2. Solanum *Alkaloids. Part II. Solasonine.*

By LINDSAY H. BRIGGS, ROBERT P. NEWBOLD, and NORMAN E. STACE.

Further analyses now support formulæ $C_{45}H_{73}O_{16}N$ and $C_{27}H_{43}O_2N$ for the glycosidic alkaloid solasonine (*ex S. sodomæum*) and its free base solasodine, respectively. The difference between the glycoside and the free base leads to the formulation of solasonine analogously to solanine by the union of the trisaccharide containing rhamnose, galactose, and glucose units with one molecule of solasodine and not two as suggested by Oddo. Solasodine now differs from solanidine only by an extra oxygen atom and, like it, contains the steroid nucleus and resembles most other steroids in possessing one hydroxyl group in a *cis*-position at C_3 and a double bond at C_5–C_6. It forms a monoacetyl derivative soluble in acids, *dihydrosolasodine* on catalytic hydrogenation with palladised charcoal, and adds on two bromine atoms in acetic acid solution. Dehydration with alcoholic hydrogen chloride yields $\Delta^{3:5}$-solasodiene with an ultra-violet absorption spectra characteristic of double bonds in different rings. The nitrogen is not tertiary as previously suggested, but combined with the second oxygen atom or the related carbinol-amine as a quaternary hydroxide. The action of nitrous acid yields a quaternary *nitrite*, which is an anhydro-salt identical with the so-called azosolasodine of Oddo. Methyl and ethyl iodide both react, forming the hydriodide in both cases and not the methiodide and ethiodide as suggested previously. Hydrogenation of solasodine and solasodiene with a platinum oxide catalyst yields tetrahydrosolasodine (dihydro*chano*solasodanol) and *hexahydrosolasodiene* (*dihydro*chano*solasodan*) respectively by saturation of the normal double bonds and further, it is suggested, by opening up of the heterocyclic rings. A full formula for solasonine embodying these results is proposed.

FROM the green fruit of *Solanum sodomæum* ("Dead Sea Apple") a glycosidic alkaloid has been isolated by Oddo and Colombano (*Gazzetta*, 1905, **35**, i, 27), Romeo (*ibid.*, 1905, **35**, ii, 579), and Soldaini (*Boll. Chim. Farm.*, 1905, **44**, 769, 808, 843), which is hydrolysed by dilute acids to a mixture of sugars and a basic aglycone. Both the glycosidic base and the free base differed from the corresponding compounds, solanine and solanidine respectively, obtained from *S. tuberosum* (potato) and other *Solanum* species by various workers (cf. Henry, "The Plant Alkaloids," 1939, p. 642) and to differentiate them Oddo proposed the names solanine-s for the glycosidic base and solanidine-s for the free base. To avoid this awkward nomenclature, Rochelmeyer (*Arch. Pharm.*, 1937, **275**, 336) has renamed these compounds solasonine and solasodine respectively.*

Over a period of thirty years papers by Oddo and co-workers on the constitution of solasonine have appeared (Oddo and Caronna, *Ber.*, 1936, **69**, 283, and earlier papers) based on the formulæ $C_{54}H_{96}O_{18}N_2,H_2O$ for the glycosidic base and $C_{18}H_{31}ON$ for the aglycone, solasodine. Recent analyses (Briggs, *Nature*, 1939, **144**, 247) support formulæ $C_{45}H_{73}O_{16}N$ and $C_{27}H_{43}O_2N$ for solasonine and solasodine respectively, confirmed in the latter case by Rochelmeyer (*Arch. Pharm.*, 1939, **277**, 329). The discrepancy between the present formulæ and those suggested by Oddo places a different interpretation on the experimental work of the latter.

In the first place, Oddo found that glucose, galactose, and rhamnose, besides solasodine, were produced by the hydrolysis of solasonine. From the molecular formulæ of the two bases he concluded that these three sugars were combined together with two molecules of solasodine, thus:

$C_{18}H_{30}ON$	$-C_6H_{12}O_5$	$-O-C_6H_{12}O_5$	$-O-C_6H_{12}O_4$	$-O-C_{18}H_{30}N,H_2O$ ($C_{54}H_{96}O_{18}N,H_2O$)
solasodine	glucose	galactose	rhamnose	solasodine

Since the formula $C_{45}H_{73}O_{16}N$ now proposed for solasonine differs from that of solasodine, $C_{27}H_{43}O_2N$, by 18 carbon atoms, it is clear that solasonine is built up analogously to solanine from these three sugars and only one molecule of solasodine, thus:

$C_6H_{11}O_4-O-$	$C_6H_{10}O_4$	$-O-C_6H_{10}O_4$	$-O-C_{27}H_{42}ON$ ($C_{45}H_{73}O_{16}N$)
rhamnose	galactose	glucose	solasodine

The order of the three sugars is based partly on Oddo's work and on analogy with the order of the sugars in solanine (Zemplén and Gerecs, *Ber.*, 1928, **61**, 2294; Oddo and Caronna, *ibid.*, 1934, **67**, 446). Solasonine does not react with phenylhydrazine or with hydroxylamine, so it would appear that all the

* Oddo also referred to the bases solanine and solanidine from *S. tuberosum* as solanine-t and solanidine-t, but Rochelmeyer (*loc. cit.*) has suggested altering these names to solatunine and solatubine, respectively, indicative of their origin. We agree with Henry (*op. cit.*) that this alteration is both confusing and unnecessary—the simplest procedure being to eliminate the suffix t. Other workers had already introduced a satisfactory nomenclature for the degradation products of solanidine (cf. Soltys and Wallenfels, *Ber.*, 1936, **69**, 811) based on the normal steroid nomenclature.

sugar molecules are united through their potential aldehyde structures. To the authors' knowledge the trisaccharide forming the glycosidic moiety of solasonine does not occur elsewhere in the plant kingdom other than in the *Solanum* genus.

