by the imino- and the two carboxyl groups, its remaining oxygen is the bridge atom originally present. The acid must therefore have as many rings as a saturated hydrocarbon $C_{15}H_{26}$, *viz.*, three.

We now utilise the results of the selenium dehydrogenation of solanocapsidine, with the reserve already indicated. This degradation yielded hydrocarbons and pyridine bases, and as the result of the recent observation by Soltys and Wallenfels (*Ber.*, 1936, **69**, 811) that solanidine from the potato yields methyl*cyclo*pentenophenanthrene, we were also able

to identify Diels's hydrocarbon as a degradation product of solanocapsidine. This implies the presence of four homocyclic rings A—D in the molecule; the formation of a substituted pyridine requires a heterocyclic ring E, and the bridge oxygen atom appears to require, as has been pointed out, a second heterocyclic ring F. In solanidine-t the nitrogen atom is according to Soltys and Wallenfels a member two rings, formed from the cholesterol side chain, and one of these rings must therefore be united to the five-ring D. The single nitrogen atom of solanidine-t presumably corresponds to the imino-nitrogen of solanocapsine and hence we place ring E by the side of ring D, and ring F at the end of the molecule. The inset formula is merely given to illustrate these general ideas.



It has been shown that the oxidation product of the nitroso-compound contains the two heterocylcic rings E and F and a third ring D. Its two carboxyl groups would then be carbon atoms 8 and 9, and the nine carbon atoms lost in its formation must be 1—7, 10 and 18. If solanocapsine had 25 carbon atoms, only eight would be lost, a number not readily accounted for if derived from the sterol rings A and B. Since the acid contains almost certainly 17 carbon atoms, this is an additional argument for the C_{26} formula of solanocapsine. The above scheme also accounts for the three *C*-methyl groups which appear to be present (as in solanidine-t). Unlike solanidine-t, solanocapsine gives no precipitate with digitonin, which may be due to a stereochemical difference or to the absence of a hydroxyl in 3.

As has been pointed out, the hydroxyl group must adjoin the amino-group, and the double bond of the nitroso-compound must be attached to one of the carbon atoms bearing these groups, or lies possibly between them. These conditions are satisfied by placing the amino- and the hydroxyl group at 8 and 9 (or 9 and 8) respectively. The heterocyclic ring E is represented after the drastic action of selenium by a mixture of bases including 2-methyl-5-ethyl- and 4-methyl-2-ethyl-pyridine. Since both these bases are formed from γ-picoline ethiodide at 320°, the temperature of the selenium dehydrogenation, one or both pyridines may result from a secondary reaction. As formulated above, ring E gives some indication how these pyridine homologues might arise, but it is not possible to utilise their formation very fully. Ring F is even more speculative, but it should be noted that the side chain of cholesterol has been retained (apart from C_{27}) and that the bridge oxygen is attached to C_{22}, which atom also has an oxygen bridge in certain saponins of *Digitalis* (not very remote from *Solanum*; cf. Simpson and Jacobs, *J. Biol. Chem.*, 1935, **109**, 573; Tschesche and Hagedorn, *Ber.*, 1935, **68**, 1412; 1936, **69**, 797). Solangustidine, $C_{27}H_{43}O_2N$ (Tutin and Clewer, J., 1914, **105**, 565), differs from solanidine-t in having an extra oxygen atom and in solanocapsine this difference is increased by an additional nitrogen atom in the amino-group.

Experimental.

Isolation.—The dried leaves were percolated with 80% alcohol; after evaporation of the alcohol the residue was mixed with dilute acetic acid and filtered, the filtrate washed with ether, and the pale yellow aqueous layer basified and shaken with ether; on evaporation the latter left a pale brown solid (1·2—1·3% of the leaves). The crude alkaloid could not be crystallised and the only crystalline salt obtainable was the chromate. A solution of potassium chromate was added to one of the alkaloid in dilute acetic acid, and the amorphous voluminous precipitate dried and dissolved in hot alcohol; no precipitate formed on cooling, but on the addition of a little aqueous potassium chromate solution, a chromate of solanocapsine soon separated in well-formed crystals; crystallisation could also be induced with ammonium chromate, but not with sodium chromate or chromic acid; yield of crystalline chromate, 1·0% of the leaves. The mother-liquor contained an amorphous alkaloid giving a soluble chromate (solanocapsidine). When solanocapsine chromate was heated with 5*N*-hydrochloric acid, the solution became green and a white hydrochloride separated, which was filtered off, washed with hydrochloric acid, and crystallised from 5 parts of hot water or, better, from alcohol and ether.

