

**The constituents of the rhizome and roots of *Caulophyllum thalictroides* /  
by Frederick B. Power and Arthur H. Salway.**

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THE CONSTITUTION  
OF THE BRIDGEMAN  
CAULOPHYLLUM

BY  
FREDERICK B. POWER  
AND  
ARTHUR H. SALWAY

*(From the Transactions of the Chemical Society)*

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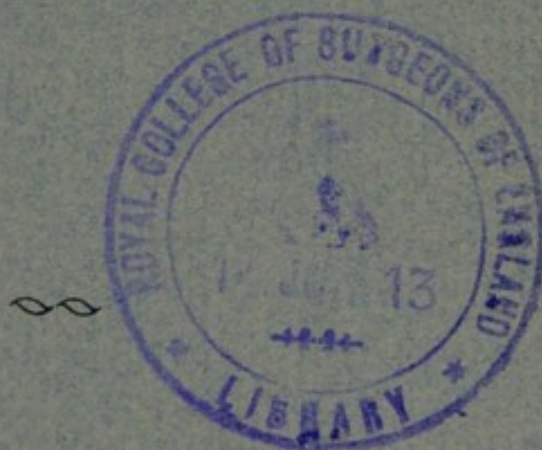
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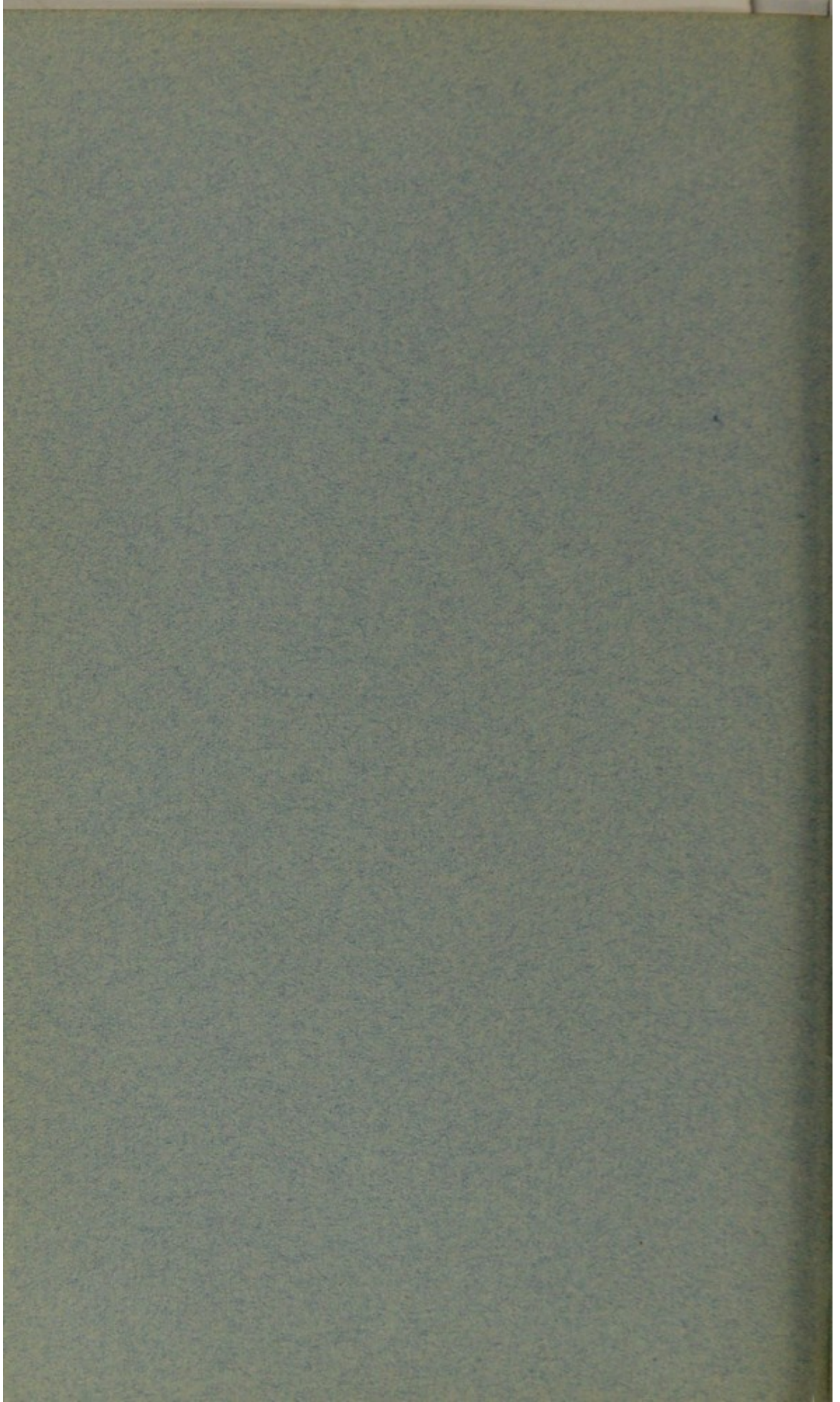
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XXIII.—*The Constituents of the Rhizome and Roots of Caulophyllum thalictroides.*