It may be suggested in passing that, since solasodine differs from solanidine only by an additional oxygen atom and since also solasonine and solanine are similarly built up from the same sugars, the older formula for solanine should be replaced by $C_{45}H_{73}O_{15}N$ of the partial structure

$C_6H_{11}O_4$	$-O-C_6H_{10}O_4$	$-O-C_6H_{10}O_4$	$-O-C_{27}H_{42}N$ ($C_{45}H_{73}O_{15}N$)
rhamnose	galactose	glucose	solanidine

The formula $C_{27}H_{43}O_2N$ now proposed for solasodine is supported by analyses of the free base, its salts and a number of derivatives. Solasodine gives analytical figures agreeing with the formula $C_{27}H_{45}O_3N$ when normally dried for combustion, but with $C_{27}H_{43}O_2N$ when more vigorously dried. This water of crystallisation is only lost with difficulty from solasodine and most of its derivatives. On biochemical grounds a compound containing 27 carbon atoms is also to be preferred to the formula $C_{26}H_{43}O_3N$ originally suggested (Briggs, *J. Amer. Chem. Soc.*, 1937, **59**, 1404, 2467; cf. Saiyed and Kanga, *Proc. Indian Acad. Sci.*, 1936, **4**, *A*, 255), since there are no well-authenticated steroid derivatives containing 26 carbon atoms with the exception of the bases solanocapsine and solanocapsidine (Barger and Fraenkel-Conrat, J., 1936, 1537), to which the same argument also probably applies.

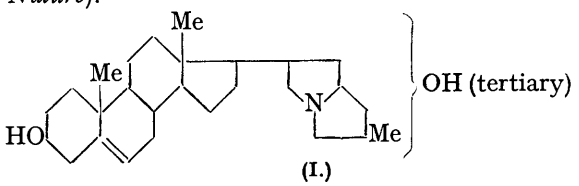
On selenium dehydrogenation, solasodine yields pyrrole bases and methyl*cyclo*pentenophenanthrene, thus indicating its steroid structure (Rochelmeyer, *Arch. Pharm.*, 1936, **274**, 543).

According to Oddo solasodine contains two active hydrogen atoms (Zerewitinoff determination) and forms an amorphous diacetyl derivative. Since it gave by the action of nitrous acid a compound "azosolasodine" containing a further nitrogen atom, Oddo concluded, on the basis of the formula $C_{18}H_{31}ON$, that solasodine contains both a hydroxyl and a secondary amino-group. We have confirmed the fact that completely dry solasodine contains two active hydrogen atoms. We have also prepared "azosolasodine" of the same melting point, but find that, when this is treated with dilute aqueous or alcoholic ammonia, solasodine is regenerated, thus indicating the salt-like character of "azosolasodine." This at first suggested that the nitrogen is tertiary, which was apparently confirmed by the facile action of methyl and ethyl iodide to yield quaternary salts, m. p. 286° (decomp.) and 284° (decomp.), respectively. Moreover, Simon's reaction (*Compt. rend.*, 1897, **125**, 536) for secondary amines is negative with solasodine (and also solasoline). A Herzig–Meyer estimation indicates the absence of a methylimino-group (and incidentally methoxy- and ethoxy-groups) and, since no alkyl groups other than methyl are known to be attached to tertiary nitrogen atoms in naturally occurring alkaloids, it is concluded that the nitrogen forms part of two rings.

To explain the presence of two active hydrogen atoms in solasodine, both oxygen atoms must be present as hydroxyl groups. A carbonyl group is excluded by the fact that solasodine may be recovered by decomposition of the Grignard compound in the Zerewitinoff estimation. Solasodine forms a monoacetyl derivative, m. p. 195° (Briggs, *Nature*, 1939, **144**, 247; Rochelmeyer, *Arch. Pharm.*, 1939, **277**, 329), which is readily soluble in dilute acids, thus confirming the presence of one hydroxyl group. Solasodine gives a precipitate with digitonin (Rochelmeyer, *Arch. Pharm.*, 1937, **275**, 336, and present work), whereas the acetyl compound does not. This places the hydroxyl which can be acetylated in position 3 in the *cis*-position to the methyl group on C_{10}. It was suggested by one of us that the remaining hydroxyl group, since it is not acetylated, is probably tertiary.

Solasodine is unsaturated, forming a dihydro-derivative and a dibromo-derivative by addition (see later). It must therefore contain one double bond, provisionally placed, by analogy with other steroids, at C_5–C_6.

On the above evidence, and assuming a cholesterol carbon skeleton and one point of attachment of the basic structure to the homocyclic portion, the structure (I) was suggested by one of us (Briggs, *Nature*).



(I.)

Further evidence has now confirmed some of these conclusions, but modifications and corrections have also to be made.

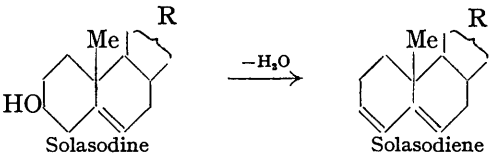
Hydrogenation of solasodine in acetic acid solution, a palladium–norite catalyst being used, yields *dihydrosolasodine*, $C_{27}H_{45}O_2N$, m. p. 209·5—211·5°. Acid conditions are necessary for the hydrogenation, as solasodine is not reduced in alcoholic solution, but is immediately reduced on the addition of cinnamic acid added to test the activity of the catalyst. The presence of one normal carbon-to-

carbon double bond is confirmed by the fact that addition of bromine in acetic acid solution ceases after the addition of two atoms.

Rochelmeyer (*Arch. Pharm.*, 1939, **277**, 329), using the more reactive platinum oxide catalyst, obtained a tetrahydrosolasodine, $C_{27}H_{47}O_2N$, m. p. 286—288·5°. We had already prepared the same compound of slightly higher melting point, by the same procedure. Since dihydrosolasodine does not give the ordinary tests for unsaturation with tetranitromethane, antimony trichloride or bromine, we regard this tetrahydro-derivative in the meantime as being formed by saturation of the ordinary double bond and ring fission of the heterocyclic rings (see below for further details).

Oddo and Cesaris have reported (*Gazzetta*, 1914, **44**, ii, 191) that the action of alcoholic hydrogen chloride on solasodine yields solasodine ether, $(C_{18}H_{30}N)_2O$, m. p. 176—177°, by loss of water between two molecules. We have now shown that methyl- or ethyl-alcoholic hydrogen chloride removes one molecule of water intramolecularly with the formation of solasodiene,* $C_{27}H_{41}ON$, m. p. 169·5—170·5°. The compound of higher melting point, 176—177°, was also isolated by Rochelmeyer (*Arch. Pharm.*, 1937, **275**, 336) by working up the mother-liquors in the purification of solasodine obtained by the acid hydrolysis of solasonine. He regarded this as a new alkaloid, solanosodine, but we prefer to regard it as a by-product in the hydrolysis, since we have also obtained the same product on working up the mother-liquors after the hydrolysis of pure solasonine [cf. also the formation of solanidiene (solanthrene) during the hydrolysis of solanine; Soltys and Wallenfels, *loc. cit.*]. The melting point of solasodiene obtained by other workers is higher than that of our product, probably owing to an impurity, since the melting point of our product was unchanged by repeated crystallisation from different solvents and traces of solasodine actually raised the melting point. That the hydroxyl group is lost from the C_3 atom during this process is shown by the fact that solasodiene no longer gives an insoluble digitonide.

