THE ALKALOIDS OF SOLANUM PSEUDOCAPSICUM

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CONTENTS.

REVIEW of the LITERATURE on SOLANUM AIKALOIDS.

The Solanaceae probably are the only family including species of very poisonous nature and others which are generally used as food plants. I need only mention those few names: Atropa belladonna (The deadly Nightshade), Hyoscyamus niger (The Henbane), and on the other hand Solanum lycopersicum (The Tomato) and Solanum tuberosum (The Potato). Here I shall confine myself to the genus Solanum. It is now generally known that even Solanum tuberosum contains a toxic Alkaloid and we have learned how to avoid the danger of poisoning. A short survey of the history of the potato in Europe however will show us that that has not always been so.

The introduction of the potato cultivation into Britain by Sir Walter Raleigh's colonists and into the South of Europe by Spanish monks caused great enthusiasm and the Herbals of the time contain descriptions of the delicate taste of roast potatoes. This popularity of the potato however did not last and in the middle of the 17th century potatoes had almost disappeared from the European countries/

countries with the exception of Spain. They were believed to cause Leprosy and fevers and their consumption was entirely forbidden in Burgundy and other countries. That is not as absurd as it appears to be. In some cases the wrong parts of the plant which are more poisonous than the tubers must have been eaten and the tubers, when raw, sprouting or not quite ripe contain a considerable amount of Alkaloid, so that chronic poisoning may have occurred. The diagnosis of chronic poisoning is often difficult and eczema and ulcers of the skin which are frequent symptoms of solanine poisoning might have looked fairly similar to the primary effect of Leprosy. If these poor patients were then 'treated' as leprous, e.g. confined to the company of lepers their wounds were sure to be very soon infected. For about a century not much was heard of the potato. When the time of Rationalism came people began to believe less, to observe more and to take account of cause and effect; only then the cultivation of the potato could actually be undertaken on a large scale. Frederick the Great in the Seven Years' War greatly favoured the consumption of potatoes/

potatoes and Parmentier, who as prisoner of war in Germany learned to like their taste, reintroduced them into France. He showed how well the potato grew on a hopeless piece of land that he was given by the State. He gave a bunch of flowers from first potatoes to Louis XVI who wore it as a button-hole, and so made this flower the fashion of the year. Since then the cultivation and consumption of potatoes has continuously increased; occasional poisonings together with chemical and pharmacological science have taught us where to expect and how to avoid the toxic substance.

When the Alkaloid was for the first time isolated (1) it was tested biologically; two grains were proved to be toxic for a small dog. Somnolence and vomiting were the symptoms. Not much later a curious disease was observed which affected cattle fed on molasses originating from distilleries where potatoes were used. (2) (3) This disease only occurred during the months of June to September and could be connected with the sprouting season of the potatoes used. The sprouts were proved to contain much more solanine than the tubers and the disease disappeared when this danger was taken into account.

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The average content of solanine in the tubers has been determined in numerous investigations to be about 0.02-0.075 per mille (59,6); the content in haulm, leaves, fruit, flowers, in the skin of the tubers, in unripe green tubers and in the shoots is higher (up to 1.5% in young spring shoots) (7). If light falls on the tubers the amount of solanine is increased, the conditions of the soil and artificial manuring influence it (8). Occasionally potatoes are found with up to ten times the average amount of solanine. This quality is not hereditary (9), the next generation can again be quite normal. By cooking the water soluble Alkaloid is partly extracted and discarded with the water. That is the reason why cattle fed on raw potatoes unpealed and possibly sprouting are much more exposed to intoxication than man (50). Nevertheless abnormally high content of solanine has caused serious poisonings on several occasions (50,10). So fifty-six soldiers in Berlin were badly affected until the supply of potatoes was stopped and those potatoes were proved to contain 0.2-0.4 per mille solanine. Every man who fell ill had consumed about 0.3 gr of the alkaloid. Another epidemic poisoning occurred in Glasgow in 1917. The symptoms of solanine/

solanine poisoning vary considerably.(50) It is chemically related to the saponins and shares their haemolytic action.(11) It is a strong irritant, causing vomiting, enteritis, diarrhoea, ulcer of the skin of the members and around the mouth and of the mucosae, weakness, prostration, convulsions and paralysis.(50) The heart is also affected. Solanine is excreted very slowly. When a not yet toxic quantity is consumed regularly it accumulates in the body and after a certain time the toxic level is reached. On the other hand in the course of time the organism gets accustomed to the poison. Of the other Solanum Alkaloids Solanocapsin(12) has a definite action on the heart, especially the sinus. It has been suggested to use it in cases of A.V. block, extrasystoles and other disturbances of the automaty of the heart. Nothing is known about the physiological activity of Solangustin or Solanine s.

The first Solanum Alkaloid was isolated by Desfosses in 1820.(1) He found the active principle of Solanum nigrum and the same substance in Solanum dulcamara (Bittersweet).(13) He proposed to call the substance solanine (solanée in the first original paper). He could not isolate it from Solanum tuberosum/

tuberosum. He described it as a white crystalline powder, weakly alkaline. Prophetic intuition made him characterise this powder with the words "absolument semblable à de la cholestérine." He prepared salts with hydrochloric, sulphuric, nitric and acetic acid, but none of them were crystalline. It was a weaker base than all the others known at the time. In the plant it was present as a malic acid salt. It caused somnolence and vomiting when he gave two grains to a small dog.

Soon after solanine was discovered it was also isolated from Solanum tuberosum. Baup in Lausanne found it first (54) and Otto isolated it again a short time later. A practical agricultural problem called upon the chemist and it was solved in a convincing manner. (2,3) Cows which were being fed with molasses from distilleries sometimes developed a curious disease. This only happened during the months of June to September, and only those cows were affected which had not received this food for a long while. Investigations showed that potatoes were used in those distilleries and the fact that June to September was the sprouting season of potatoes lead to the conclusion that possibly a toxic/

toxic substance was contained in the sprouts. Actually Otto succeeded in isolating solanine from potato sprouts. It appeared to be identical with the substance found by Desfosses in Solanum dulcamara and Solanum nigrum. It was analysed in J. v. Liebigs laboratory by one of his pupils;[14] the first of a long series of analysis between 1834 and 1934, in the course of which no single author agreed with any of the previous ones about the empirical formula of the alkaloid, up to a few years ago. The very small percentage of Nitrogen makes its exact determination very difficult and small differences in the Nitrogen percentage naturally influence the size of the molecule and the empirical formula to a large extent. The fact that Liebigs Nitrogen determination comes nearest to the value of the now accepted formula is a triumph for the old master, but not for analytical chemistry in general. Actually the difficulty is not only an analytical one but the purification of the pure Glucoalkaloid and the separation from traces of products of partial hydrolysis is no easy task in itself. A few years later Otto failed to obtain any crystalline solanine from the same source.[15] He only found an amorphous substance which he had already previously/

previously observed in the mother liquors. He came to the conclusion that the Alkaloid content must be very changing and he believed that certain resins acting as acids or 'electronegativ substances' might sometimes keep the Alkaloid in solution.

Shortly after that Reuling (Apotheker in Umstadt)[16] extracted potato shoots with dilute sulfuric acid and obtained nicely crystalline solanine. Wakenroder[17] found the crystalline and the amorphous substance; he prepared many salts.

The first chemical progress was made by Zwenger and Kind[18] in 1859. They observed that Solanine could be hydrolysed by means of dilute hydrochloric or sulfuric acid; the salt of a new base crystallised out which they called Solanidine. In the mother liquor they found glucose and obtained it crystalline. So Solanine was the first representative to be found of a new class of natural products: The Gluco-Alkaloids. In their first paper the authors did not go into details but only mentioned that solanidine sublimed and gave a Platinum chloride salt. Gmelin[19] shortly after

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that confirmed the formation of solanidine but he believed solanine as well as solanidine to be glucosides, containing no nitrogen. His nitrogen determinations varied between 0 and 2% and he therefore believed the nitrogen to be due to impurities. He tried to determine the glucose in the hydrolysis mother liquor quantitatively (by the Fehling method) and stated that 65.3% of the solanine were found as sugar. This paper was soon opposed by Zwenger and Kind[20] who this time gave more exact details than in their first paper. They strongly and rightly insisted on the nitrogen in the Glucoalkaloid solanine and in the Alkaloid solanidine. They gave analytical results for solanine, its hydrochloride, sulphate, platinum chloride salt and oxalate and for solanidine and its hydrochloride (which fit perfectly to Gmelin's C-H- and Cl- results, he had no N!). Their formula and their equation for the mechanism of hydrolysis were not very far from the modern view of the question: $C_{43}H_{69}NO_{16} + 3H_2O = C_{25}H_{39}NO + 3C_6H_{12}O_6$

Solanine — Solanidine & Glucose

(written according to modern equivalents).

On treating solanine with more concentrated acids the authors/

authors obtained a new non-crystalline base which they call solanicine.

The next paper by Kletzinsky[21] contained a new formula and two curious degradation products: on treating solanine with sodium amalgam butyric acid and nicotine were supposed to be formed. Another paper about that time[22] gave a different empirical formula for solanine and unfortunately a very different one for solanidine (C_{26} H_{41} NO_2) with two oxygen atoms instead of one. Those two oxygens did not find any opposition until 1912 and agreement in this question was only reached in 1933. The author also described two acetylation products: a hexaacetyl-solanine and a pentaacetyl-solanidine. One cannot help wondering how a compound even if it had 2 alcoholic oxygens and an acetylable nitrogen, could give a penta-acetyl derivative.

Firbas[23] in 1890 investigated the amorphous substance which was always found together with solanine. He proved that it was different from solanine and called it solaneine. He gave the empirical formula of C_{52} X93 NO18 to solanine and C_{52} H_{83} NO_{13} to solaneine, that corresponds to a loss of five molecules of water. Solaneine on hydrolysis gave/

gave the same solanidine and sugar as solanine.

Cazeneuve and Breteau[24] isolated 0.1% Solanin from potato sprouts by extraction with lime, with a slightly higher melting point (the melting points are never very sharp, owing to decomposition and sublimation). Their analysis fits best for a formula C_{28} H_{47} NO_{10}, $2H_2O$.

A great number of papers by different authors appeared in the next few years. Votoček, Vondraček and Schulz[25-29] investigated the sugars formed during hydrolysis. They at first succeeded to prove the presence of a methylpentose (by the formation of methylfurol), in the next year they mentioned a hexose which was not glucose and they wondered whether glucose was there as well. But soon they succeeded in part, simultaneously with other authors, to isolate and identify the osazones of d-galactose, d-glucose and rhamnose.