By FREDERICK BELDING POWER and ARTHUR HENRY SALWAY.

*Caulophyllum thalictroides* (Linné), Michaux (Nat. Ord., *Berberidaceæ*), commonly known, among other names, as "Blue Cohosh," is a plant indigenous to North America, and is the only known species of the genus. Although the rhizome and roots of this plant, or preparations therefrom, are considerably employed in medicine, the drug is not at present recognised by any of the national Pharmacopœias.

*Caulophyllum* appears to have been first chemically examined by F. F. Mayer (*Amer. J. Pharm.*, 1863, **35**, 99), who stated it to contain a saponaceous principle and a colourless alkaloid, although the latter was not actually isolated. A. E. Ebert (*ibid.*, 1864, **36**, 203) also observed the presence of a substance analogous to saponin, but failed to obtain an alkaloid. It was, however, definitely shown by J. U. Lloyd ("Drugs and Medicines of North America," Vol. II., 1887, p. 153, and *Proc. Amer. Pharm. Assoc.*, 1893, **41**, 115) that *caulophyllum* contains an appreciable amount of an alkaloid, which he designated "caulophylline," but its composition was not determined. Although he did not succeed in crystallising the base, the hydrochloride was described as forming acicular crystals. The present authors have obtained the respective alkaloid in a pure, crystalline state, and have proved it to be methylecystisine.

A saponin-like substance was also isolated from *caulophyllum* by Lloyd (*loc. cit.*, 1887, p. 151), who was the first to obtain it in a crystalline and apparently pure state, and found it to be a glucoside. This compound, the general properties of which were described, was termed "leontin," with reference to an old botanical name (*Leontice*) of the plant. Several analyses of the substance, conducted by H. Trimble, led the latter to assign to it the formula  $C_{16}H_{26}O_5 \cdot H_2O$ . Although from the results of the present investigation the percentage composition of the compound appears to have been accurately determined, thus affording evidence of its purity, yet the formula deduced therefrom is incorrect. A consideration of the products of hydrolysis, which have now for the first time been determined, has shown the compound to be represented by the formula  $C_{54}H_{88}O_{17} \cdot 4H_2O$ , and it is proposed to designate it *caulosaponin*. It has, furthermore, been shown that *caulophyllum* contains a second saponin-like glucoside, which, although present in much smaller proportion than that above mentioned, has also been obtained in a crystalline state and completely characterised. It



possesses the formula  $C_{66}H_{104}O_{17}$ , and has been termed *caulophyllo-saponin*.

Gilbard (*Analyst*, 1911, **36**, 270) has suggested a test for the identification of the so-called "caulophyllin," an impure resinous product obtained from *caulophyllum*, which is used to some extent medicinally. The colour reaction upon which this test depends is due to the presence of the above-mentioned glucosides.

A summary of the substances isolated in the present investigation, and their derivatives, together with some physiological tests, is given at the end of this paper.

#### EXPERIMENTAL.

The material employed for this investigation consisted of the rhizome and roots of *Caulophyllum thalictroides* (Linné), Michaux. It was perfectly authentic, having been specially gathered in North Carolina, and kindly supplied to us by Professor J. U. Lloyd, of Cincinnati, Ohio, to whom our best thanks may here be expressed.

A small portion (10 grams) of the material was first tested for the presence of an alkaloid, and with a positive result.