The original double bond in solasodine was provisionally placed at C_5–C_6 by analogy with the majority of other steroid compounds, including the proof of this position of the double bond in solanidine by Rochelmeyer (*Ber.*, 1938, **71**, 226). This position has been confirmed by the following facts. That the double bonds are conjugated is indicated by a positive Rosenheim reaction (*Biochem. J.*, 1929, **23**, 47; cf. also Schoenheimer and Evans, *J. Biol. Chem.*, 1936, **114**, 567) and an immediate intense crimson coloration with antimony trichloride in chloroform solution. The ultra-violet absorption spectrum has been observed by Rochelmeyer (*Arch. Pharm.*, 1939, **277**, 329), who found a maximum at 2340 A., log ε 4·34; we also had measured the absorption spectrum, obtaining a slightly higher value at 2345 A., log ε 4·44. Both values are consistent with conjugated double bonds existing in separate rings. *i.e.*, in C_3–C_4 and C_5–C_6 positions.



Solasodine Solasodiene

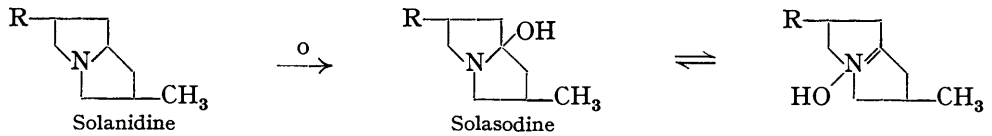
Such double bonds should have the *trans*-configuration and therefore would not be expected to add on maleic anhydride in the normal manner, a fact which we have confirmed experimentally. Also addition of bromine in acetic acid solution ceases after the addition of two atoms (see later). Velstra (*Nature*, 1939, **144**, 485) has shown that $\Delta^{3:5}$-cholestadiene with conjugated double bonds in separate rings also adds on only two atoms of bromine.

Rochelmeyer (*Arch. Pharm.*, 1939, **277**, 329) has found that oxidation of solasodine with Oppenauer's reagent yields a ketone, $C_{27}H_{41}O_2N$, m. p. 184—185°, which we regard as Δ^4-solasoden-3-one, the double bond shifting in the process to the αβ-position in relation to the carbonyl group, *i.e.*, to the C_4–C_5 position, as is usual in such oxidations in the steroid series. This compound no longer gives a precipitate with digitonin, thus indicating the oxidation of the C_3 hydroxyl to a carbonyl group. We have also obtained a compound, m. p. 186°, which is probably identical with Δ^4-solasoden-3-one, by oxidising solasodine with copper powder (cf. Diels, Gädke, and Körding, *Annalen*, 1927, **459**, 21, and a similar experiment on solanidine by Schöpf and Hermann, *Ber.*, 1933, **66**, 298; Rochelmeyer, *ibid.*, 1938, **71**, 226). This compound gives a positive test with Zimmermann's reagent (*Z. physiol. Chem.*, 1935, **233**, 257; 1936, **245**, 47; Kaziro and Shimada, *ibid.*, 1937, **249**, 220), thus confirming the presence of a carbonyl group at C_3.

It can thus be stated with some degree of certainty that one hydroxyl group of solasodine is at position 3 and the normal carbon-to-carbon double bond is at C_5–C_6.

* We suggest the name solasodan for the basic saturated but unsubstituted structure of solasodine, which on this nomenclature would become solasodenol but we prefer to retain the original name for the parent substance.

It was originally suggested that the second hydroxyl in solasodine was tertiary owing to the fact that only a monoacetyl derivative is formed. Various tests for tertiary alcohols were negative, *e.g.*, with Denigès's reagent (*Compt. rend.*, 1898, **126**, 1145, 1277), and a tertiary alcohol should be dehydrated at least as readily as the secondary alcoholic group at C_3 by the action of alcoholic hydrogen chloride (*loc. cit.*) or aluminium oxide at 250° (Rochelmeyer, *Arch. Pharm.*, 1939, **277**, 329), but in both cases the only product is solasodiene. It is now clear, however, that the second hydroxyl group is present combined with the nitrogen as a quaternary hydroxide or the related carbinol-amine and we suggest that the basic portion of solasodine may be formulated as follows, a possible mode of phytosynthesis being from mild oxidation of solanidine (cf. the formation of ψ-strychnine and ψ-brucine from the true bases; Leuchs, *Ber.*, 1937, **70**, 1543; Leuchs and Tessmar, *ibid.*, p. 2369):



Solanidine Solasodine

We would emphasise that the basic ring structure of solanidine suggested by Clemo, Morgan, and Raper (J., 1936, 1299) is the only structure possible, provided that two assumptions are made—that the carbon skeleton is the same as in cholesterol and that the basic ring structure has only one point of attachment to the steroid ring system. In the first case there is no exception in the whole of the steroid field to the fact that the carbon side chains of C_{27} sterols whose structures are known are all the same as in cholesterol. Further, the formation of Diels's hydrocarbon on selenium dehydrogenation of both solanidine (Soltys and Wallenfels, *Ber.*, 1936, **69**, 811) and solasodine (Rochelmeyer, *Arch. Pharm.*, 1936, **274**, 543) supports the second assumption. For these reasons we have included the same structure in solasodine.

In contrast with the berberine alkaloids and ψ-strychnine, solasodine appears to behave in many of its chemical reactions as the quaternary hydroxide rather than the related carbinolamine or ketone-amine. Solasodine is alkaline to litmus in alcoholic solution. The compound formed by the action of acetic acid and sodium nitrite on solasodine gives the analytical figures required for $C_{27}H_{42}O_3N_2$, indicating the loss of water in the process. We regard this compound, the " azosolasodine (azosolanidine-s) " of Oddo, as a quaternary *nitrite* rather than the nitrosoamine of the related ketone-amine, since treatment with dilute aqueous ammonia regenerates solasodine. The compound is not formed when hydrochloric acid replaces acetic acid in the preparation, solasodine hydrochloride being formed instead. Oddo and Caronna had also observed (*Ber.*, 1936, **69**, 283) that reduction of " azosolasodine " with zinc and acetic acid, followed by treatment with alkali, regenerates solasodine. In this case it is suggested that the main action is concerned not with the reducing agent but with the alkali treatment.