Another paper by Hilger[30] which does not help much further: He believed to have found crotonic aldehyde together with dextrose as products of hydrolysis of solanine (Merck). He produced this curious equation: $2C_{52}$ H_{97} NO_{18} = $2C_{39}$ H_{61} NO_2 + $3C_6$ H_{12} O_6 + $2C_4$ H_6 O (Crotonaldehyde) + $12H_2O$. He

Solanine Solanidine

confirmed/

confirmed Firbas' views on solaneine but gave it the formula C_{52} H_{87} NO_{13} (compared with Firbas': C_{52} H_{83} NO_{13}). It hydrated itself and gave solanine on standing for eight months in acetone plus water. Fortunately this paper does not remain uncriticised for long. Wittmann and Zeisel[31,32] could not find a trace of crotonic aldehyde while hydrolysing 115 g of solanine. They also succeeded in identifying rhamnose and dextrose and they speak of the presence of another hexose. Their formulas for solanidine were not better than all the preceding ones since 1859(C_{40} H_{61} O_2 N. One year later: C_{41} H_{65} O_2N). Altogether the history of solanine chemistry reminds one, if it is permitted to use this comparison, of the children's game 'Hide the thimble'. One could easily characterise the papers as ranging between very cold and very hot. Zwenger and Kind's papers in 1859 were rather warm, some of those just mentioned very cold.

But we are now coming to a long series of papers by Oddo, Colombano and co-workers which is still going on and which slowly brought definite progress to our knowledge of the alkaloid. They worked at first with a solanine obtained from the berries/

berries of Solanum sodomaeum. A few years later Colombano (33, 34) proved the non-identity of this solanine with the potato solanine and he proposed to call the one isolated from solanum tuberosum solanine t, the other one originating from solanum sodomaeum solanines. To avoid confusion I shall treat Solanines at a later time when referring to the other Solanum alkaloids found in different plants. Colombano (33,34) in 1911 gave a new analysis for solanine t and proved the identity of the solanine obtained from potato shoots, flowers and Schuchardt's commercial product and the non-identity with solanine s. His formula for Solanidine t was C_{25} H_{39} NO, He stated that the Oxygen is not present in an oxo-grouping.

In 1917 Heiduschka and Sieger (35) published analytical data for solanine, solanidine and a dehydration product which they obtained by means of different dehydrating agents from solanidine. They arrived at the formula C_{51} H_{91} NO_{18} for solanine and C_{34} H_{57} NO_2 for solanidine. They suggested to judge the degree of purity of solanine by the specific rotation ($[\alpha]_D^0$ -42.16 in 2% Hll) instead of by the unreliable melting points. They investigated

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the South American drug Palo Natri (Sol. Tomatillo) and found 0.04% solanine, identical with solanine t. The same authors published another paper in 1935 (36) which I have to report here, leaving the chronological order for once. For this paper when read in 1935 appeared like a geological fault, or like the continuation of their 1917 publication (which in itself was a step back into the past century) bound by mistake in a wrong volume of the Berichte, eighteen years too late. In this paper the authors completely neglect the work of those twenty years and especially of the last two years in which definite agreement about the formula of solanidine has been reached by six different authors. They acetylated solanidine and hydrolysed it again and they calculated all their results according to their old formula $C_{34} H_{57} NO_2$ (whereby they were not concerned by differences of 1% between calc. and found!) although there is no more doubt anywhere that the actual formula is $C_{26} H_{41} NO$, or a homologue thereof.

From 1917 on there is a period of respite before the great attack of modern chemistry on solanine begins. In 1929 Zemplén and Gerecs (37) investigated/

investigated once again the hydrolysis of solanine, but with new methods. They prepared a trideca-acetyl-solanine from which by hydrolysis with HBr they obtained acetylation products of solanine-glucose on the one side, and galactose-rhamnose on the other. They attributed the formula of $C_{44}H_{71}NO_{15}$ to solanine and of $C_{26}H_{41}NO$ to solanidine. They attacked Oddo's scheme of hydrolysis for solanine s (see later) which they misunderstood to apply to solanine t. They apparently had not read his previous papers where he and Colombano proved the difference between the two glucoalkaloids.[38] Oddo very soon drew the attention to this fact and to Colombano's formula for solanidine: $C_{25}H_{39}NO$.

In 1933 Dieterle and Schaffnit[39] isolated another alkaloid from solanum tuberosum which they proposed to call solanthrene. They collected 0.2 g from 40 kg potato sprouts. It had the formula $C_{26}H_{41}N$(172°). They agreed with Zemplén and Gerecs' formula for solanidine $C_{26}H_{41}ON$. Solanthrene is not identical with the dehydration product solanicine, obtained by Heiduschka and Sieger. It can be hydrogenated catalytically and yields dihydrosolanthrene $C_{26}H_{43}N$. The nitrogen is tertiary/

tertiary, but not methylated.

Schöpf and Herrmann (40) prefer the formula $C_{27}H_{43}ON$ for solanidine. Like solanthrene this is also a tertiary base with no methyl group on the nitrogen. The oxygen is present in form of an alcoholic OH. They obtained monoacetyl-, monoformyl- and monopalmityl- derivatives. On pyrodecomposition of solanidine hydrochloride or better the palmitylester or its hydrochloride in vacuo they split off water and obtained solaniden ($C_{27}H_{41}N$ m.p. 166°) which yielded a dihydroderivative on catalytic reduction: solanidan ($C_{27}H_{43}N$, m.p. 161°). They put the question whether their solaniden was identical with Dieterle's solanthrene or dihydrosolanthrene. They also undertook oxydation experiments. With chromic acid at least 10 oxygens were taken up with the same speed but the animo acid formed could not be isolated. With Copper - as in the method introduced by Sexton for sterols - they got the corresponding ketone, solanidon, which proved that the OH group was secondary. This ketone with amyl nitrite and sodium ethoxyde gave a di-isonitroso derivative. That indicated the grouping $-CH_2-CO-CH_2-$ for the ketone and $-CH_2-CHOH-CH_2-$ for solanidine.

They/

They believed solanidine to be saturated, it must then contain at least seven rings. Three sidechain methyl groups were also proved by Kuhns method. Treatment with phosphorus pentachloride yielded a trichlorosolanine, Hofmann degradation was not possible, solanidine was recovered unchanged.

Three more papers of interest were published in 1933. One by Oddo and Caronna is so closely connected with another one published two years later that the two shall be recorded later together. Soltys[41] agreed with Schöpf on $C_{27} H_{43} ON$ for solanidine. He succeeded, however, in hydrogenating the base catalytically thereby obtaining a tetrahydrosolanidine. In calculating this reduced the necessary rings to four or five. He also isolated solanthrene from the hydrolysis mother liquors (his starting material was Mercks solanine puriss. cryst.) but gave it the formula $C_{25} H_{39} N$ in contradistinction to $C_{27} H_{43} ON$ for solanidine. Solanthrene was not present in Mercks solanine, it was not formed from solanidine during hydrolysis, he concluded therefore that it must be present as a glucoalkaloid too, which is astonishing regarding the fact that it contains no oxygen and must be connected with the sugar by the nitrogen/

nitrogen (which is tertiary!) It also yielded a tetrahydroderivative on catalytic reduction.

Bergel and Wagner (42) finally brought more clearness into the disorder which had been caused by so much simultaneous work at different places. They were able to link up the different papers and to fill in the gaps. They agreed with Soltys and Schöpf on $C_{27}H_{43}ON$ for solanidine. (Dieterle: $C_{26}H_{41}ON$, Colombano: $C_{25}H_{39}ON$). For solanthrene, however, they found the formula $C_{27}H_{41}N$ and proved it conclusively by its identity with Schöpf's solaniden. Also the iodomthylates were identical. They were able to tetrahydrogenate solanthrene (like Soltys), but with solanidine they could only obtain a dihydroderivative. Solaniden, again, yielded a tetrahydroderivative which was also identical with tetrahydrosolanthrene. Solanidan (dihydrosolaniden, Schöpf) could not be obtained, but the pyrodecomposition of palmityl-dihydro-solanidine hydrochloride gave a dihydrosolaniden which was not identical with solanidan. It probably is an isomer, its remaining double bond being formed by dehydration whereas Schöpf prepared his solanidan by an incomplete hydrogenation. All these connections will be better illustrated by a scheme/

scheme which I shall give later on. (see page 33).

Nothing of interest was published in 1934. 1935 brings Heiduschka and Siegers' paper which I mentioned before and a new paper by Oddo and Caronna.(43,44) For the sake of clearness I shall abstract this paper together with their 1933 paper. They have studied the hydrolysis of solanine s and t. Solanine s will be mentioned later. With solanine t they have repeated Zemplén and Gerecs' experiments: Acetylation and Hydrobromic Acid Hydrolysis. They obtained the same trideca-acetyl derivative which they proved actually to be the acetate and hydrate of the free tridecaacetylsolanine. They originally believed solanine t (like solanine s!) to be formed by simple addition of the base and the sugars without loss of water which fitted nicely with their analytical results but they have now agreed with Zemplén and Gerecs on the loss of three molecules of water in the formation of the glucoalkaloid. Their formula is $C_{43}H_{69}NO_{15}$ (based on solanidine as $C_{25}H_{39}NO$). Zemplén and Gerecs believe it to be the homologue: $C_{44}H_{71}NO_{15}$.