In order to ascertain whether an enzyme were present, 100 grams of the ground material were macerated with water at the ordinary temperature for two days. To the expressed and filtered liquid about twice its volume of alcohol was added, when a gelatinous precipitate was produced. This was collected, washed with a little alcohol, and dried in a vacuum over sulphuric acid, when it amounted to 0.3 gram. It gave the biuret reaction, and slowly hydrolysed amygdalin, thus proving the presence of an enzyme.

Another portion (25 grams) of the ground material was completely extracted in a Soxhlet apparatus with various solvents, when the following amounts of extract, dried at  $100^{\circ}$ , were obtained:

Petroleum (b. p. $35-50^{\circ}$ ) extracted	0.15 gram	=	0.60 per cent.
Ether	0.65	"	= 2.60 "
Chloroform	0.81	"	= 3.24 "
Ethyl acetate	0.42	"	= 1.68 "
Alcohol	4.90	"	= 19.60 "
Total .....	6.93 grams	=	27.72 per cent.

For the purpose of a complete examination, 22.37 kilograms of the ground material were completely extracted with hot alcohol, when, after the removal of the greater portion of the alcohol, 8.28 kilograms of a dark-coloured, viscid extract were obtained.

Two kilograms of the above-mentioned extract were mixed with water, and the mixture distilled in a current of steam. The distillate was extracted with ether, and the solvent removed, when



about 1 gram of a pale yellow essential oil was obtained. This had a pleasant odour, and yielded the colour reaction for furfuraldehyde.

After the above operation there remained in the distillation flask a dark-coloured aqueous liquid (A), which contained in suspension a considerable quantity of grey, amorphous material (B), and, on cooling, the whole formed a soft, gelatinous mass. The separation of the amorphous material from the aqueous liquid was effected by agitating the mixture with hot amyl alcohol, which dissolved all the solid substance, with the exception of a very small amount of indefinite material which was removed by filtration. The amyl alcohol extract was subsequently washed with water, the washings being added to the main portion of the aqueous liquid.

#### *Examination of the Aqueous Liquid (A).*

The aqueous liquid, which had been treated with amyl alcohol as above described, was next extracted many times with ether. The ethereal liquids were united, washed, dried, and the solvent removed, when 2 grams of a viscid, brown residue were obtained. This was agitated with alcohol, when a sparingly soluble solid separated, which, when crystallised from a mixture of pyridine and alcohol, was obtained in colourless leaflets, melting and decomposing at 275—280°. The substance yielded an acetyl derivative melting at 169°, which, together with its colour reactions, indicated it to be citrullol,  $C_{23}H_{45}O_2(OH)_3$ . It was subsequently obtained in larger amount from an ethereal extract of the above-mentioned grey, amorphous material, and was then completely identified.

The aqueous liquid, after extraction with ether as above described, frothed strongly on agitation, and evidently contained some saponin-like substance which had not been removed by the previous treatment with amyl alcohol. With the object of effecting the complete removal of this substance, the aqueous liquid was again shaken repeated with hot amyl alcohol, these extracts being then united, washed with a little water, and the solvent removed by distillation under diminished pressure. A quantity (25 grams) of a dark brown solid was thus obtained, which was glucosidic, and possessed the characters of a saponin. It was dissolved in alcohol, and the solution kept for some time, when a colourless, crystalline substance separated, which, after recrystallisation from alcohol, melted and decomposed at 250—255°. This compound was found to be identical with a glucoside which was obtained in larger amount from the amorphous material extracted by the first treatment of the aqueous liquid with amyl alcohol, and has been designated *caulosaponin*. It is fully described in connection with the examination of the grey, amorphous product (B).



The aqueous liquid was next treated with a slight excess of basic lead acetate, which produced a relatively small amount of a dark brown precipitate. This was collected, washed, suspended in water, and decomposed by hydrogen sulphide, but no definite substance could be isolated from it. The filtrate from the basic lead acetate precipitate was deprived of lead by means of hydrogen sulphide, and the clear, filtered liquid concentrated under diminished pressure to a convenient volume. It then readily responded to the tests for an alkaloid, and was also found to contain a quantity of reducing sugar. From a small portion of the liquid, *d*-phenylglucosazone (m. p. 210°) was prepared.