It has now been shown that the facile action of methyl iodide and ethyl iodide on solasodine does not yield the methiodide and ethiodide respectively, but in both cases forms solasodine hydriodide. The product from both these reactions has the same melting point as the hydriodide, the melting point of which is not depressed on admixture. It must be noted, however, that depression of melting point must be interpreted with caution in this series where the salts melt with decomposition and it has been observed that a mixture of the hydrobromide, m. p. 309·5° (decomp.), with the hydrochloride, m. p. 316·5—317·5° (decomp.), has m. p. 314—314·5° (decomp.). However, treatment of the products formed by the action of methyl iodide and ethyl iodide on solasodine with dilute aqueous ammonia regenerates solasodine. The action of methyl iodide to give the hydriodide is more simply explained through the quaternary hydroxide, *i.e.*, $\geqslant N\cdot OH + CH_3I \longrightarrow \geqslant NI + CH_3\cdot OH$, rather than the carbinol-amine, which would be expected to give an *N*-methylated product as in the action of methyl iodide on ψ-strychnine (Blount and Robinson, J., 1932, 2305; Leuchs, *Ber.*, 1937, **70**, 2455).

A further reaction of solasodine as the quaternary hydroxide is afforded by the results of bromination. In chloroform solution, exactly three atoms of bromine per mole of solasodine are required before decoloration ceases, and in acetic acid solution decoloration ceases when two atoms of bromine have been added. In the first case, two atoms of bromine are utilised in addition to the normal double bond and the extra atom of bromine is possibly acquired by reaction of the quaternary hydroxide to form the quaternary bromide and hypobromite: $2 \geqslant N\cdot OH + Br_2 \longrightarrow \geqslant NBr + \geqslant N\cdot OBr + H_2O$. In the second case the quaternary hydroxide is first converted into the acetate and this portion of the molecule no longer reacts with bromine (cf. bromination of diketonucidine, and its perchlorate; Holmes and Robinson, J., 1936, 603). The products from both methods of bromination could not be crystallised satisfactorily from non-aqueous solvents, but when crystallised from a mixture of water, acetone, and alcohol containing a little hydrobromic acid, both formed the same *hydrobromide* (needles), m. p. 303°

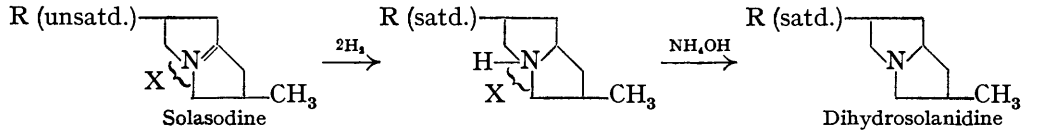
(decomp.), undepressed on admixture. Analysis, however, indicated the loss of one atom of bromine, probably by hydrolysis during the crystallisation (cf. cholesterol dibromide; Lifschütz, *Z. physiol. Chem.*, 1919, **106**, 271).

Similarly, bromination of solasodiene in chloroform solution required three atoms before decoloration ceased, and in acetic acid solution absorption of bromine ceased after the addition of two atoms. The product from the first reaction was isolated as a colourless hydrobromide, m. p. 205—209°, which, however, rapidly darkened in air and was not analysed. Further experiments on this phase are in hand.

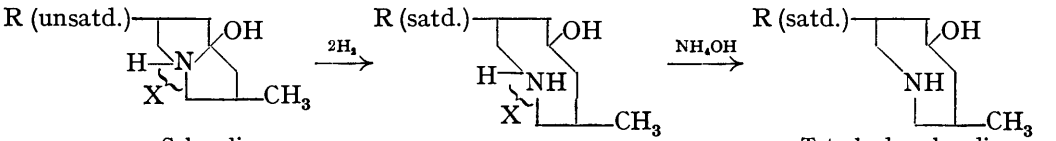
In an attempt to replace both hydroxyl groups by chlorine atoms, to produce a dichloro-derivative which on reduction might possibly give solanidene under the previous formulation, the action of thionyl chloride on solasodine in pyridine solution was investigated. Although all the reactants were thoroughly dried, solasodine hydrochloride formed immediately when they were mixed in the cold—a result which is more readily explained by means of the quaternary hydroxide form.

The existence of solasodine as a stable quaternary hydroxide rather than the related carbinol-amine is supported by the fact that it does not form an ethyl or methyl ether when it is crystallised from ethyl or methyl alcohol, neither does it form an acetone compound in the same way. However, should solasodine exist under certain conditions as a carbinolamine, the hydroxyl in this form must be tertiary as indicated and not secondary as in the two alternative positions, since solasodine and acetyl solasodine were recovered unchanged after attempted oxidation with potassium ferricyanide and chromic acid respectively.

The normal salts, with the exception of the nitrite, appear to be, not anhydro-salts, but derivatives of the carbinol-amine (cf. ψ-strychnine) and in some cases contain further water of crystallisation which is not lost on normal drying. This conclusion is based partly on analyses of salts of solasodine and those of solauricidine (see following paper). The results of catalytic hydrogenation with platinum oxide are also best explained on this basis. As mentioned previously, solasodine with this catalyst yields tetrahydrosolasodine (dihydro*chano*solasodanol), m. p. 286—288·5°, which still retains two oxygen atoms. If solasodine did not function as a carbinol-amine, reduction might be expected to give dihydrosolanidine, thus :

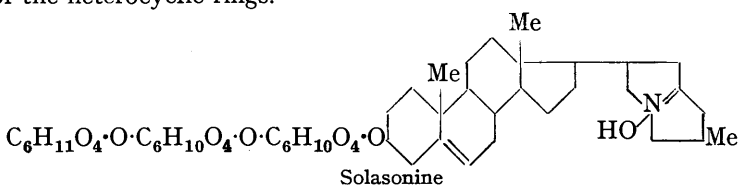


and it is therefore suggested that hydrogenation proceeds through the carbinol-amine by a type of Emde degradation as follows :



In dihydrosolasodine the ordinary carbon-to-carbon double bond has been saturated and the basic portion of the molecule still functions as a quaternary hydroxide, since the actions of hydrogen iodide and ethyl iodide both yield the same quaternary iodide, m. p. 284° (decomp.), which regenerates dihydrosolasodine on treatment with dilute aqueous ammonia.