The Italian authors split trideca-acetylsolanine with hydrobromic acid and obtained different acetyl/

acetyl derivatives of rhamnose on the one side and of solanidine-glucose-galactose on the other. By means of caustic potash or sodium methylate they couldsplit that again into galactose and solanidine-glucose. Without going into experimental details it is sufficient to show that the empirical formula of solanine and the connections of the fragments of the molecule are cleared up and can be expressed by the following scheme:

$$C_{43}H_{69}NO_{15} = C_{25}H_{38}N-O-C_6H_{10}O_4-O-C_6H_{10}O_4-O-C_6H_{10}O_4$$

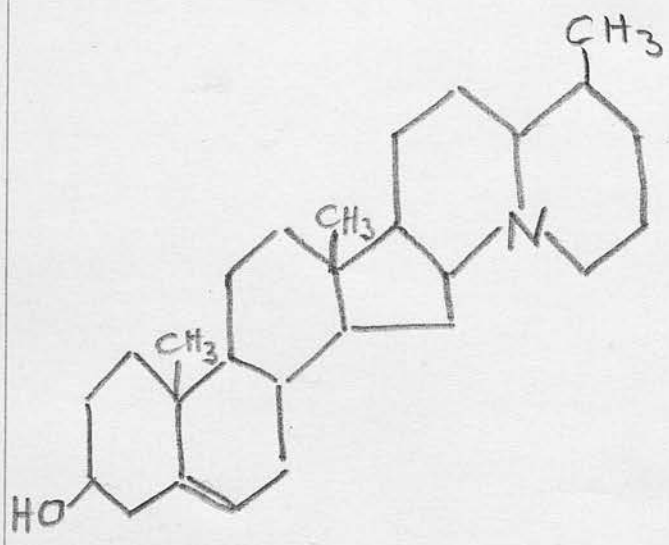
Solanine t : Solanidine t -, d-glucose -, d-galactose - rhamnose.

So far the active groups in solanidine and the connection of this base with the sugars had been elucidated; the next paper by Dieterle and Rochelmeyer (45) gives us the first glimpse of the possible carbon skeleton. Dieterle dehydrogenated solanidine with selenium and could isolate and identify Phenanthrene, Chrysene and Pyridine. The other pridinhomologues and hydrocarbons which he found are not yet identified. He furthermore proved the identity of dihydrosolanthrene with solanidan(Schöpf). A dihydrosolanid<u>e</u>n which was prepared according to Bergel from dihydrosolanidine palmitylester was not identical with/

with their dihydrosolanthren. Both naturally yielded the same tetrahydrosolanthrene. All this may seem a little confusing, it is actually beautifully clear and the experimental facts of different authors fit together in a perfect manner. To illustrate the relations of the different substances obtained an attempt will be made to fit them all into a comprehensive scheme (P. 33) after abstracting the newest paper on solanine. Soltys and Wallenfels (46) isolated the alkaloids from 120 kg potato sprouts. They could prove that Solaneine (Firbas), the amorphous alkaloid was a mixture of solanine and solanidine which it is not easy to separate. On hydrolysing pure solanine (m.p. 285) three fourths of the basic substances were found as solanidine and one fourth was solanthrene. Solanthrene therefore cannot have been present as a glucoside but must have been formed during hydrolysis. Solanidine itself on treatment with dilute HCl did not split off water but the ether, similar in this respect to the palmitylester, might facilitate this reaction. Soltys agreed with the other authors about the relation of solanthrene, solanidine and the different hydrogenation products to one another and suggested to call all the derivatives according to the

Geneva/

Geneva nomenclature. Solanidine (which then would become solanidenol) might be retained as the historical name but the others ought to be called according to the names in brackets in the following scheme. (page 33)
On ozonisation solanidine gave a mono-ozonide which did not split in the usual way but gave back solanidine unchanged. With digitonine he obtained a precipitation which according fo Fernholz, Tschesche, Butenandt is a characteristic reaction for sterols with a hydroxylgroup in position 3. He then dehydrogenated solanthrene (solanidien) with selenium and isolated Diels hydrocarbon, $C_{18}H_{16}$ which he compared with a sample obtained from Diels. So far the experimental evidence. He then puts all the established facts together and tries to construct therefrom the most probable structural formula.



It must be accepted with a certain reserve. The facts on which it is based are: There must be six rings, four of which the methyl-cyclopentenophenanthren accounts for, the nitrogen is tertiary, not methylated, there are 3 side chain methyl groups, one doublebond, one alcoholic OH in position three of the sterol sceleton.

OTHER SOLANUM ALKALOIDS.

Desfosses isolated the first solanum alkaloid from solanum nigrum.[1] The year after he found it in solanum dulcamara,[13] and in the course of the 19th century it was obtained from almost every solanum species.[51,55] Baup isolated it from sol. tuberrosum,[54] Payen and Chevalier from solanum verbascifolium,[53] Pelletier from solanum mammosum,[52] Kennedy from solanum lycopersicum (Tomato),[48] Missaghi from solanum sodomaeum,[47] etc.

Moitessier in 1856[49] published a paper on solanine isolated from solanum dulcamara. He was the first to doubt whether all solanum species contained the same solanine and he definitely believed his solanine to be different from the potato solanine. He gave no comparative analytical evidence but stated that/

that the physical properties were definitely different. His analytical data correspond to a formula $C_{40} H_{66} N_2 O_{13}$. He obtained ethylsolanine, amylsolanine, and ethyl-amylsolanine by treatment with the corresponding iodides. The combustions agree with his formula. No worker on solanine t could repeat this ethylation and no one takes his idea of the existence of different solanum alkaloids seriously. The fact that his analysis shows more nitrogen than those of any other author is no definite evidence, since among so many bad analyses one must always be the worst. But here this question is raised for the first time. The difficulty lies in the fact that 'solanine' is not very well defined. The melting points vary and the great number of different analyses must have been caused by solanine being more or less contaminated with its products of hydrolysis. The other solanines - and we know now that there are more than one - have similarly indefinite qualities and it may not be easy at times to discriminate between several nondescripts.

In 1902 Davis (60) again isolated solanine from bittersweet and was convinced of its identity with/

with the potato alkaloid, without ever doubting or giving any definite evidence. He apparently had no knowledge whatsoever of the literature on the subject, for his formulas for the would-be solanine solanidine and solaneine show none of the connections which link up those three substances with one another. ($C_{42} H_{75} O_{12} N$, Solanine; $C_{41} H_{71} O_2 N$ for Solanidine and $C_{48} H_{78} O_{13} N$ for Solaneine). He finds 'solanidine' in leaves and shoots, 'solanine' in the berries of the plant. Solanine is present in the plant as a mallic acid salt (Desfosses stated that, too); it is alcohol insoluble and no glucoalkaloid whereas solaneine is a glucoalkaloid.

Masson (61) in 1912 again claimed the non-identity between solanine t and his glucoalkaloid from solanum dulcamara. The melting points of his solanine and solanidine were similar but the solubilities in ether differed from those of the corresponding substances from potatoes. He called this new glucoalkaloid Solacéin; [this name contains no indication of the origin of the substance and it is too similar to 'solaneine' (Firbas) and solacine (Heiduschka). One might call it solanine d instead if its non-identity were definitely proved.] This paper/

paper is never opposed. Nevertheless the alkaloid from sol. dulcamara is called only solanine in the later literature. No one appears to have investigated it chemically since then.

Missaghi (47) in 1875 isolated solanine from solanum sodomaeum, a common plant on the Italian coast; he believed it to be identical with solanine from potatoes. 30 years later Oddo and Colombano (62) isolated it again and gave it the formula $C_{23} H_{39} NO_8$ and for the hydrated form $C_{23} H_{39} NO_8 1/2H_2O$. For solanidine which they obtained in the usual way by hydrolysis they found the formula $C_{19} H_{29} NO$. Both values show a much higher nitrogen content than all previous solanine and solanidine combustions. In the following papers (63,64) they gave other methods of extraction (dilute sulphuric acid instead of alcohol) and they suggested to judge the purity of the substance by its microscopic appearance rather than by its unreliable melting point. They gave it a new formula after very careful preparation, avoiding all possibly hydrolysing factors. Romeo (70) who also worked with solanine from solanum sodamaeum attributed to it a different formula and a higher melting point.

A/

A few years later after Colombano had proved the difference between solanine s and solanine t (33,34) Oddo continued his work on solanine s. (65-69) His new bimolecular formula $(C_{27}\ H_{46}\ NO_9)_2H_2O$ for solanine s was analytically almost the same as his previous one but the formation of neutral and basic salts could only so be explained. On hydrolysis he obtained solanidine s and he could identify the osazone of galactose and indicate the presence of another hexose and a methylpentose. Solanidine s was given as $C_{18}\ H_{31}\ NO$ and the following equation was suggested for the hydrolysis:

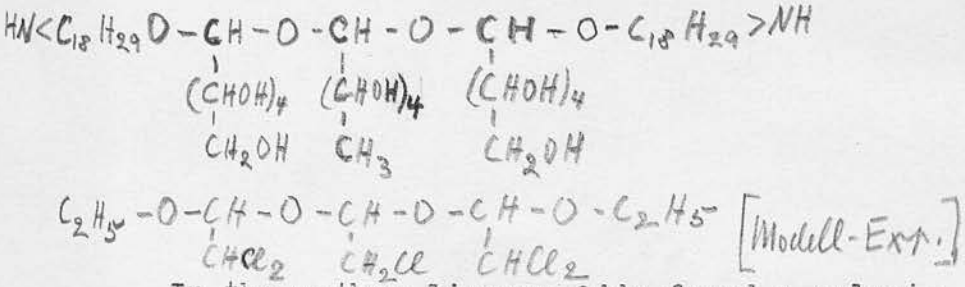
$(C_{27}\ H_{46}\ NO_9)_2, H_2O + H_2O + H_2 = 2C_{18}H_{31}NO + C_6H_{12}O_6 +$
Solanine s Solanidine d-galactose,
$C_6H_{12}O_6 + C_6H_{12}O_5$
Hexose, Methylpentose.

The sugars formed during hydrolysis could have acted as hydrogen donators in the reaction.

In the next paper Oddo (67) studied the qualities of solanidine s. He obtained a diacetyl-derivative and proved by Zerewitinoff's method the presence of two active hydrogens. He isolated a complicated nitrosocompound which did not help much further. There are no double bonds in the molecule.

The/

The next paper (68) gave two hydrogens more to solanine s, which fits into the hydrolysis equation more easily. The authors proved furthermore the presence of d-glucose besides galactose and a methylpentose. They obtained a saturated hydrocarbon from the mother liquors. Two years later (69) in 1914 they gave the following scheme by which the five constitutents of solanine s could be connected without loss of water. At the same time all the carbonyl groups must be linked up with one another for solanine s gave no phenylhydrazon. They undertook model experiments with curious acetales which in their alcohol-aldehyde linkage might correspond to the conditions in the glucoalkaloid.