*Isolation of Methylecystisine, C<sub>11</sub>H<sub>13</sub>ON<sub>2</sub>(CH<sub>3</sub>).*

In order to isolate the alkaloid from the above-mentioned aqueous liquid, the entire remaining portion of the latter was made alkaline with sodium hydroxide and repeatedly extracted with chloroform. The chloroform extracts were united, washed with a little water, dried, and the solvent removed, when about two grams of a viscid, brown residue were obtained, which gave the reactions for an alkaloid. For the purpose of purifying this material, it was dissolved in dry chloroform, and a current of dry hydrogen chloride passed into the solution, when a colourless hydrochloride of the base was precipitated. This was collected, and crystallised from a mixture of alcohol and ethyl acetate, when it separated in colourless prisms, decomposing at 250—255°. The air-dried substance was analysed with the following results:

0.0967 gave 0.1726 CO<sub>2</sub> and 0.0594 H<sub>2</sub>O. C=48.7; H=6.8.

0.1212 „ 10.3 c.c. N<sub>2</sub> at 20° and 757 mm. N=9.7.

0.1105 „ 0.1078 AgCl. Cl=24.1.

C<sub>12</sub>H<sub>18</sub>ON<sub>2</sub>Cl<sub>2</sub>.H<sub>2</sub>O\* requires C=48.8; H=6.8; N=9.5;  
Cl=24.1 per cent.

In order to obtain the free base, the hydrochloride was dissolved in a little water, the solution made alkaline with sodium hydroxide, and then extracted six times with chloroform. The united chloroform extracts were washed with a very small quantity of water, then dried, and the solvent removed. The residue, which soon solidified, was recrystallised from a mixture of benzene and light petroleum, when the base was obtained in colourless, prismatic needles, melting at 137°. For the purpose of its complete examination, the entire remaining portion of the original alcoholic extract of the drug was worked up in the manner already described. The

\* The water of crystallisation in this salt could not be directly determined, since the substance slowly loses hydrogen chloride on dehydration.



total amount of pure alkaloid thus obtained, calculated as the free base, was about 5 grams. It was analysed, and its molecular weight determined, with the following results:

0.1076 gave 0.2794 CO<sub>2</sub> and 0.0780 H<sub>2</sub>O. C=70.8; H=8.0.

0.1122 ,, 13.4 c.c. N<sub>2</sub> at 21° and 762 mm. N=13.6.

0.4666, in 27.23 benzene, gave  $\Delta t - 0.387^\circ$ . M.W.=221.

C<sub>12</sub>H<sub>16</sub>ON<sub>2</sub> requires C=70.6; H=7.8; N=13.7 per cent. M.W.=204.

The alkaloid was optically active, and a determination of its specific rotatory power gave the following result:

0.2256, made up to 20 c.c. with water, gave  $\alpha_D - 5^\circ 0'$  in a 2-dcm. tube, whence  $[\alpha]_D - 221.6^\circ$ .

A small amount of the alkaloid was dissolved in a known volume of *N*/10-sulphuric acid, and the excess of the latter titrated with *N*/10-barium hydroxide, using iodoeosin as indicator in the presence of ether.

0.1305 neutralised 6.4 c.c. *N*/10-H<sub>2</sub>SO<sub>4</sub>, which is the theoretical amount required for C<sub>12</sub>H<sub>16</sub>ON<sub>2</sub> as a monacidic base.

The alkaloid was readily soluble in water, alcohol, chloroform, or benzene, but less readily in ether. The aurichloride was obtained in golden-yellow needles, which decomposed at 205°.

0.1550 gave 0.1512 CO<sub>2</sub>, 0.0443 H<sub>2</sub>O, and 0.0561 Au. C=26.6;  
H=3.2; Au=36.2.

C<sub>12</sub>H<sub>17</sub>ON<sub>2</sub>,AuCl<sub>4</sub> requires C=26.5; H=3.1; Au=36.2 per cent.

The composition of the above-described alkaloid and its salts, together with its general characters, indicated it to be methylcytisine. This compound had not hitherto been known to occur in nature, although it has previously been prepared by the methylation of cytisine, C<sub>11</sub>H<sub>14</sub>ON<sub>2</sub>, an alkaloid found in the common laburnum (*Cytisus Laburnum*, Linné) and other species of *Cytisus*, as well as in various other plants. It represents the alkaloid previously obtained by J. U. Lloyd (*Proc. Amer. Pharm. Assoc.*, 1893, **41**, 115), and designated by him "caulophylline," as its composition had not then been determined. Methylcytisine *picrate* appears not to have previously been prepared. This salt crystallised from hot water in long, yellow needles, which sintered at about 200°, and melted completely at 228°.