Solasodiene on hydrogenation with a platinum oxide catalyst forms *hexahydrosolasodiene* (*dihydrochanosolasodan*), $C_{27}H_{47}ON$, m. p. 184—186°, which still retains one oxygen atom. It is suggested that here also hydrogenation proceeds through the carbinol-amine, saturation of the normal conjugated double bonds and fission of the heterocyclic rings.



Solasonine

As a basis for further degradative work we therefore propose the above quaternary hydroxide form for solasonine, and investigations on the heterocyclic portion of the molecule are in active progress.

There are marked differences in the chemical behaviour of the berberine type of alkaloids and ψ-strychnine and still further differences between ψ-strychnine and solasodine—differences which may possibly be due to the size of the rings concerned or more probably to the number of double bonds present.

Rochelmeyer (*Arch. Pharm.*, 1939, **277**, 329) has recorded a series of colour reactions of solasodine and solasodiene with reagents usually applied to sterols. As previously reported (*Nature*), it has now been found that the bases in this series give a series of beautiful colour reactions in acetic acid–sulphuric acid solution in the presence of substituted aromatic aldehydes, especially those substituted in the *p*-position. The addition of the aldehydes considerably modifies the colour reactions produced by acetic acid–sulphuric acid alone, which is a modified Liebermann reaction (*Ber.*, 1885, **18**, 1803).

An exceptionally fine play of colours is also given by solasodine in acetic acid–sulphuric acid solution in the presence of resorcinol; this serves as a very easy method of distinguishing solasodine from solanidine, which gives quite a different coloration.

An unsuccessful attempt has been made to evaluate these colour reactions by carrying out the reaction with sterol derivatives such as cholesterol and digitonin, with heterocyclic bases such as carbazole, pyrrole, and nicotine, and the alkaloid jacobine, which contains the pyrrolizidine nucleus similar to that now proposed for solasodine (cf. Henry "The Plant Alkaloids," 1939, pp. 636—642; Clemo and Metcalfe, J., 1936, 606; Prelog and Heinbach, *Ber.*, 1939, **72**, 1101). All these give characteristic intense colorations differing from those of solasodine or solanidine. We would suggest that other workers in a more fortunate position in regard to the variety of steroid compounds available might investigate these colour reactions further (cf. Woker and Antener, *Helv. Chim. Acta*, 1939, **22**, 1309; Scherrer, *ibid.*, p. 1329). The hydro-derivatives of solasodine give much less intense colorations, which are therefore connected with the unsaturated centre as well as the basic portion.

Tutin and Clewer (J., 1914, **105**, 565) isolated from *S. angustifolium* a glucosidic base, solangustine, which is hydrolysed by acid to glucose and solangustidine, $C_{27}H_{43}O_2N$. Since the latter is now isomeric with solasodine, the two aglycones are probably very closely related.

Experimental.

Extraction of Solasonine.—Besides the method described in Part I (preceding paper) for the isolation of solasonine the following wet process has been devised, obviating the use of alcohol. Green berries of *S. sodomæum* were minced and pressed, and the juice kept for 4—8 hours. The clear supernatant liquor was drawn off by suction and filtered in a gravity filter with frequent changes of the filter paper. The filtrate was boiled and similarly filtered while hot. The clear filtrate was boiled, and ammonia passed through it until it was alkaline; boiling was then continued for 5 minutes. After cooling, the granular precipitate was collected by suction, dissolved in 2% acetic acid, and reprecipitated with ammonia from the boiling solution. This treatment was continued until the material was pure; solasodine was then obtained as described in Part I. Crystallisation from aqueous alcohol or dioxan effects little change in the m. p. of the crude hydrolysis product, which contains solasodiene, but after crystallisation from methyl alcohol the m. p. rises sharply and has now been raised to 200·5—202·5°.

In addition to the analyses for solasonine and solasodine recorded in Part I analyses already recorded (Briggs, *J. Amer. Chem. Soc.*, 1937, **59**, 1404, 2467) have been recalculated on a C_{27} basis for solasodine.

Solasonine (*ex S. aviculare*) (Found: C, 60·2; H, 8·4; N, 1·5. Calc. for $C_{45}H_{73}O_{16}N,\frac{1}{2}H_2O$: C, 60·5; H, 8·3; N, 1·6%).

A sample of solasonine kindly presented by Professor Oddo was submitted for analysis without preliminary drying (Found: C, 56·1, 56·0; H, 8·6, 8·7; N, 1·8, 1·7. Calc. for $C_{45}H_{73}O_{16}N,4\frac{1}{2}H_2O$: C, 56·0; H, 8·5; N, 1·45%).

Solasodine (*ex S. aviculare*) (Found: C, 78·3; H, 10·4; N, 3·3. Calc. for $C_{27}H_{43}O_2N$: C, 78·54; H, 10·5; N, 3·4%).

A sample of solasodine from Professor Oddo was analysed without preliminary drying (Found: C, 75·2, 75·1; H, 10·5, 10·6; N, 3·3, 3·4. Calc. for $C_{27}H_{43}O_2N,H_2O$: C, 75·2; H, 10·4; N, 3·2%).

M (micro-Rast), 388, 375. Calc. for $C_{27}H_{43}O_2N$: *M*, 413.

In a determination of active hydrogen (Zerewitinoff method) in anisole solution, 66·89 mg. of solasodine, previously dried for several hours in a high vacuum at 100° over phosphoric oxide, evolved 7·30 c.c. of methane at 25°/750 mm., corresponding to 1·91 atoms of active hydrogen per mole. By working up the reaction mixture in the usual way, pure solasodine was recovered.

Determinations of the CMe value (Kuhn–Roth method) for solasodine gave 2·39 and 2·12 groups per mole. In *M*/5000-alcoholic solution solasodine gives general absorption only and therefore does not contain a centre capable of producing a selective effect.

Acetylsolasodine.—A mixture of solasodine (500 mg.), dry pyridine (5 c.c.), and acetic anhydride (1 c.c.) was refluxed for 2 hours. After cooling, the mixture was poured into water and made alkaline with ammonia. The precipitated acetyl derivative (520 mg.), after successive crystallisation from dioxan–water, ethyl acetate,

and ethyl acetate–alcohol, formed narrow plates, m. p. 195° (Found: C, 76·6; H, 10·4; N, 3·4. Calc. for $C_{29}H_{45}O_3N$: C, 76·5; H, 9·9; N, 3·1%). Rochelmeyer (*Arch. Pharm.*, 1939, **277**, 329) records m. p. 193—194°. The acetyl derivative was immediately soluble in dilute acetic acid and did not give an immediate precipitate with digitonin.