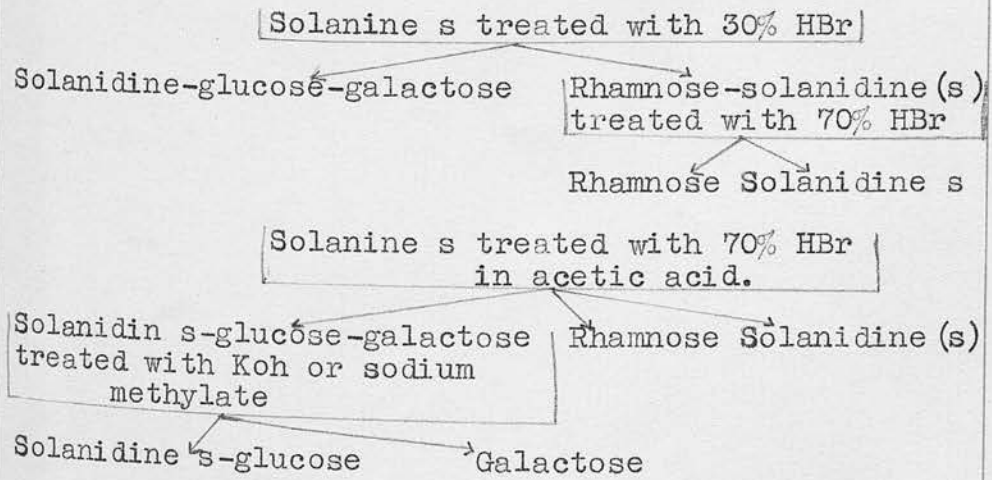


In the mother liquors Oddo found a solanidine ether of the following structure $HN<C_{18}H_{29} - O - C_{18}H_{29}>NH$, which he could also prepare by means of dehydrating agents although only with bad yield. He treated this substance with nitrous acid and obtained nitroso compounds which lose all nitrogen when treated with concentrated hydro-chloric-acid and yielded a substance $C_{18}H_{33}N$. The relation between this and several other degradation products was not

cleared/

(44)

cleared up. The next paper on solanine s was concerned with the connection of the five parts of the molecule. While the authors agree with Zemplèn and Gerecs that the fragments of the solanine t molecule are attached to one another with loss of three molecules of water, they still retain the view that solanine s is a simple addition product of the constituents without loss of water. The empirical formula contains even one molecule of water too much which is probably attached to one of the nitrogen atoms. Oddo hydrolysed the acetylderivatives of the glucoalkaloid by the same methods which were used for solanine t and the products obtained on working with hydrobromic acid of different concentration will be indicated in the following scheme:

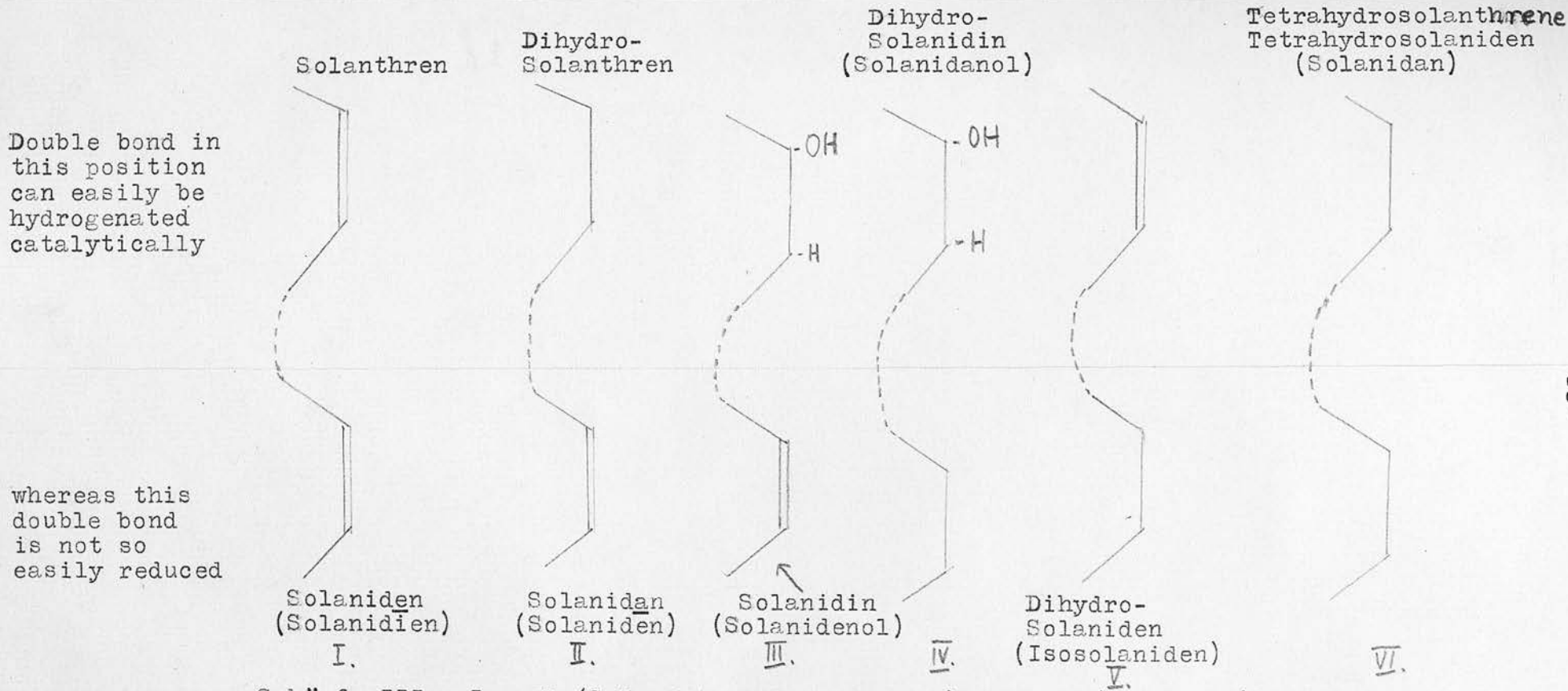


So the following structure is proved for solanine s:

$C_{18}H_{30}N\text{-}O\text{-}C_6H_{12}O_5\text{-}O\text{-}C_6H_{12}O_5\text{-}O\text{-}C_6H_{12}O_4\text{-}O\text{-}C_{18}H_{30}N$, H_2O

Solanidin s-glucose-galactose -rhamnose-solanidine s

Tutin and Clewer (72) in 1914 investigated the constituents of a South American drug, 'Duraznillo Blanco' which has been identified as another solanaecea, solanum angustifolium. They found a new glucoalkaloid besides other interesting substances. The analysis of the base which they called solangustin corresponds to $C_{33}H_{53}O_7N$. On hydrolysis it yielded dextrose and the aglucon which they called solangustidin with the formula $C_{27}H_{43}O_2N$. Solangustin differing from solanine from all other sources had very insoluble salts. The base itself was insoluble in almost everything. It yielded a monaacetylderivative which was still basic. It is interesting to note that the authors found a phytosterol glucoside ($C_{33}H_{56}O_6$) and the free phytosterol ($C_{27}H_{46}O$) as well. It is not phantastic to suppose that there will be connections between the sterol $C_{27}H_{46}O$ and the alkaloid $C_{27}H_{43}O_2N$, especially now that we know that the sterol sceleton plays an important part in other solanum alkaloids.



Schöpf: III - I - II (Solanidin-palmitylester/solaniden/solanidan)
Bergel, Dieterle: I - IV. (Solanthren, Solaniden/Tetrahydrosolanthren)
Bergel: III - IV - V. (Solanidin/Dihydrosolanidin/(palmitylester): Dihydrosolaniden V, isomer of II)
Dieterle: I - II (like Schöpf, but starting from Solanthrene)

TABLE of ANALYSIS for SOLANINE t.

1834	Blanchet (Liebig)	61.98	8.90	1.64
1860	Zwenger & Kind	60.01	8.40	1.37
	Gmelin	62.00	8.70	
1867	Kletzinski	61.02	8.47	3.39
1888	Cazeneuve & Breteau	60.30	8.67	2.53
1890	Firbas	61.24	9.13	1.37
	Hilger	60.78	8.95	1.75
		61.65	9.75	1.59
1914	Colombano	61.40	8.25	2.20
1935	Calculated	61.90	8.32	1.64

TABLE of ANALYSIS for SOLANIDINE t.

1860	Zwenger & Kind	80.93	11.20	3.80
	Gmelin	84.5	10. 8	
1890	Firbas	81.45	10.69	2.40
1914	Colombano	81.58	11.24	3.60
1890	Hilger	78. 8	10. 6	3.6
1933	Bergel	81.38	10. 8	3.67
	Calculated for			
	$C_{27} H_{43} ON$	81.54	10. 9	3.7
	$C_{25} H_{39} ON$	81.30	10.56	3.98

Solanocapsine and Solanocapsidine:

In 1929 Maria Breyer Brandwijk (56) investigated the leaves of Solanum pseudocapsicum. This is a plant which has been introduced into South Africa and now grows wild there; it is also cultivated in gardens for the sake of its beautiful red berries which, however, are not edible. It is known to be poisonous. Brandwijk isolated an alkaloid from the leaves, the yield being about 25% of the weight of the dried leaves. The alkaloid could not be obtained crystalline and pure; it did not appear to be hydrolysable. In pharmacological tests it proved very active especially on the heart.

Barger and Schlittler again isolated the alkaloid from an alcoholic extract of the leaves of Solanum pseudocapsicum. (12) On closer inspection it proved not to be homogeneous. From the mixture a crystalline base could be isolated which was considered to be the aglycone of a glucoalkaloid present in the original extract. The amorphous base was called solanocapsine and the crystalline one solanocapsidine accordingly. Since this starting material was available Professor Barger suggested that I should take up the matter for further investigation.

Solanocapsidine/

Solanocapsidine crystallises in fine needles m.p. 222°. It is easily soluble in alcohol, benzene, chloroform, much less so in ether. The empirical formula cannot yet be regarded as definitely settled. $C_{25} H_{42} O_2 N_2$ appears to be the most likely although the analytical results of some of the derivatives fit somewhat better to a formula $C_{25} H_{44} O_2 N_2$ or its higher homologue $C_{26} H_{46} O_2 N_2$. The base has three active hydrogen atoms, four at higher temperature and three side chain methyl groups (estimated by Kuhn's method). The hydrochloride crystallises well and is rather insoluble in cold water. Its empirical formula $C_{25}H_{42}O_2N_2 2HCl$ shows that both nitrogens are basic. The sulphate and the picrate have also been prepared.