A second batch of leaves, collected earlier in the season, yielded the same crystalline hydrochloride without passing through the chromate. The concentrated ethereal solution of the

crude alkaloids, obtained as above, was shaken with 2*N*-hydrochloric acid (instead of the dilute acetic acid previously employed); when the aqueous layer was heated on the water-bath, in order to remove dissolved ether, solanocapsine hydrochloride crystallised (0·77% of the leaves). Later it was found that the above concentrated ethereal solution of the crude alkaloids, if not shaken with hydrochloric acid, slowly deposited a greyish-green microcrystalline substance, m. p. *ca.* 275°, from which solanocapsine is perhaps formed by the action of warm hydrochloric acid. From the mother-liquors of the crystalline hydrochloride there was obtained ultimately 1·1% of amorphous solanocapsidine, which ammonia precipitated from the solution of its acetate as a jelly; no crystalline derivative could be isolated. The mother-liquor of the crystalline hydrochloride gave positive Molisch and pentose reactions, but no sugar derivative could be isolated.

Solanocapsine, precipitated from the solution of its hydrochloride by ammonia, crystallises from 50% alcohol in long flat prisms, m. p. 222°, $[\alpha]_D$ + 25·5° [Found : loss at 100° in a vacuum over P_2O_5, 4·6; C, 71·2; H, 10·3; N, 6·5; *M* (Rast, in camphor), 460. $C_{26}H_{44}O_2N_2,H_2O$ requires H_2O, 4·1; C, 71·9; H, 10·6; N, 6·5%; *M*, 434. Found for the anhydrous substance : C, 74·1; H, 10·8; *M*, 432. $C_{26}H_{44}O_2N_2$ requires C, 75·0; H, 10·5%; *M*, 416]. On exposure to air the anhydrous substance regains its original weight. The above analyses fit better for the formula $C_{25}H_{42}O_2N_2$, but the free base may not have been quite pure; its liberation from the hydrochloride is attended with loss. The *dihydrochloride* on the other hand gave figures agreeing more closely with $C_{26}H_{44}O_2N_2$. It crystallises from water in needles melting indefinitely above 280° (Found : loss at 120° in a vacuum over P_2O_5, 3·5; C, 61·2, 61·3; H, 9·7, 9·7; N, 5·3; Cl, 13·9. $C_{26}H_{44}O_2N_2,2HCl,H_2O$ requires H_2O, 3·6; C, 61·5; H, 9·5; N, 5·5; Cl, 14·0%. Found for the anhydrous salt : C, 63·5; H, 9·8. $C_{26}H_{44}O_2N_2,2HCl$ requires C, 63·8; H, 9·4%). The sulphate, B,H_2SO_4, forms flat prisms, m. p. 324°, from very little water, or from alcohol–ether. The picrate, crystallised from dilute alcohol, melts at 194°.

Solanocapsine contains no *O*-CH_3, no *N*-CH_3 groups, but apparently three *C*-methyl groups (Dr. H. Roth found 1·9 equivalents of acetic acid). Three active hydrogen atoms react at room temperature, four at 100° (Found 2·9, 4·1 respectively). Diazomethane does not react with solanocapsine, and no methylenedioxy-group is present. Solanocapsine (10 mg.) in 10 c.c. of alcohol, mixed with 10 c.c. of 1% alcoholic digitonin solution and 2 c.c. of water, remained clear and only deposited traces of a precipitate on keeping for a day.

Dehydration product, apo*solanocapsine*. 60 Mg. of solanocapsine hydrochloride were heated for 4 hours with 5 c.c. of 10% methyl-alcoholic potassium hydroxide at 100°. After addition of water and extraction with ether an amorphous residue was obtained, soluble in light petroleum. It did not yield a condensation product with acetone (Found : C, 78·3; H, 11·0; N, 6·8. $C_{26}H_{42}ON_2$ requires C, 78·4; H, 10·6; N, 7·0%).

Action of nitrous acid. When solanocapsine in dilute acetic acid was treated with sodium nitrite (1 mol.), only a slight precipitate was formed, but a second molecule caused a copious precipitate and evolution of nitrogen. The product was a neutral crystalline *nitroso*-compound (from alcohol), m. p. 194°. *apo*-Solanocapsine yielded the same product; in both cases the yield was 90% (Found : C, 72·6, 72·4; H, 9·6, 9·5; N, 6·1, 6·1. $C_{26}H_{40}O_3N_2$ requires C, 72·9; H, 9·3; N, 6·5%). There are two active hydrogen atoms (Found : 2·1, 1·9, 2·1, 2·0, 2·1).