Although the characters of the above-described alkaloid were in quite complete agreement with those of methylcytisine, as recorded in the literature (compare Buchka and Magalhães,\* *Ber.*, 1891, **24**, 678; Partheil, *Arch. Pharm.*, 1892, **230**, 448; and Rauwerda, *ibid.*, 1900, **238**, 484), a small amount of the latter compound was pre-

\* The melting point of 245°, as given by Buchka and Magalhães (*loc. cit.*), for methylcytisine, is obviously an error.



pared from a commercial specimen of cytisine for the purpose of comparison. It melted at  $135^{\circ}$ , and when mixed with the alkaloid from caulophyllum no depression of the melting point ensued. The identification of the last-mentioned alkaloid as methyleytisine was thus completely effected.

*Quantitative Determination of the Alkaloid in Caulophyllum.*—Having determined the composition and characters of the alkaloid in caulophyllum, it seemed desirable to formulate a method for ascertaining the proportion in which it exists in the drug. The following method of procedure was found to give satisfactory results:

Twenty grams of caulophyllum, in No. 60 powder, were introduced into a suitable flask, 100 c.c. of chloroform and 10 c.c. of aqueous sodium carbonate (10 per cent. solution) added, and the whole was vigorously shaken from time to time during a period of four hours. The mixture was then filtered, and 50 c.c. of the chloroform liquid (=10 grams of caulophyllum) transferred to a separator, in which it was vigorously shaken with 10 c.c. of *N*/10-sulphuric acid. After separating the acid liquid from the chloroform, the latter was again shaken with 10 c.c. of *N*/10-sulphuric acid. The two portions of acid liquid were united, extracted with 20 c.c. of ether, which removed a small quantity of emulsified chloroform, then made alkaline by the addition of 5 c.c. of aqueous sodium carbonate (10 per cent. solution), and agitated with three successive portions of chloroform of 20 c.c. each. The united chloroform extracts were washed twice with water, using each time 2 c.c. of the latter, and the chloroform then carefully removed by distillation. The residual alkaloid was dissolved in 10 c.c. of *N*/50-sulphuric acid, 10 c.c. of ether added, the solution transferred to a stoppered bottle, and the excess of sulphuric acid determined by titration with *N*/50-barium hydroxide, using iodoeosin as the indicator. It was thus found that 2.1 c.c. *N*/50-sulphuric acid were required to neutralise the alkaloid, and as it has already been shown that methyleytisine,  $C_{12}H_{16}ON_2$ , under the above conditions of titration, possesses the character of a monacidic base, the corresponding amount of alkaloid would be  $2.1 \times 0.00408$  or 0.0086 gram. This is equivalent to 0.086 per cent. of methyleytisine in the drug.

In a second assay of the caulophyllum, the digestion with chloroform and aqueous sodium carbonate was prolonged for twenty hours, but the process was otherwise conducted as before. The amount of alkaloid thus obtained was equivalent to 0.078 per cent. of the drug, and the two determinations may therefore be considered to agree within the limits of experimental error. From this result it was also apparent that the digestion of the drug for a period of more than four hours presents no advantage.



The accuracy of the above-described method for the quantitative determination of the alkaloid was controlled by dissolving 0.0098 gram of pure methylcytisine in 50 c.c. of chloroform, and treating this solution in precisely the same manner as the chloroform extract of the drug. The amount of alkaloid indicated by the final titration was 0.0096 gram.

*Examination of the Grey, Amorphous Material (B).*

As previously noted, the aqueous liquid remaining after the distillation of the original alcoholic extract with steam contained a quantity of grey, amorphous material in suspension, which was removed by extraction with hot amyl alcohol. This amyl alcohol solution was concentrated to a small bulk under diminished pressure, and a large volume of ether added, which precipitated a greyish-white solid.