On liberating the base from the solution of the hydrochloride by means of strong alkali a partial dehydration takes place which also occurs during every recrystallisation. Owing to this fact the yield of crystalline solanocapsidine in every recrystallisation is only about 50%. The rest can be recovered from the colloidal and milky mother liquors after concentration by extraction with ether./

ether. It is an amorphous substance, a mixture of solanocapsidine with aposolanocapsidine. Aposolanocapsidine could be obtained quantitatively by treating solanocapsidine with methyl alcoholic potassium hydroxide at 100° for four hours. It was easily soluble in ether and hot petroleum ether or acetone. By analysis it proved to be a dehydration product of solanocapsidine: $C_{25} H_{40} ON_2$.

Solanocapsidine was treated with sodium nitrite in acetic acid solution; the evolution of gas was observed while a neutral precipitate was formed. This indicated the presence of a primary amino group which would cause nitrogen evolution and a secondary one which would form a nitrosamine. The nitroso compound could be crystallised with difficulty from dilute alcohol; after repeated recrystallisation its m.p. was 194°. The analysis indicated a dehydrated nitroso compound. The fact that the nitrogen values were always found too low together with the difficulty in crystallising the compound suggested that the dehydration had not always gone quantitatively. Aposolanocapsidine on treatment with nitrous acid showed the same phenomena, the product obtained was identical with the nitroso compound formed from solanocapsidine. This indicated that water is split off at the same

place/

place in the molecule during formation or recrystallisation of the nitroso compound as during formation of the apo-compound. The nitroso compound showed two active hydrogens in a great number of estimations although only one active hydrogen was expected. The significance of this fact is not yet clear.

The nitroso compound could be hydrogenated catalytically. The dihydro-nitroso compound was nicely crystalline, m.p. 212°. It could be recrystallised from alcohol. The analysis fitted to the expected empirical formula ($C_{25} H_{42} O_3 N_2$).

In a series of experiments the nitroso compound was oxidised with potassium permanganate under mild conditions. Two products were obtained crystalline, a dicarboxylic acid and a neutral substance. The acid crystallised from acetone-water or acetic acid, m.p.227°. Analysis and equivalent weight estimation indicated the formula $C_{17} H_{29} O_5 N$. It had weak amphoteric properties being soluble in strong HCl. Its methyl and ethyl esters were prepared but could not be crystallised. They were both basic. The acid showed three active hydrogens. The neutral substance crystallised from acetone-water, m.p. 218°. The mixed m.p. of the two oxydation products was 205°.

The/

The analysis of the neutral substance indicated the formula $C_{14} H_{23} O_2 N$. The results of molecular weight estimations were completely incompatible with this or any other formula which might have been expected.

Solanocapsidine dissolved in boiling acetone; after standing for a time or boiling for a few minutes a beautifully crystalline substance separated which was almost insoluble in acetone; it could be recrystallised from ethyl acetate-acetone, m.p. 233°. Analysis showed that a condensation between solanocapsidine and acetone with loss of one molecule of water had taken place. The compound had only one active hydrogen, consequently two of the original three active hydrogens of the alkaloid must have been eliminated by condensation with acetone. Acetone is readily hydrolysed off by acids, even in the cold, not so in alkaline solution. After treatment with dilute HCl solanocapsidine could be recovered and the presence of acetone in the mother liquors demonstrated. Aposolanocapsidine gave no acetone compound, consequently the hydroxyl group which has disappeared in the dehydration must be involved in the acetone compound/

compound formation.

The acetone compound has been acetylated with acetic anhydride. The compound obtained however proved to be monoacetyl-solanocapsidine. The acetone must have hydrolysed off when the solution was warmed with water on the water bath to decompose excess of acetic anhydride.

Solanocapsidine was energetically treated with acetic anhydride for five hours to obtain quantitative acetylation. The product was non basic and on analysis proved to be diacetyl-solanocapsidine. Since both nitrogens were originally basic, they must both have been acetylated.

Solanocapsidine was treated with semicarbazide and p-nitro phenylhydrazine but no keto derivatives could be isolated.

No double bonds could be detected in solanocapsidine.

Solanocapsine could not be obtained crystalline. All its salts were amorphous, too, with the exception of a chromic acid salt which however showed curious properties. It only crystallised in presence of potassium chromate. Solanocapsine is easily soluble/

soluble in alcohol and benzene, less in chloroform and still less in ether. Its hydrochloride is easily soluble in water in contradistinction to the hydrochloride of solanocapsidine; it is much less soluble in dilute HCl. The amorphous base was analysed and the empirical formula proved to be $C_{25}\ H_{40}\ O_4\ N_2$. This formula excluded the possibility of solanocapsine being the aglycone of solanocapsidine. Nevertheless many hydrolysing experiments were undertaken with strong hydrobromic acid, but the base obtained showed properties similar to solanocapsine and was different from solanocapsidine. In the mother liquors no sugars could be detected. Solanocapsine has four active hydrogen atoms.

Solanocapsine was treated with selenium in sealed tubes at 320-340° for 14-16 hours. In a series of experiments different conditions were tried out (open tube, longer and shorter periods of heating, higher temperature) but none was found equally successful. From the non-basic products four fractions could be isolated by distillation, one of which could be proved to be methycyclopenteno-phenanthrene (Diels' hydrocarbon). The mixed m.p. with a sample of the hydrocarbon and the mixed m.p. of the trinitobenzene complex with the corresponding/

corresponding compounds which Professor Cook was kind enough to supply showed no depression. The hydrocarbons which distilled at higher temperature could not yet be identified. They could be characterised by their trinitrobenzene derivatives. By fractionated crystallisation two trinitrobenzene derivatives could be separated, one was golden-orange coloured, the other deep red. The lighter coloured one melted at 130°, the red substance of which only traces could be isolated melted at 170°.

The basic products from the selenium dehydrogenation could be steam-distilled. The residue of the ether extract of the steam distillate was distilled in vacuo. A yellow oil came over at 100-120° (14 mm) which had a strong and characteristic smell. It was not very soluble in water; its perchlorate, platinum salt and hydrochloride were very soluble. On treating with very little methyl alcohol the oily platinum salt solidified, m.p.178°. The picrate and gold salt were oily. A picrolonate could be isolated, which melted at 85-90°

Solanocapsidine appears to have the empirical formula $C_{25}H_{42}O_2N_2$. Both nitrogen atoms are basic. The formation by the action of nitrous acid of a non-basic substance which still retains two nitrogens is evidence for the existence of a primary and a secondary amino group. Solanocapsidine has three active hydrogen atoms, four on heating. Two are accounted for by the amino and imino groups; the amino group can also be responsible for the fourth active hydrogen which only reacts at 95° with the Grignard reagent. There is one more active hydrogen which is most probably present as a hydroxyl group. One of the two oxygens of the base is easily removed under the influence of dehydrating agents. This indicates the possibility that the hydroxyl group may be tertiary. Solanocapsidine on energetic acetylation only yields a diacetyl derivative which is non-basic. Consequently both nitrogens, but not the hydroxyl group must have been acetylated, another piece of evidence for a tertiary hydroxyl group. Solanocapsidine could not be oxidised with potassium ferri-cyanide, the specific oxidising agent for a -CHOH-NH- grouping. Solanocapsidine did not give a ketone when treated

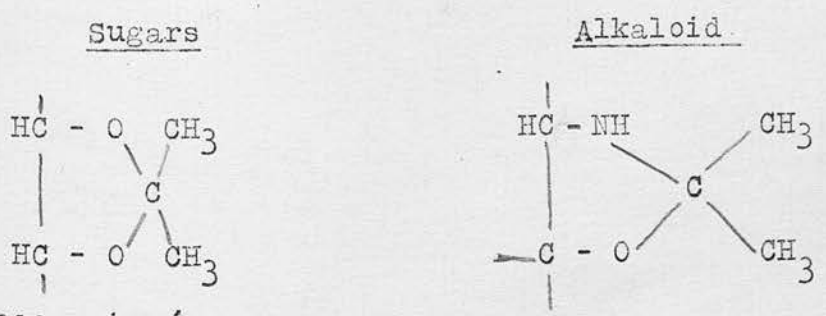
with/

with copper (according to Sexton's[57] method for the oxidation of the secondary hydroxyl in sterols, also employed successfully by Schöpf[40] for solanidine from which he obtained solanidon by this process). Those two negative results also indicate the absence of a secondary hydroxyl group. So one may regard the nature of one of the oxygens as settled. For the second oxygen atom in solanocapsidine there is unfortunately only negative evidence. The alkaloid has no alcoholic properties apart from those which are accounted for by the tertiary hydroxyl group. It gives no ketone derivatives; no ester or amide could be hydrolysed in alkaline medium. The only possibility which is left is an oxide ring, an intramolecular ether, as it exists in tigogenin and other saponines.[71] If that were the case strong acid hydrolysis ought to split the ring. Under the influence of strong hydrobromic acid at 200° for eight hours aposolanocapsidine gave a product which appeared somewhat different in its properties from the starting base; in particular it was much less soluble in petroleum ether. It was not possible to analyse it. The decreased solubility in petroleum ether makes it appear quite likely that in this product

the/

the ether linkage had been replaced by two hydroxyl groups, but no definite evidence could be obtained.