3 : 5-*Dinitrobenzoylsolasodine.*—Solasodine (100 mg.), dissolved in dry pyridine (1 c.c.), was refluxed for ½ hour with a solution of 3 : 5-dinitrobenzoyl chloride (200 mg.) in dry pyridine (3 c.c.). The precipitate which formed was collected after dilution with water, treated with dilute aqueous ammonia, and crystallised from alcohol, forming yellowish needles, m. p. 191·5—193°.

Phenyl *iso*thiocyanate failed to form a derivative with solasodine, and α-naphthyl *iso*cyanate brought about dehydration, yielding *s*-dinaphthylurea and a basic product, m. p. 165°, undepressed on admixture with solasodiene.

Action of Methyl Iodide and Ethyl Iodide on Solasodine.—When solasodine (200 mg.) and methyl iodide (1 c.c.) in dry xylene (2 c.c.) were heated to boiling, a colourless precipitate formed within a few minutes (yield, 250 mg. after 2 hours). The product crystallised from methyl alcohol–ether in colourless prisms, m. p. 285—286° (decomp.), undepressed by solasodine hydriodide, m. p. 291° (decomp.) (Found: C, 59·2; H, 8·1; I, 23·4. Calc. for $C_{27}H_{43}O_2N,HI$: C, 59·9; H, 8·1; I, 23·5%).

The action of ethyl iodide on solasodine (previously dried for several hours over phosphoric oxide at 110°) under similar conditions also gave the hydriodide, m. p. 284° (decomp.), undepressed by the authentic hydriodide (Found: C, 60·6; H, 8·2; N, 2·7; I, 24·5, 22·1. Calc. for $C_{27}H_{43}O_2N,HI$: C, 59·9; H, 8·1; N, 2·6; I, 23·5%). The iodine values recorded here represent ionic iodine obtained by direct titration according to Leipert's method (Pregl Festschrift, 1929, p. 266).

In both cases, treatment with hot dilute aqueous ammonia, followed by crystallisation from methyl alcohol, regenerated pure solasodine, m. p. 198—200°, undepressed by an authentic specimen.

Action of Nitrous Acid on Solasodine.—Sodium nitrite (170 mg.), dissolved in the least amount of water, was added dropwise to a solution of solasodine (500 mg.) in cold alcohol (5 c.c.) and glacial acetic acid (0·25 c.c.). The gelatinous precipitate formed was collected and crystallised repeatedly from 80% alcohol and finally from alcohol to yield the quaternary *nitrite*, m. p. 260·5—262·5° (decomp.) (Found: C, 73·2; H, 9·6; N, 6·2. $C_{27}H_{42}O_3N_2$ requires C, 73·3; H, 9·6; N, 6·3%). Oddo and Caronna (*loc. cit.*) record m. p. 260° (decomp.) for this product, referred to as "azosolasodine." Treatment with hot dilute aqueous ammonia regenerated solasodine.

Action of Thionyl Chloride on Solasodine.—Dry solasodine (1·16 g.), dissolved in dry pyridine (43 c.c.), was cooled in ice, and redistilled thionyl chloride (1 g.) added slowly; a precipitate formed immediately. After standing at 0° for 17 hours, the product was poured into water (200 c.c.). The product so formed was crystallised repeatedly from 80% alcohol to give solasodine hydrochloride in needles, m. p. 307—308° (decomp.) (Found: C, 70·5, 70·4; H, 9·9, 9·9; Cl, 7·5, 7·5. Calc. for $C_{27}H_{43}O_2N,HCl,\frac{1}{2}H_2O$: C, 70·6; H, 9·9; Cl, 7·7%). The product gave the test for ionic halogen with silver nitrate and after treatment with hot dilute aqueous ammonia regenerated solasodine, which crystallised from 80% alcohol in hexagonal plates, m. p. 199—200°, undepressed by an authentic specimen.

Hydrogenation of Solasodine.—(a) *With a palladium–norite catalyst.* Solasodine (500 mg.), dissolved in alcohol, was subjected to hydrogenation at the ordinary temperature and pressure with a palladium–norite catalyst freshly prepared from palladium chloride (50 mg.) and ignited norite (500 mg.). Hardly any absorption occurred in 5 hours. To test the activity of the catalyst, cinnamic acid (250 mg.) in alcoholic solution was added. Absorption was then extremely rapid, the theoretical amount of hydrogen required for the cinnamic acid being absorbed within 5 minutes; absorption then proceeded more slowly for some hours. The catalyst was removed, the filtrate concentrated somewhat, and the hot solution made alkaline with ammonia. *Dihydrosolasodine* crystallised in needles; after recrystallisation from 75% alcohol and dioxan–water it formed hexagonal plates, m. p. 208·5—210·5° (Found: C, 78·3; H, 10·9. $C_{27}H_{45}O_2N$ requires C, 78·0; H, 10·9%). $[\alpha]_D^{25°}$ − 63·5° (l = 0·5 dcm., c = 8·824 in chloroform). Dihydrosolasodine was also obtained more conveniently in glacial acetic acid solution at 45 lb. pressure. In this case, the acetic acid solution was concentrated by distillation in a vacuum before treatment with ammonia. Dihydrosolasodine did not give the test with Denigès's reagent for tertiary alcohols.

The hydriodide, precipitated in colourless prisms on addition of a concentrated solution of potassium iodide to dihydrosolasodine dissolved in alcohol–acetic acid, had m. p. 284° (decomp.) after recrystallisation from alcohol.

(b) *With a platinum oxide catalyst.* Solasodine could not be hydrogenated in alcoholic solution at atmospheric pressure with Adams's platinum oxide catalyst, acid conditions again being necessary.

Solasodine (400 mg.), dissolved in a mixture of alcohol (5 c.c.) and glacial acetic acid (1 c.c.), was hydrogenated at 46 lb. pressure for several hours in the presence of Adams's catalyst (200 mg.). The solution was then decanted from the catalyst, concentrated somewhat, and made alkaline with ammonia. The product could be separated by repeated crystallisation into possibly dimorphic forms, (i) thick plates, m. p. 292·5—296·5°, from alcohol–water, and (ii) octahedral crystals from dioxan–water, m. p. 285—291°, not depressed on admixture with (i). Rochelmeyer records m. p. 285·5—288° for this tetrahydro-derivative (Found: C, 77·8,

77·9; H, 11·2, 11·3. Calc. for $C_{27}H_{47}O_2N$: C, 77·6; H, 11·35%). Hydrogenation could also be effected in glacial acetic acid solution. Tetrahydrosolasodine (dihydrosolasodanol) does not react with tetranitromethane or with antimony trichloride.