*Isolation of a Crystalline Glucoside, Caulosaponin,  $C_{54}H_{88}O_{17}, 4H_2O$ .*

The above-mentioned greyish-white solid was collected, and amounted to 94 grams. It was dissolved in hot alcohol, and the solution kept for some time, when a crystalline, glucosidic substance was deposited. This was crystallised several times from alcohol, and was finally obtained in colourless, slender needles, melting and decomposing at 250—255°. The amount of pure substance isolated from 2 kilograms of the original alcoholic extract was 16 grams. For the purpose of its complete examination, a further and larger quantity was subsequently obtained by working up the remainder of the alcoholic extract in the manner already described:

0.1173, when heated at 115°, lost 0.0077  $H_2O$ .  $H_2O = 6.6$ .

0.1017 \* gave 0.2394  $CO_2$  and 0.0796  $H_2O$ .  $C = 64.2$ ;  $H = 8.7$ .

0.1074 \* „ 0.2520  $CO_2$  „ 0.0836  $H_2O$ .  $C = 64.0$ ;  $H = 8.6$ .

$C_{54}H_{88}O_{17}, 4H_2O$  requires  $H_2O = 6.7$  per cent.

$C_{54}H_{88}O_{17}$  requires  $C = 64.3$ ;  $H = 8.7$  „ „

A comparison of the composition and properties of this compound with those of the glucoside previously isolated by J. U. Lloyd, and described by him under the name of "leontin" (*Drugs and Medicines of North America*, Vol. II., 1887, p. 151), renders it evident that the substances are identical. In view of the fact, however, that the compound has now been completely characterised, and that, by an examination of its hydrolytic products, it has been shown to possess the formula  $C_{54}H_{88}O_{17}, 4H_2O$ , instead of  $C_{16}H_{26}O_5, H_2O$ , as originally assigned to it (*loc. cit.*), it is deemed desirable to give it the new and distinctive name of *caulosaponin*. This is the more

\* Anhydrous substance.



important as the name "leontin" appears also to have been given to a preparation of caulophyllum which does not represent the pure glucoside.

*Caulosaponin*,  $C_{54}H_{88}O_{17} \cdot 4H_2O$ , is insoluble in water, ether, chloroform, or benzene, but is moderately soluble in hot alcohol, although sparingly so in cold. It possesses phenolic properties, and dissolves readily in solutions of the alkali hydroxides. When the substance is dissolved in acetic anhydride, a little chloroform added, and subsequently a few drops of concentrated sulphuric acid, a purplish-red coloration is produced, which gradually fades. A solution of caulosaponin in water containing a little alcohol yields, on agitation, an abundant and persistent froth, and the substance is therefore a member of that class of compounds which have been designated as saponins. So far as known to us, only one other well-characterised substance of this class has previously been obtained in a crystalline form (compare *Arch. Pharm.*, 1912, 250, 427).

*Deca-acetylcaulosaponin*,  $C_{54}H_{78}O_{17}(CO \cdot CH_3)_{10}$ .—This derivative of caulosaponin was prepared by heating the latter with acetic anhydride for two hours. The mixture was then poured into water, and the precipitated solid collected, washed, and dried in a vacuum desiccator over sulphuric acid and solid potassium hydroxide. The product was thus obtained as a white powder, which melted at  $135-140^\circ$ . It was readily soluble in the usual organic solvents, but could not be crystallised:

0.1323 gave 0.3017  $CO_2$  and 0.0899  $H_2O$ . C=62.2; H=7.6.

$C_{74}H_{108}O_{27}$  requires C=62.2; H=7.6 per cent.

It is thus evident that caulosaponin contains ten hydroxyl groups.

#### *Hydrolysis of Caulosaponin.*

*Formation of Caulosapogenin*,  $C_{42}H_{62}O_2(OH)_4$ , and *Dextrose*.

Twenty grams of caulosaponin were dissolved in 500 c.c. of alcohol, then 150 c.c. of a 10 per cent. aqueous solution of hydrogen chloride added, and the mixture heated on a water-bath for several hours, when a crystalline hydrolytic product separated from the hot liquid. After removal of the alcohol in a current of steam, the mixture was filtered, the filtrate being set aside for the subsequent examination of the sugar. The crystalline product was well washed with water, and purified by recrystallisation from dilute pyridine. It was thus obtained in colourless, anhydrous, rhombohedral prisms, which decomposed at about  $315^\circ$ :

0.0893 gave 0.2474  $CO_2$  and 0.0806  $H_2O$ . C=75.6; H=10.0.