So far the properties of the oxygen and nitrogen atoms in solanocapsidine have been discussed; now an attempt will be made to indicate certain possibilities regarding the position of these active groups relative to one another and in the carbon skeleton. Solanocapsidine forms a condensation product with acetone whereby two of its three active hydrogens disappear. This reaction indicates a spatial proximity of two of the three active groups. Aposolanocapsidine, the dehydrated product gives no acetone compound, consequently the hydroxyl group must be involved in this reaction. The formation of acetone compounds is well known in the sugar series where condensation involves two hydroxyl groups attached to the sugar chain, but there appear to be no recorded cases in which one of the hydroxyls is replaced by an amino group. Nevertheless this appears to be the only possible explanation in that case. The type of product formed could be illustrated by the following scheme:



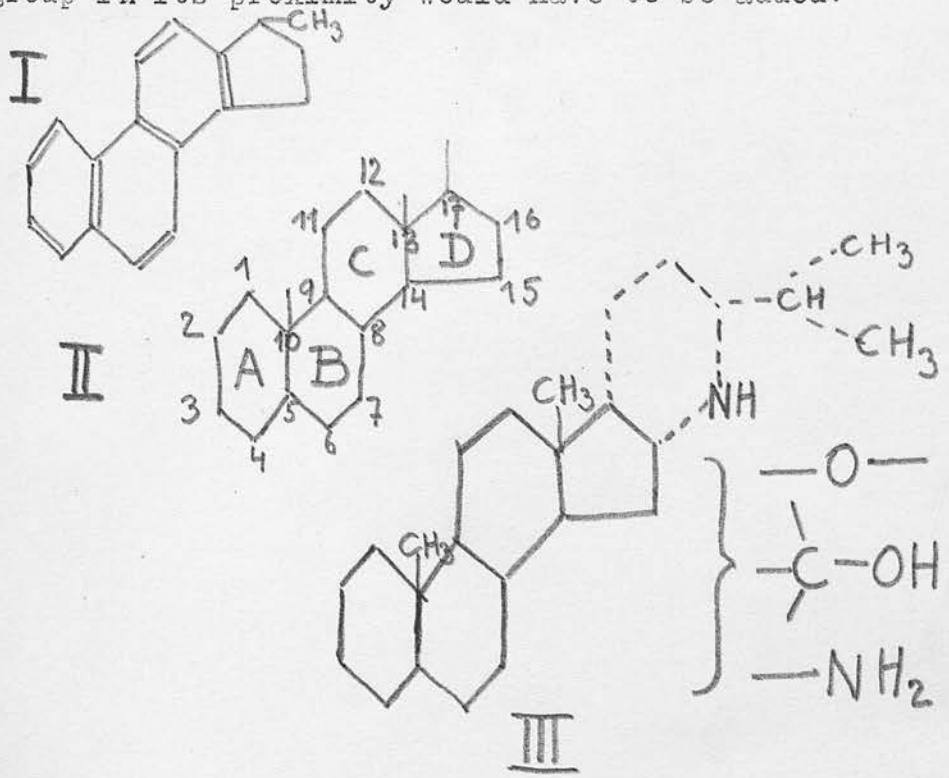
Solanocapsine/

Solanocapsine, the amorphous alkaloid from Solanum pseudocapsicum, contains more oxygen than solanocapsidine, but apart from that the two bases show marked similarity in their composition and in their properties. Solanocapsine has the formula $C_{25} H_{40} O_4 N_2$ and has four active hydrogens, solanocapsidine is $C_{25} H_{42} O_2 N_2$, with three active hydrogens.

Solanocapsine was dehydrogenated with selenium and methylcyclopentenophenantrene(Diels' hydrocarbon, $C_{18} H_{16}$ I) could be obtained and identified. The fact that solanocapsine was amorphous and that the relation of solanocapsine to solanocapsidine has not yet been cleared up made it desirable to repeat this experiment with crystalline solanocapsidine; this unfortunately was impossible owing to lack of material. Diels' hydrocarbon is the typical product which is formed from substances containing the sterol nucleus II by selenium dehydrogenation (e.g. plant sterols, sex hormones, cardiac aglycones, etc.). There is, therefore, a strong presumption that substances yielding Diels' hydrocarbon contain the sterol skeleton. Simultaneously with these experiments Soltys (46) obtained Diels/

Diels' hydrocarbon by selenium dehydrogenation of solanidien. Thus the fundamental similarity of solanidine and solanocapsine becomes evident. Solanidine however has a secondary hydroxyl group which Soltys places in position 3 of the sterol skeleton, (because it gives a precipitation with digitonine, a reaction which according to Fernholz,[58] Butenandt[59] and others is specific for a hydroxyl group in position 3 under certain stereomeric conditions,) whereas solanocapsidine has only a tertiary hydroxyl group and does not precipitate with digitonine. The hydroxyl group might be in an angular position between two rings, as is the case in certain cardiac aglycones. If it were in position 5 and if the amino group, which together with it forms the acetone condensation product were in position 3 then strophanthidine which has hydroxyl groups in 3 and 5 might also give an acetone compound. That however is not the case. The nitroso compound on oxidation yielded an acid with seventeen carbon atoms and a neutral substance with fourteen carbon atoms. It is very likely that the oxidation attacks the double bond which corresponds to the hydroxyl group and a formation of C_{14} or C_{17} oxidation/

oxidation products indicates that the double bond might be somewhere in the middle of the molecule (position 7-8, 8-14, 9-11, 14-15) and not in position 4-5. Solanocapsidine like solanidine has 3 side chain methyl groups (estimated by Kuhn's method) two of which are very likely in the angles of the sterol skeleton (position 10, 13) similar to sterols and cardiac aglycones. The bases formed by selenium dehydrogenation have not yet been identified. Their properties are similar to those of pyridine homologues. A piperidine ring condensed with ring D of the sterol skeleton with an isopropyl sidechain attached to it might possibly represent the structural skeleton of solanocapsidine on to which an oxide bridge, a hydroxyl group in one of the angles and an amino group in its proximity would have to be added. III.



PART II.

EXPERIMENTAL

LIST of EXPERIMENTS.

1. Solanocapsidine and its salts.

Solanocapsidine hydrochloride (isolated from the leaves of Solanum pseudocapsicum and separated from the amorphous alkaloid solanocapsine by Barger and Schlittler) was contaminated with 30% aposolanocapsidine hydrochloride. In a series of experiments it was dissolved in hot water and the base was precipitated with ammonia; the suspension was boiled again after a few seconds and filtered after cooling. The amorphous base was crystallised from 50% alcholol in long needles, yield 50%. The yield of every recrystallisation was between 40 and 60%. After repeated recrystallisation the m.p. was constant at 222°. When dried at 100° in vacuo the substance lost about 4-5% of its weight.

Solanocapsidine hydrochloride (60 mg) was dissolved in abs. alcohol and an alcoholic KOH solution was added; KCl was filtered off, water was added and the solution left to crystallise: 25 mg solanocapsidine were obtained (50% of the theoretical yield) no more crystalline base could be isolated from the mother liquor.

Solanocapsidine hydrochloride (60 mg) was dissolved/

dissolved in water and sodium carbonate solution was added. The jelly was filtered (without boiling before) and dried in a desiccator. On crystallising from 50% alcohol 25 mg (50%) solanocapsidin were found.

Solanocapsidine (180 mg) were recrystallised - yield 100 mg; 100 mg were again recrystallised - yield 45 mg: 45 mg were again recrystallised - yield 25 mg.

82.5 mg solanocapsidine (dried at 40° to constant) were dried in vacuo at 100° for 3 hours, weight 78.7 mg, after another hour weight unchanged. Loss 3.8 mg, equals 4.6%.

Solanocapsidine hydrochloride was recrystallised repeatedly from water and analysed.

Solanocaps.picrate was prepared by adding a concentrated aqueous solution of picric acid to the alcoholic solution of the base. It could be recrystallised from dil. alcohol; m.p. 194°.

The/

The analytical results were as follows:

3.698 mg subst. gave ... 10.045 mg CO_2
... 3.570 mg H_2O

Found: 74.1% C
10.8% H
(Dried at 100° in vacuo)

Calc.: $C_{25}H_{42}O_2N_2$: 74.6% C.
10.5% H

($C_{25}H_{44}O_2N_2$: 74.2% C
11.0% H

3.364 mg subst. gave... 8.785 mg CO_2
... 3.090 mg H_2O
1.761 mg subst. gave... 0.097 cc, 763 mm, 19°

Found: 71.2% C
10.3% H
6.5% N
(without drying at high temperature)

Calc.: $C_{25}H_{42}O_2N_2,H_2O$
71.4% C
10.5% H
6.7% N

Loss of weight 4.6% equals 1 Mol H_2O, water of crystallisation.

Zerewitinoff Estimation: 3 active hydrogens.

Solanocapsidine hydrochloride:

4.832 mg subst. gave ... 11.240 mg CO_2
4.140 mg H_2O

Found: 63.5
9.8

Calc: $C_{25}H_{42}O_2N_{21}$ 2HCl: 63.2% C
9.3% H

(Dried at 120° in vacuo)

($C_{26}H_{42}O_2N_2$, 2HCl: 63.5% C
9.8% H)

Loss of weight while drying 3.5% = 1 Mol. H_2O.

4.887 mg subst. gave 10.945 mg CO_2
4.240 mg H_2O

5.098 mg subst. gave 11.465 mg CO_2
4.430 mg H_2O

2.888 mg subst. gave 0.127 cc N; 22° 761 mm

9.938 mg subst. gave 5.370 mg Ag Cl

Found: 61.2 : 61.3% C
9.7 : 9.7% H
5.3% N
13.9% 11

$C_{25}H_{42}O_2N_2$, 2HCl, H_2O : 60.9% C
9.3% H
5.7% N
14.4% Cl

($C_{26}H_{46}O_2N_2$, 2 HCl, H_2O : 61.3% C
9.8% H
5.5% N
13.9% Cl

(Without drying at high temperature)

2. Dehydration of Solanocapsidine: Aposolanocapsidine

60 mg solanocapsidine hydrochloride were treated in a sealed tube for four hours with 5 cc of a 10% methylalcoholic KOH solution at 100°. Water was added and the suspension was extracted with ether. The ether residue was amorphous; it could be dissolved in petroleum ether and separated after concentration to a small bulk. Aposolanocapsidine was soluble in acetone and no acetone insoluble condensation product crystallised out after prolonged heating. This experiment was repeated several times.

Analysis:

1.803 mg subst. gave ... 5.180 mg CO_2
1.770 mg H_2O
1.206 mg. subst.gave ... 0.069 cc, 765 mm, 17.5°

Found: 78.3% C
11.0% H
6.8% N

Calc.: $C_{25}H_{40}ON_2$: 78.1% C.
10.4% H.
7.3% N

($C_{26}H_{44}ON_2$: 78.0% C
11.0% H
7.0% N)

3. Reaction of Solanocapsidine with Nitrous Acid.

Solanocapsidine was dissolved in dilute acetic acid and after adding an excess of sodium nitrite the solution was allowed to stand at room temperature. After a few minutes the solution became turbid and bubbles of gas were observed to be given off/

off. After several hours the suspension was filtered. The amorphous neutral precipitate after drying weighed about 90% of the starting material. It could be crystallised from dilute alcohol by very slow and careful cooling; it was often amorphous or microcrystalline. M.p. was 194°.

Aposolanocapsidine (50 mg) was treated with nitrite in acetic acid solution and 42 mg amorphous nitroso compound were collected. It was recrystallised in the usual way and proved identical with the nitroso compound from solanocapsidine (m.p. 193°).

The formation of the nitroso compound from solanocapsidine was repeated several times.