Hydrogenation of the above nitroso-compound. An alcoholic solution was shaken with platinum oxide in a hydrogen atmosphere. After filtration, addition of water produced a crystalline precipitate; recrystallised from absolute alcohol, this had m. p. 211—212° (Found : C, 71·9; H, 9·8; N, 6·8. $C_{26}H_{42}O_3N_2$ requires C, 72·6; H, 9·8; N, 6·5%).

Diacetyl solanocapsine. Solanocapsine was boiled with acetic anhydride for 5 hours; the precipitate formed on addition of water was insoluble in hot dilute mineral acids. It was amorphous and was purified by repeated solution in hot benzene–ligroin and cooling; m. p. 150—160° [Found : C, 71·2; H, 9·6; N, 5·5. $C_{26}H_{40}O_2N_2(CH_3{\cdot}CO)_2$ requires C, 72·0; H, 9·6; N, 5·6%].

Condensation of solanocapsine with acetone. When 25 mg. of the crystalline base were boiled for a few minutes with acetone, crystals began to separate; yield, 24 mg.; recrystallised from ethyl acetate–acetone, the *compound* had m. p. 233°. An acetone solution of 180 mg. of solanocapsine deposited at room temperature in 8 hours 112 mg. of the same substance (Found : C, 76·1, 75·4; H, 10·6, 10·1; N, 6·6, 6·5. $C_{29}H_{48}O_2N_2$ requires C, 76·3; H, 10·5; N, 6·1%). There is only one active hydrogen (Found : 0·97 at 25°, 1·02 at 95°). When shaken with water, the compound loses no acetone (negative iodoform test), but shaken with dilute hydrochloric acid, basified, and filtered, it is reconverted into solanocapsine and the filtrate gives a positive test.

Acetylation of the acetone compound. 112 Mg. were treated for 15 minutes at 100° with acetic anhydride in pyridine. Water was added, and the acetic anhydride decomposed by heating. After being made alkaline, the solution deposited in 3 days 100 mg. of an amorphous product, insoluble in ether, which, crystallised from alcohol, had m. p. 238° (Found : C, 73·0; H, 10·2; N, 6·1. $C_{26}H_{43}O_2N_2{\cdot}CO{\cdot}CH_3$ requires C, 73·3; H, 10·0; N, 6·1%). The basic substance is *monoacetyl solanocapsine*; the acetone group has been removed.

Oxidation of solanocapsine. Mercuric acetate, used according to Gadamer, removed 5·4 molecular proportions of hydrogen and produced a colourless amorphous base, m. p. 127—142°. 60 Mg. of solanocapsine with 200 mg. of potassium hydroxide and 160 mg. of potassium ferricyanide in methyl alcohol–water solution were largely unchanged after 1 hour at room temperature; 20 mg. were recovered as the acetone compound. 50 Mg. of solanocapsine were heated at 11 mm. with 100 mg. of copper powder and then distilled in a high vacuum; only a trace of distillate was obtained. On extraction of the copper powder with acetone an amorphous base, similar to *apo*solanocapsine, was obtained; it gave no phenylhydrazone.

Oxidation of the nitroso-compound. A number of experiments were carried out with potassium permanganate, in acetone or pyridine, at temperatures ranging from 20—85°. The solutions were then diluted with water, decolorised with sulphur dioxide, freed from acetone (when this solvent was used), and extracted with ether; the latter was extracted with sodium carbonate solution. The ether left a neutral crystalline residue; recrystallised from acetone–water, this formed needles, m. p. 218°. The sodium carbonate solution on acidification yielded a crystalline precipitate, m. p. 226—227° after recrystallisation from acetone–water or glacial acetic acid. The mixture of the two oxidative products melted at 205°.

Examples : 200 Mg. of the nitroso-compound and 200 mg. of permanganate (= 4O) in pyridine after 16 hours at 30° yielded 50 mg. of the acid and 50 mg. of the neutral substance. 200 Mg. of the nitroso-compound and 100 mg. of permanganate (= 2O) after 24 hours at room temperature yielded 120 mg. of the neutral substance and very little acid. The combined yield ranged up to 75%, but the proportion between the two products varied greatly and could not be related to the conditions employed.

The *acid* is soluble in hot concentrated hydrochloric acid (Found : C, 62·4; H, 8·5; N, 4·0; equiv., 170. $C_{17}H_{27}O_5N$ requires C, 62·8; H, 8·3; N, 4·3%). The acid contains three active hydrogen atoms (Found : 3·0, 2·75).

It is not possible as yet to assign a definite formula to the *neutral substance* [Found : C, 69·7, 69·2; H, 9·7, 9·4; N, 5·9, 5·7; *M*, in camphor, 340, 351. $C_{26}H_{42}O_4N_2$ (?) requires C, 70·0; H, 9·4; N, 6·3%; *M*, 446].