0.0791 ,, 0.2195  $CO_2$  ,, 0.0716  $H_2O$ . C=75.7; H=10.1.

$(C_7H_{11}O)_x$  requires C=75.7; H=9.9 per cent.



The molecular weight of the above-described compound could not be directly determined on account of its sparing solubility in suitable solvents. An examination of its derivatives showed, however, that it possesses the formula  $C_{42}H_{66}O_6$ , and that it contains four hydroxyl groups, one of which is phenolic. As it is a new compound, it is proposed to designate it *caulosapogenin*.

*Caulosapogenin*,  $C_{42}H_{62}O_2(OH)_4$ , is insoluble in water, chloroform, or benzene, and sparingly soluble in absolute alcohol, but more readily so in alcohol containing a little water. It also dissolves in aqueous alkali hydroxides in the presence of alcohol, and is therefore phenolic in character. When caulosapogenin is dissolved in acetic anhydride, a little chloroform added, and subsequently a few drops of concentrated sulphuric acid, a rose-red coloration is produced which gradually disappears. When a solution of the substance in aqueous alcohol is agitated, a copious frothing is produced, but the permanency of the latter is not so great as in the case of the glucoside itself.

*Tetra-acetylcaulosapogenin*,  $C_{42}H_{62}O_6(CO \cdot CH_3)_4$ .—This compound was prepared by heating caulosapogenin for some time with acetic anhydride, the solution being then concentrated and poured into water. The product, which soon solidified, was collected, washed well with water, and dried over sulphuric acid and solid potassium hydroxide, when it formed a white, amorphous powder, which melted at  $120^\circ$ . It was extremely soluble in the usual organic solvents, but could not be crystallised:

0.1040 gave 0.2743  $CO_2$  and 0.0866  $H_2O$ . C=71.9; H=9.2.

$C_{50}H_{74}O_{10}$  requires C=71.9; H=8.9 per cent.

*Diacetylcaulosapogenin*,  $C_{42}H_{64}O_6(CO \cdot CH_3)_2$ .—The above-described tetra-acetyl derivative, when heated with ammonium carbonate in the presence of alcohol, readily loses two acetyl groups. The resulting *diacetyl* compound crystallises from dilute alcohol in thin, colourless needles, which melt at  $160-162^\circ$ :

0.1221 gave 0.3288  $CO_2$  and 0.1036  $H_2O$ . C=73.4; H=9.4.

$C_{46}H_{70}O_8$  requires C=73.6; H=9.3 per cent.

Diacetylcaulosapogenin possesses phenolic properties, and yields a crystalline sodium derivative.

*Diacetylmonosodiocaulosapogenin*,  $C_{42}H_{63}O_6Na(CO \cdot CH_3)_2$ .—This compound is best prepared by agitating an ethereal solution of tetra-acetyl- or diacetyl-caulosapogenin with aqueous sodium carbonate, when the *sodium* derivative separates in colourless needles:

0.1818, when heated at  $115^\circ$ , lost 0.0094  $H_2O$ .  $H_2O=5.2$ .

0.1488 \* gave 0.0138  $Na_2SO_4$ . Na=3.0.

$C_{46}H_{69}O_8Na, 2H_2O$  requires  $H_2O=4.5$  per cent.

$C_{46}H_{69}O_8Na$  requires Na=3.0 per cent.

\* Anhydrous substance.



The number of acetyl groups in this sodium derivative was directly determined by heating the substance with a known volume of *N*/10-alcoholic sodium hydroxide, and titrating the excess of alkali with standard acid:

0.3191 gave on hydrolysis acetic acid equivalent to 8.45 c.c. *N*/10-NaOH.  $\text{CO}\cdot\text{CH}_3=11.4$ .

$\text{C}_{42}\text{H}_{63}\text{O}_6\text{Na}(\text{CO}\cdot\text{CH}_3)_2$  requires  $\text{CO}\cdot\text{CH}_3=11.1$  per cent.