Analysis:

4.484 mg subst. gave ... 11.920 mg CO_2
3.830 mg H_2O
2,362 mg subst. gave ... 0.126 cc 24°,750 mm

2.906 mg subst. gave ... 0.151 cc, 22°, 765 mm.

4.442 mg subst. gave ... 11.785 mg CO_2; 3.77 mg H_2O

Found: 72.6; 72.4% C
9.6; 9.5% H
6.1 6.1% N

Calc.: $C_{25}H_{38}O_3N_2$: 72.5% C
9.2% H
6.8% N

($C_{26}H_{42}O_3N_2$: 72.6% C
9.8% H
6.5% N)

Zerewitinoff: (calc. for M = 414, $C_{25}H_{38}O_3N_2$:
2.19; 1.97; 1.93; 2.13; 2.09; 2.21.

4/

decolorised with SO_2. Acetone was removed on the water bath and the acidic suspensions were extracted with ether. The ether was extracted with sodium carbonate solution and after drying evaporated to dryness. The residue was crystalline, a neutral substance which was recrystallised from acetone-water (in needles), m.p.218°.

The sodium carbonate solution on acidifying gave a crystalline precipitate which was recrystallised from acetone-water or strong acetic acid, m.p. 226°-227°.

The mixed melting point between the two oxydation products was 205°.

Examples of experiments:

200 mg nitroso compound were dissolved in pyridine and after adding 200 mg $KMNO_4$ it was left in the incubator at 30° for sixteen hours. It was worked up in the usual way (indicated above) and 50 mg acid and 50 mg neutral substance were obtained.

200 mg nitroso compound with 100 mg $KMNO_4$ at room temperature twenty-four hours: 120 mg neutral substance and very little acid.

A great number of experiments of this kind were/

4. Hydrogenation of the Nitroso Compound:

300 mg nitroso compound (prepared from solanocapsidine) were dissolved in glacial acetic acid and hydrogenated with platinum oxide as catalyst for eight hours. 10 cc of hydrogen were taken up. Water was added to the solution and the crystalline precipitate was filtered off and recrystallised from absolute alcohol. The m.p. was 211-212°. The yield was about 70%. On adding more water to the mother liquor another crystallisate was formed which however had a lower melting point and contained obviously some not yet hydrogenated starting material.

Analysis:

2.741 mg subst. gave .. 7.230 mg CO_2; 2.410 mg H_2O

1.360 mg subst. gave .. 0.078, 764 mm 16°

Found: 71.9% C
9.8% H
6.8% N

Calc. $C_{25}H_{40}O_3N_2$: 72.1% C
9.6% H
6.7% N

5. Oxydation of the Nitroso Compound with Permanganate

In a series of experiments the nitroso compound was oxidised with potassium permanganate. The solvents were pyridin or acetone, the temperatures employed ranged between room temperature and water bath. The solutions were diluted with water, decolorised/

were carried out under slightly varying conditions, studying the influences of solvent, temperature and duration of the experiment on the formation of the two products. No definite rule could be found. The yields were up to 75% when taking the two products together, the relation between the yield of the two was very changing.

The acid is soluble in strong HCl in the heat. The methyl ester was prepared by adding diazomethane to the ether solution of the acid, the ethyl ester was prepared in alcoholic solution with HCl, both esters could not be crystallised; they were basic.

Analysis/

Analysis of the Acid:

2.623 mg subst. gave ... 6.000 mg CO_2
2.000 mg H_2O

5.220 mg.subst. gave ... 758 mm, 26° 0.230

3.618 mg. subst.gave ... 0.75 cc CH_4, 24° Pyridin

1.585 mg. subst.gave ... 0.35 cc CH_4, 24° Pyridin

Found: 62.4% C
8.5% H
4.0% N

Calc. $C_{17}H_{29}O_5N$: 62.4% C
8.8% H
4.3% N

Zerewitinoff: (fpr M = 327, $C_{17}H_{29}O_5N$: 3.0; 2.75 : 3 active Hydrogens.

Equivalent weight estimation: 170 corresponds to M = 340 of a dibasic acid.

Analysis of the Neutral Substance:

3.932 mg subst. gave ... 10.115 mg CO_2
3.440 mg H_2O
0.027 mg ash

0.242 mg . in 4.240 mg. camphor, 6.5°

0.203 mg . in 3.670 mg. camphor, 6.5°

Found: 70.7 %C
9.9 %H

Calc. $C_{14}H_{23}O_2N$ 70.9%C
9.7%H

(Dried at 120° in varns)

M = 237 ($C_{14}H_{23}O_2N$)

M=340; 351

2.541 mg subst. gave ... 2.20 mg H_2O; 6.50 mg CO_2
2.415 mg subst. gave ... 751 mm, 23° 0.124
2.833 mg subst. gave ... 2.39 mg H_2O; 7.19 mg CO_2
6.630 mg. subst. gave ... 758 mm, 26° 0.232

Found 69.7; 69.2% C.
9.7; 9.4% H
5.9, 5.7% N

Calc. $C_{15}H_{25}O_2N$, $\frac{1}{2}H_2O$: 69.2% C
10.0% H
5.4% N

(Without drying at high temperature)

6. Condensation of Solanocapsidine with Acetone.

25 mg crystalline solanocapsidine were dissolved in boiling acetone and quickly filtered. After heating the solution for a few minutes on the water bath, crystals began to separate which were completely insoluble in much boiling acetone. 24 mg were collected which after recrystallisation from ethyl acetate-acetone melted at 233°.

180 mg amorphous solanocapsidine were finely powdered, heated for a few seconds with acetone and filtered. After standing at room temperature for eight hours, the crystallisate was filtered off, 112 mg were collected, m.p. 226°. After recrystallisation the m.p. was 232°.

The experiment was repeated several times.

Analysis/

Analysis:

7.590 mg subst. gave ... 0.40 cc CH_4 21°
0.41 cc CH_4 95° Pyridin

7.153 mg subst. gave ... 0.36 cc CH_4 21°

4.877 mg subst. gave ...13.615 mg CO_2
4.610 mg H_2O

1.802 mg subst. gave ... 0.103 cc, 25° 763 mm

3.486 mg subst. gave ... 9.640 mg CO_2
3.140 mg H_2O

2.875 mg subst. gave ... 0.157 cc, 765 mm 18°

Found: 76.1 : 75.4% C
10.6 : 10.1% H
6.6 : 6.5% N

Calc. $C_{28} H_{46} O_2 N_2$: 76.0% C
10.4% H
6.3% N

M = 474

M = 442

Zerewitinoff: (M = 442) : 1.05, 1.00 : 1 active Hydrogen.

50 mg acetone compound were shaken with water and filtered. The aqueous mother liquor gave negative iodoform test (no acetone present). Then the same crystallisate was shaken for some time with dilute HCl, basified and filtered. The mother liquor now gave a positive iodofrom reaction for acetone. The base on the filter could be crystallised and proved to be solanocapsidine. (m.p. 220°).

7. Acetylation of the Acetone Compound

112 mg acetone compound was treated for fifteen minutes on the water bath with acetic anhydride in pyridine. Water was then added and the mixture heated on the water bath to decompose excess of acetic anhydride. The solution was basified and after standing for three days the amorphous white product was filtered. Yield - 100 mg. It was insoluble in ether. It could be crystallised from 60% alcohol, m.p. 238° (decomp.).

Analysis:

3.876 mg subst. gave 10.270 mg CO_2
3.500 mg H_2O
1.990 mg subst. gave 0.105 cc, 22.5°.758 mm.

Found:		Calc: $C_{27}H_{44}O_3N_2$:	
	73.0% C		73.0%C
	10.2% H	($C_{25}H_{41}O_2N_2COCH_3$)	9.9% H
	6.1% N.		6.3% N.

8. Acetylation of Solanocapsidine.

110 mg solanocapsidine were refluxed with acetic anhydride for five hours. The solution was then poured into water and heated. The residue after filtering the hot solution weighed 100 mg. It was not soluble in hot dilute HCl and H_2SO_4. It was amorphous, but could be dissolved in benzene-ligroine and separated on cooling; it was analysed after repeating this process three times. m.p. 150-160°

Analysis:

3.710 mg subst. gave ... 3.19 mg. H_2O;

5.260 mg subst. gave ... 0.254cc, 750mm, 22°

Found: 71.2% C
9.6% H
5.5% N

Calc. $C_{29}H_{46}O_4N_2$: 71.7% C
9.4% H
5.7% N

$(C_{25}H_{40}O_2N_2 \cdot 2CH_3CO)$

9. Acid Hydrolysis of Aposolanocapsidine

45 mg aposloanocapsidine were heated in a sealed tube with 2.5 cc alcohol and 2.5 cc HBr (S.G.1.49) for four hours at 160°. After concentration in vacuo water was added and the suspension shaken out with ether. The residue (35 mg) was amorphous and only partly soluble in boiling ligroin. The/

The substance was once more collected and again heated in a sealed tube with 2cc alcohol and 4 cc HBr for six hours at 200-210. The reaction product was worked up in the same way as before, the product (15 mg) was insoluble in ligroin and could not be crystallised and purified. The experiment could not be repeated owing to lack of material.

Oxidation of Solanocapsidine with Potassium Ferri-cyanid.

60 mg solanocapsidine hydrochloride were dissolved in methyl alcohol and 200 mg KOH in methyl alcohol and 0.5 cc of a 33% potassium ferri-cyanide solution were added. Then enough methyl alcohol and water was added to bring everything in solution and the mixture was shaken for one hour. The solution was then concentrated in vacuo and extracted with ether. The ether residue consisted chiefly of solanocapsidine unchanged, 20 mg could be isolated as acetone compound, m.p. 231, mixed m.p. with acetone compound showed no depression

Oxidation of Solanocapsidine with Copper

50 mg solanocapsidine were mixed with 100 mg copper powder and heated at 11 mm slowly up to 300°. Then the tube was connected with the high vacuum, but only traces distilled out. The copper

was/

was extracted with alcohol, the residue and the distillate dissolved in acetone. On evaporation an amorphous substance was obtained in bad yield which had qualities similar to aposolanocapsidine. It gave no phenylhydrazone.

Precipitation Test of Solanocapsidine with Digitonine

10 mg solanocapsidine were dissolved in 10 cc alcohol and 10 cc of 1% alcoholic digitonine solution was added. Then 2 cc of water were added and the solution which remained clear was left standing. After a day traces of fine precipitate had formed which could not be isolated.