Action of Ethyl Iodide on Dihydrosolasodine.—Dihydrosolasodine (100 mg.), dissolved in dry benzene or xylene (2 c.c.), was refluxed for 15 hours with ethyl iodide (1 c.c.). The colourless precipitate which formed crystallised from 50% alcohol in needles, m. p. 281° (decomp.), raised to 283° on admixture with the hydriodide. Treatment of a suspension of the product (80 mg.) in water (6 c.c.) with amomnia at 100° for 2 hours regenerated dihydrosolasodine, which crystallised from alcohol in plates, m. p. 209·5—211·5°, undepressed by an authentic specimen.

Bromination of Solasodine.—(a) *In chloroform.* When bromine in chloroform solution was added dropwise to a cooled solution of solasodine (400 mg.) in the same solvent, decoloration ceased only when three atoms of bromine had been added. The chloroform was distilled off in a vacuum; the residue crystallised on trituration with alcohol. When recrystallised from a mixture of water, alcohol and acetone containing a little hydrobromic acid, it formed colourless needles, m. p. 303° (decomp.).

(b) *In glacial acetic acid.* 8·5 C.c. of a solution of bromine in glacial acetic acid (containing 160 mg., 1 mol.) were added dropwise to a cooled solution of solasodine (431 mg., 1 mol.) in the same solvent (4 c.c.). Decoloration occurred almost immediately and addition of a further 0·5 c.c. of the bromine solution gave a permanent coloration. Sodium bromide (515 mg., 5 mols.) was then added, followed by water until precipitation of the *hydrobromide* was complete. The product (450 mg.), on crystallisation from a mixture of water, alcohol, and acetone containing a little hydrobromic acid, formed colourless needles, m. p. 302° (decomp.), undepressed by the bromination product obtained in (a). The product gave an immediate test for ionic bromine with silver nitrate solution (Found: Br, 24·5. $C_{27}H_{43}O_2NBr,HBr$ requires Br, 27·9%).

Dehydration of Solasodine.—Solasodine could not be dehydrated satisfactorily by heating with anhydrous formic acid or with potassium hydrogen sulphate, but was smoothly dehydrated with methyl- or ethyl-alcoholic hydrogen chloride. Solasodine (200 mg.) was dissolved in cold methyl alcohol (20 c.c.), and dry hydrogen chloride passed in until the mixture had increased in weight by 20%. When heated to 100°, the solution cleared and later needles of solasodiene hydrochloride separated, m. p. 318° (decomp.) after washing with ether. When a suspension of the hydrochloride was treated with hot dilute aqueous ammonia and cooled, solasodiene was obtained, which after repeated crystallisation from aqueous dioxan, methyl alcohol and ethyl alcohol of various concentrations formed plates of constant m. p. 169·5—170·5° (Found: C, 82·0; H, 10·5; N, 3·6. Calc. for $C_{27}H_{41}ON$: C, 82·0; H, 10·5; N, 3·5%). $[\alpha]_D^{25°} - 86·9°$ ($l = 0·5$ dcm., $c = 2·6016$ in chloroform). In determinations of active hydrogen (Zerewitinoff method) in anisole solution, 49·43 mg. and 41·78 mg. of solasodiene evolved 2·96 c.c. and 2·55 c.c. of methane at N.T.P. respectively, corresponding to 1·04 and 1·08 atoms of active hydrogens per mole. Solasodiene gave a yellow coloration with tetranitromethane, an immediate intense red coloration with antimony trichloride in chloroform solution, and a positive Rosenheim reaction for conjugated double bonds.

Solasodiene (7·1 mg.) in alcohol (4·5 c.c.) was added to digitonin (31·4 mg.) in warm water (1·5 c.c.); a precipitate did not form in 48 hours.

A mixture of solasodiene (100 mg.) in benzene (2·5 c.c.) and thrice sublimed maleic anhydride (1 g.), heated for 24 hours at 100° with exclusion of moisture, became deep red. A crystalline adduct could not be obtained (cf. Rochelmeyer, *Arch. Pharm.*, 1937, **275**, 336).

In alcoholic solution (M/5000) solasodiene exhibited a marked band at λ 2345 A., log ε 4·44, together with an inflexion at *ca.* λ 2400 A., log ε *ca.* 4·17, consistent with the presence of two conjugated double bonds distributed over two rings (cf. Rochelmeyer, *Arch. Pharm.*, 1939, **277**, 329; *Ber.*, 1938, **71**, 226).

Hydrogenation of Solasodiene.—Solasodiene (1 g.) in glacial acetic acid (40 c.c.) was hydrogenated at 48 lb. pressure in the presence of platinum oxide (0·2 g.) for 5 hours. The catalyst was then filtered off, most of the solvent removed by vacuum distillation, and the residue made alkaline with ammonia and heated for 3 hours at 100°. After crystallisation from dioxan–water and aqueous alcohol the product formed flat needles, m. p. 184—186° (Found: C, 80·8, 80·85; H, 11·85, 11·9. $C_{27}H_{47}ON$ requires C, 80·7; H, 11·8%). $[\alpha]_D^{25°} - 18°$ ($l = 0·5$ dcm., $c = 6·424$ in chloroform).

Hexahydrosolasodiene (*dihydro*chano*solasodan*) did not react with tetranitromethane, antimony trichloride or Denigès's reagent.

Bromination of Solasodiene.—A solution of bromine in chloroform was gradually added to a solution of solasodiene (100 mg.) in the same solvent (2 c.c.) at 0°. Decoloration ceased after the addition of 3 atoms of bromine; the solvent was then evaporated, yielding a brown product which quickly darkened in air. One drop of concentrated hydrobromic acid was added to a solution of the product in alcohol, followed by addition of water until precipitation occurred. The mixture cleared on warming and, on cooling, colourless crystals formed which after recrystallisation from 50% alcohol formed flat needles, m. p. 205—209°. The compound rapidly darkened in air and was not analysed.