Solanocapsidine (see isolation above).—This substance differs from solanocapsine in forming a readily soluble hydrochloride and chromate. Neither the free base nor any of its salts could be crystallised. 200 Mg. of *solanocapsidine* were mixed with anhydrous sodium sulphate and extracted in a Soxhlet apparatus for 24 hours with ether, which removed 60 mg.; 120 mg. were then extracted by chloroform in 6 hours. The extracts were separately shaken with hydrochloric acid, and the base isolated; both fractions melted at about 305° and they appeared to be identical (Found : C, 69·3, 69·9; H, 10·0, 9·4; N, 6·2. $C_{26}H_{42}O_4N_2$ requires C, 70·0; H, 9·4; N, 6·3%. $C_{26}H_{44}O_4N_2$ requires C, 69·7; H, 9·8; N, 6·3%. Active hydrogen found : 3·8, 3·9).

Selenium dehydrogenation of solanocapsidine. Numerous experiments were carried out by heating in open or, better, in sealed tubes; *e.g.*, 3 g. of the base with 10 g. of selenium for 14 hours at 320—340°. The odour of ammonia was detected; the product was ground to a fine powder, mixed with anhydrous sodium sulphate and carbonate, and extracted with ether (Soxhlet). The red fluorescent solution was washed with hydrochloric acid and with water, dried, and evaporated. The red oil remaining was fractionated in a high vacuum; (I) b. p. 100—150°; (II) 160—170°, a yellow, strongly fluorescent oil which soon crystallised; (III) *ca.* 190°, partly crystalline; (IV) 210—250°, partly decomposed. By dehydrogenation at 360° for 6—22 hours, no fraction (II) and only traces of (III) were produced. The crystals from (II) were collected on porous plate, the best yield being 18 mg. from 1·7 g. of solanocapsidine. Recrystallised from alcohol, the crystals still had a bluish-violet fluorescence and melted at 123°; a mixture with authentic methyl*cyclo*pentenophenanthrene melted at 130° (Found with 1·1 mg. : C, 91·7 + residue of 2·1 C ?; H, 7·6. Calc. for $C_{18}H_{16}$: C, 93·1; H, 6·9%). 1·5 Mg. each of the hydrocarbon and trinitrobenzene were boiled together in a few drops of alcohol; on cooling, fine yellow crystals separated, m. p. 147° after recrystallisation from alcohol, and 148° when mixed with an authentic specimen prepared from methyl*cyclo*pentenophenanthrene. The picrate also melted at the temperature recorded for this substance (117°). Fraction (III) yielded only a very small quantity of crystals, which could not be obtained pure. The crude

fraction yielded two trinitrobenzene compounds, a minute quantity of dark red prisms, m. p. 168—170°, and more orange-yellow needles, m. p. 132°, which could not be identified.

The hydrochloric acid extracts (above) from all the experiments were united, heated with alcohol (1/4 vol.), filtered from resin, and distilled with steam; nothing significant passed over. The solution was then basified and again distilled with steam; the distillate was turbid and alkaline to litmus, and had a strong odour. On extraction with ether and drying, a colourless oil was obtained, which distilled at 90—100°/18 mm. The *picrate* from 200 mg., although crystalline, melted indefinitely at 120—130°. After ten crystallisations from alcohol the m. p. became constant at 163° (Found: C, 46·9; H, 4·0; N, 15·5. $C_8H_{11}N,C_6H_3O_7N_3$ requires C, 47·9; H, 4·0; N, 15·9%). The picrate could also be crystallised from ethyl acetate and from water. 2-Methyl-5-ethylpyridine, prepared for comparison, had the same characteristic odour. Its picrate melted at 162°, and the m. p. was not depressed by the picrate of the degradation product. Both picrates smelt strongly of the base. From the collected alcoholic mother-liquors of the above picrate from solanocapsidine a second isomeric *picrate* (m. p. *ca.* 125°) was obtained, but it could not be completely purified for lack of material. It was rather more soluble in ethyl acetate and alcohol, and less so in water, than the picrate of 2-methyl-5-ethylpyridine (Found: C, 48·0; H, 4·9; N, 15·6%).

Synthetic 4-methyl-2-ethylpyridine showed the same properties; m. p. 120°; the mixture of the synthetic with the degradation product melted not sharply at 120—123°. In preparing 4-methyl-2-ethylpyridine from γ-picoline ethiodide at 320° there was obtained a mixture of bases from which, in addition to 4-methyl-2-ethylpyridine, the 2-methyl-5-ethyl isomeride was also isolated (picrate, m. p. 163°). The latter would appear to be a secondary product.

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