10. Solanocapsine and its salts.

200 mg solanocapsine were mixed with dry sodium sulphate and extracted in a soxleth for twenty four hours with ether. Only 60 mg had gone into solution. The same mixture was further extracted with chloroform; 120 mg went into chloroform in six hours. The ether and chloroform solution were extracted separately with dilute HCl, the acidic solutions were basified and filtered. The residues on both filters were dissolved in benzene and precipitated/

precipitated with ligroin. This was repeated several times and both products were analysed although they had the same properties and melted both at about 305.

In a great number of experiments attempts were made to crystallise the base or one of its salts. Gold salt, platinum salt, methiodide, perchlorate, picrate, flavianate were amorphous.

0.3 g solanocapsidine were dissolved in dilute acetic acid and 6 cc 10% potassium chromate solution was added: a thick yellow precipitate resulted (400 mg). Dissolved in hot 90% alcohol; nothing crystallised on cooling, nothing after adding more water. After adding 1 cc of 10% potassium chromate solution a crystallisate appeared which could be recrystallised from 25% alcohol, but only on adding new chromate solution every time. It was analysed.

Solanocapsine:

1.420 mg subst. gave ... 3.610 mg CO_2; 1265 mg H_2O

3.211 mg subst. gave ... 0.170 cc, 750 mm, 16.5°

1.896 mg subst. gave ... 4.865 mg CO_2
1,560 mg H_2O

Found: 69.3; 69.9% C.
10.0; 9.4% H
6.2; % N

Calc. $C_{25}H_{40}O_4N_2$: 69.4% C
9.3% H
6.5% N

($C_{26}H_{42}O_4N_2$: 70.0% C
9.4% H
$C_{26}H_{44}O_4N_2$: 69.7% C
9.8% H
6.3% N

Zerewitinoff (M = 432, $C_{25}H_{40}O_4N_2$) 3.97; 4.00

4 active Hydrogens.

11. Acid Hydrolysis Experiments with Solanocapsine

In several experiments solanocapsine was heated in sealed tubes with 30-70% HBr in alcohol for 4-18 hours at 150°-220°. The solution was then diluted with water, basified and filtered. The base on the filter gave soluble hydrochlorides and hydrobromides in contradistinction to the salts of solanocapsidine and the base could not be crystallised. The mother liquors were tested for sugars but Molisch and Fehling tests were negative.

12. Selenium Dehydrogenation of Solanocapsine.

3 g solanocapsine were mixed with 10 g selenium and heated in a sealed tube for 14 hours at 320-340°. On opening the tube a smell of ammonia could be detected apart from the strong hydrogen selenide smell. A liquid in the tube proved to be water. The whole content of the tube was ground to a fine powder and mixed with sodium sulphate (anhydrous) and sodium carbonate (anhydrous); the mixture was extracted with ether in a soxleth for twenty four hours. The red florescent ether solution was extracted with dil HCl and water, then dried and evaporated. The red oil which remained behind was distilled in a microdistillation flask at the high vacuum. Four fractions could be separated/

separated. The first fraction came between 100° and 150°. The second fraction came between 160 and 170°, a yellow oil with strong florescence which crystallised soon. The third fraction came about 20 degrees higher and chrystallised too, the fourth fraction came between 210 and 250 while the bath had to be very much over heated.

This experiment was repeated three times, with 3, 2 and 1.7 g solanocapsine as starting material.

Six experiments under slightly different conditions were carried out. In three experiments open tubes were used instead of sealed ones; in the other three experiments the sealed tubes were heated for six or twenty-two hours or at a temperature of 360° for part of the time. In these experiments no fraction 2 and only traces of fraction 3 could be isolated.

The crystals which separated in the yellow oil of fraction 2 could be collected on porous pot. Yield 8 mg in the first experiment, 18 mg the second time and 18 mg the third time from 1.7 g solanocapsine. The substance could be recrystallised from alcohol, the crystals always showed a blue-violet flourescence, m.p. 123°. The substance was analysed.

The/

The mixed m.p. with methyl cyclopenteno phenanthrene was 230°.

Equal amounts of hydro carbon (1.5 mg) and trinitrobenzene were boiled together with a few drops of alcohol. On cooling beautiful yellow crystals separated which could be recrystallised from alkohol. m.p. 147°, mixed m.p. with trinitrobenzene comples of Diels' hydrocarbon: 148°.

Traces of hydrocarbon were boiled together with picric acid in alcohol. After evaporation a reddish crystallisate was collected which melted at 117° (m.p. of picrate of Diels' hydrocarbon 117°).

Fraction 3 contained much oil and not very much crystallisate. From 67 mg. destillate only 2 mg. could be isolated crystalline. The crystals always retained some oil on their surface which could not be removed by recrystallisation. On boiling with charcoal, the hydrocarbon was absorbed on the surface and only the oil was in the filtrate. The m.p. was therefore difficult to determine; it was above 150°.

On treating crude crystallisates of this fraction with trinitrobenzene two different products could be isolated. One product which crystallised in dark red prisms melted at 168-170°; it was only isolated in traces and could not be recrystallised. The other product crystallised in golden-orange coloured needles which melted at 130°. It was recrystallised repeatedly. It could not yet be identified.

As mentioned before the ether extracts of the selenium dehydrogenation products were shaken out with dilute HCl to remove the basic substances. All those solutions which contained much resins were poured together, heated after the addition of about one-fourth of the volume of absolute alcohol, and filtered. The filtrate was steam distilled, nothing distilled/

distilled over. Then the solution was basified; a strong basic smell appeared. The cloudy solution was again steam distilled, the destillate showed the basic smell very strongly; it was cloudy at the beginning and reacted alkaline to litmus. The steam destillate was extracted with ether, the ether was dried and after evaporation the residue was distilled at 14 mm. At 90-120° a yellow oil distilled which did not crystallise. It smelt very strong. It was not very soluble in water. Phenolphthalein was not coloured red, but methylred could be used as indicator. 25 mg. were neutralised by 1.6 cc of n/10 sulphuric acid.

25 mg. base were dissolved in dilute sulphuric acid and picrolonic acid was added in aqueous solution. A precipitate was formed which solidified on standing, but was not crystalline. It melted at 80-85.

No precipitate was formed in aqueous solution with platinum chloride. After evaporation of the solvents the residue was scratched with a glass rod in a trace of methyl alcohol. The salt solidified. It melted at 178.

The base in alcohol-ether yielded a crystalline picrate.

13)/

13) Experiments with Solanine.

1. Preparation of Solanidine from Solanine.

10 g solanine puriss. cryst. Merck were the starting material.

6 g solanine were hydrolysed according to Schöpf.

They were dissolved in 16. 5 cc abs. Alk., 27.5 cc water and 5 cc HCl conc were added and the solution was boiled on the waterbath for three hours. After half an hour the crystalline hydrochloride of solanidine separated. It was filtered after cooling. Yield: 2.8 g.

1.27 g of the crude hydrochloride was boiled with 12.5% methyl alcoholic KOH in 20 cc of methyl alcohol, water was added at intervals, the methyl alcohol being allowed to distill off.

The precipitate was filtered after cooling (1.17 g) and recrystallised from much acetone. 700 mg with a m.p. of 216° were obtained.

2. Oxidation of Solanidine with $KMnO_4$

100 mg solanidine were dissolved in pyridin and allowed to stand for eight hours with 100 mg $KMnO_4$ at room temperature. No acid or neutral substances could be isolated.

The experiment was repeated with acetone as solvent and with different periods of oxidation and different/

different temperatures. From all mother liquors an amphoteric acid could be collected in very bad yield. It could not be crystallised. It was soluble in sodium carbonate and strong HCl. On boiling with strong HCl it precipitated and was then insoluble. It was soluble in ether when neutral. The ester could not be obtained crystalline either.

3. Ozonisation of Solanidine.

90 mg solanidine were dissolved in glacial acetic acid and ozonised for three hours. Water was added and the solution was warmed on the water bath extracted with ether, basified and again extracted with ether. A small quantity of an amorphous base could be isolated but not crystallised.

[Another 1.5 g solanidine hydrochloride was transformed into the free base as indicated above.]

200 mg solanidine were ozonised in glacial acetic for about 1½ hours: 130 mg of a base were obtained. The amorphous substance reduced Trommer and Ag-ions. The iodoform test was weak but positive. The base distilled at about 200° in vacuo. No semicarbazone or oxime could be prepared by boiling the base with semicarbaride acetate or hydroxylamine acetate for half an hour. Picrate was not crystalline/

crystalline. The base, in contradistinction to the starting material was easily soluble in cold dilute HCl.

4. Zinc Dust Distillation of Solanidine.

70 mg solanidine were well mixed with Zn dust and distilled with an open flame. The brownish distillate was collected, extracted with ether and the ether shaken out with dil. HCl. Only traces of a base with a strong smell reminding of coniine and of non-basic substances which showed a very strong fluoresence, could be obtained.

50 mg solanidine were mixed with 500 mg Zn dust and distilled in vacuo (12 mm) at about 250°. The yellow oily distillate crystallised and was collected together with a sublimate which had filled the whole length of the tube. Both products proved to be solanidine.

50 mg solanidine were mixed with 500 Zn dust and filled in a tube through which a slow current of hydrogen passed. It was heated to 300-350 (without vacuum) and not much of a yellow oil distilled out which partly solidified. The crystals were collected on a porous plate and recrystallized from acetone, M.p. 164°. The appearance and the melting point indicated an identity with solanthren (dehydro solanidine) but the material was insufficient for an analysis. The experiments had to be stopped owing to lack of starting material.

PART III.

SUMMARY.

SUMMARY.

Solanocapsine and solanocapsidine, the alkaloids of Solanum pseudocapsicum have been investigated. Solanocapsine appears to have the empirical formula $C_{25}H_{40}O_4N_2$. On selenium dehydrogenation it yields methylcyclopentenophenanthrene (Diels' hydrocarbon); from this the fundamental similarity of its carbon skeleton to that of the sterols is inferred.

Solanocapsidine is shown to have the empirical formula $C_{25}H_{42}O_2N_2$. In addition to a tertiary hydroxyl group it contains an amino- and an imino group. Two of these three groups are so situated in the molecule that they yield a condensation product with acetone. The second oxygen atom of solanocapsidine is probably present in the form of an ether linkage. Several derivatives and oxydation products have been obtained and analysed.

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