When bromine in acetic acid solution was added dropwise to a cooled solution of solasodiene (200 mg.) in the same solvent, decoloration occurred almost instantly until two atoms of bromine had been added, absorption then taking place very slowly. A small amount of precipitate formed, which was not increased by addition

of water, and addition of sodium bromide solution failed to precipitate an insoluble hydrobromide as in the case of the bromination of solasodine.

Oxidation of Solasodine with Copper Powder.—A mixture of solasodine (200 mg.) and copper powder (300 mg.) was heated in a metal bath at 10 mm. pressure, a water-cooled finger condenser being placed about 1 cm. above the mixture. Above its m. p. the solasodine partly sublimed, but above 250—285° evolution of gas occurred. The sublimate was mixed with the residual copper, and the process repeated at 250—255°/0·01—0·02 mm. The brown glassy sublimate (180 mg.), when added to a 1% solution of *m*-dinitrobenzene and made alkaline with sodium hydroxide solution, gave a violet coloration. The product became crystalline on trituration with acetone, and on recrystallisation from the same solvent a small amount of unchanged solasodine was obtained and another product, m. p. 186°, corresponding to that of solasodenone obtained by Rochelmeyer (*loc. cit.*) by the oxidation of solasodine with Oppenauer's reagent.

Attempted Oxidation of Acetylsolasodine (With J. J. CARROLL).—Acetylsolasodine (1·47 g.) was dissolved in glacial acetic acid (30 c.c.) added dropwise; after 4 days the colour had changed from golden-yellow to dark green. Ammonia was added to the solution after dilution with water (120 c.c.) and the product was converted in alcoholic solution into the hydrochloride, which, on cooling, formed colourless crystals, m. p. 314°, of acetylsolasodine hydrochloride. The free base, obtained in the usual way by treatment with ammonia, had m. p. 193—195°, undepressed by admixture with the starting material.

Colour Reactions of Solasodine and Related Compounds.—When concentrated sulphuric acid (1 c.c.) is carefully added to a solution of solasonine or solasodine in hot alcohol (1 c.c.), a characteristic, intense greenish-yellow fluorescence is produced similar to that of heavy lubricating oil. This coloration is not given by solanine or solanidine.

A few mg. each of solasodine and the following aromatic aldehydes were mixed with concentrated hydrochloric acid and boiled. The colours produced were as follows: *p*-dimethylaminobenzaldehyde, pink (stable); vanillin, green—colourless—pink-bluish pink; piperonal, green—fades—bluish-pink on standing; *p*-nitrobenzaldehyde, faint pink, quickly fading; anisaldehyde, greenish-blue; *p*-hydroxybenzaldehyde, greenish-blue.

Benzaldehyde, salicylaldehyde, *o*-nitrobenzaldehyde and glucose were without action. Blank tests without the alkaloid were negative, and carbazole, indole, and nicotine with the same reagents gave as a rule magenta, scarlet and crimson colorations respectively.

Much more intense and more stable colorations were given when a few mg. of solasodine or a related compound and the following aldehydes were dissolved in acetic acid (1—2 c.c.), to which sulphuric acid (1—2 c.c.) was then carefully added. Characteristic colours developed at the interface, which changed on mixing, but the full variety of colour changes did not develop until the mixture was heated; many of them disappeared on dilution. The most intense and characteristic colour reaction of solasodine itself is given with resorcinol in the same acid solvent.

	Solasodine.	Solanidine.
p-Hydroxybenzaldehyde	Red/violet dichroic-purple-blue-pale violet/chocolate dichroic	Red-red/slight violet dichroic
Anisaldehyde	Red/green dichroic-violet/green dichroic-blue-purple	Red/greenish dichroic-crimson/slight blue dichroic
Vanillin	Red-violet-sepia (or depending on conditions of heating, green-blue-violet)	Dark brown-red-wine/slight dichroism of different shade
Resorcinol	Brown-brownish green-blue-purple-purple/violet dichroic-magenta-red/violet dichroic with chocolate fluorescence-cerise/brown fluorescence	Brown/green fluorescence

	Dihydrosolasodine.	Solasodiene.	Dihydro*chano*solasodan.
p-Hydroxybenzaldehyde	Brown-green-bluish green-blue-fades	Purple-violet-blue fades to colourless/light brown dichroic-brownish red	Red-deep red-brown
Anisaldehyde	Greenish brown-green fades to a dirty brown/colourless dichroic-red dichroic-intense crimson	Violet-purple-blue-bluish green-green-purple.	Green/brown dichroic-red/green dichroic-crimson-crimson purple
Vanillin	Yellowish green-green-dirty brown-brownish green-brown	Dirty brown-green-blue (fades)-light purple-dirty brown	Brown-dark brown
Resorcinol	Brown/green fluorescence-pinkish red/green fluorescence-light brown/slight green fluorescence	Green-blue-purple/brown fluorescence-red/brown fluorescence-red	Darkens with a green fluorescence

Piperonal, *p*-dimethylaminobenzaldehyde, *p*-methoxybenzaldehyde and *p*-nitrobenzaldehyde also give a similar series of colour reactions different in each case. Solasodine alone with the acetic acid–sulphuric acid reagent gives a brown/violet dichroic-violet-wine-brown coloration, and the aldehydes themselves either do not give a coloration or only brown to red colorations with the exception of anisaldehyde, which gives the following series of colours, brownish green-brown-red/green dichroic-crimson-crimson/slight purple dichroic.

For comparison the same colour reactions were carried out with cholesterol, digitonin, jacobine, carbazole, pyrrole and nicotine. In each case different colorations were produced, but the most intense colorations

were brought about with *p*-hydroxybenzaldehyde and anisaldehyde and only these and those with resorcinol are recorded.

	Cholesterol.	Digitonin.	Jacobine.
p-Hydroxybenzaldehyde	Crimson-violet-purple	Brown-red-brown	Yellow-brown-red-dark brown
Anisaldehyde	Purple	Brown-red-brown	Brown/green dichroic-brown-red-dark brown-intense purplish red
Resorcinol	Brown-red-brown	Red/brown dichroic-red brown	Brown-red-red/green fluorescence
	Carbazole.	Pyrrole.	Nicotine.
p-Hydroxybenzaldehyde	Crimson	Very intense reddish brown	Red
Anisaldehyde	Crimson-violet	Very intense reddish brown	Red
Resorcinol	Light brown	Light brown	Light brown

Piperidine with the same reagents gives no coloration or only a light brown coloration.

The carbon, hydrogen and nitrogen analyses are by Dr.-Ing. A. Schoeller and Dr. Burger.

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