*Tetrabenzoylcaulosapogenin*,  $\text{C}_{42}\text{H}_{62}\text{O}_6(\text{CO}\cdot\text{C}_6\text{H}_5)_4$ .—This compound was prepared by heating caulosapogenin in pyridine solution with benzoyl chloride for about an hour. The mixture was then poured into water, rendered slightly alkaline with sodium carbonate, and kept for some time, when the reaction product slowly solidified. It was collected and purified by crystallisation from a mixture of chloroform and alcohol, when the substance separated in well-formed, hexagonal prisms, melting at  $288^\circ$ . An analysis and a determination of its molecular weight gave the following results:

0.1040 gave 0.2946  $\text{CO}_2$  and 0.0735  $\text{H}_2\text{O}$ .  $\text{C}=77.3$ ;  $\text{H}=7.9$ .

0.5529 in 25.2 benzene gave  $\Delta t=0.102^\circ$ . M.W.=1076.

$\text{C}_{70}\text{H}_{82}\text{O}_{10}$  requires  $\text{C}=77.6$ ;  $\text{H}=7.6$  per cent. M.W.=1082.

The preceding results have thus served to establish the correctness of the formula assigned to caulosapogenin.

*Tetrabenzoylcaulosapogenin* is readily soluble in ether, chloroform, or benzene, but only sparingly so in water or alcohol. It does not possess the phenolic properties of the original substance. Its specific rotatory power was determined, with the following result:

0.3092, made up to 20 c.c. with chloroform, gave  $\alpha_D + 3^\circ 26'$  in a 2-dcm. tube, whence  $[\alpha]_D + 111.0^\circ$ .

*Caulosapogenin Monomethyl Ether*,  $\text{C}_{42}\text{H}_{65}\text{O}_5(\text{O}\cdot\text{CH}_3)$ .—This substance was prepared by heating caulosapogenin for several hours with alcoholic sodium hydroxide and methyl iodide. When crystallised from dilute alcohol, it separated in well-formed needles, melting at  $235^\circ$ :

0.1143 gave 0.3173  $\text{CO}_2$  and 0.1059  $\text{H}_2\text{O}$ .  $\text{C}=75.7$ ;  $\text{H}=10.3$ .

The number of methoxyl groups in the compound was determined by Perkin's modification of Zeisel's method:

0.1318 gave 0.0544 AgI.  $\text{MeO}=5.5$ .

$\text{C}_{42}\text{H}_{65}\text{O}_5(\text{OMe})$  requires  $\text{C}=75.9$ ;  $\text{H}=10.0$ ;  $\text{MeO}=4.6$  per cent.

The specific rotatory power of the substance was determined with the following result:

0.1412, made up to 20 c.c. with chloroform, gave  $\alpha_D + 1^\circ 3'$  in a 2-dcm. tube, whence  $[\alpha]_D + 74.4^\circ$ .



*Oxidation of Caulosapogenin.*

With the object of obtaining further information respecting the nature of caulosapogenin, a quantity (10 grams) of the latter was dissolved in aqueous potassium hydroxide with the addition of a little pyridine, and a 4 per cent. solution of potassium permanganate gradually added, the mixture being heated on a water-bath. The oxidation proceeded rapidly at first, but after the addition of about 400 c.c. of the permanganate solution (about 10 atomic proportions of oxygen) the latter was only slowly decolorised. The mixture was then filtered under pressure, and the alkaline liquid extracted with ether, but nothing was thus removed. On subsequently acidifying the liquid, a voluminous precipitate was produced, which was collected, washed with water, and then dissolved in ether. The ethereal liquid, on keeping a short time, deposited a crystalline, acidic substance, which was recrystallised from dilute alcohol. It separated from this solvent in thin, colourless needles, which decomposed at  $310^{\circ}$ . An analysis and a determination of the molecular weight gave the following results:

0.1096 gave 0.2191  $\text{CO}_2$  and 0.0922  $\text{H}_2\text{O}$ .  $\text{C}=72.7$ ;  $\text{H}=9.3$ .

0.1606 in 25.75 acetic acid gave  $\Delta t - 0.093^{\circ}$ .  $\text{M.W.}=261$ .

$\text{C}_{16}\text{H}_{24}\text{O}_3$  requires  $\text{C}=72.7$ ;  $\text{H}=9.1$  per cent.  $\text{M.W.}=264$ .

0.1075 neutralised 4.15 c.c.  $N/10\text{-NaOH}$ .

A monocarboxylic acid,  $\text{C}_{16}\text{H}_{24}\text{O}_3$ , requires 4.10 c.c.  $N/10\text{-NaOH}$ .

Since the above-described *acid*,  $\text{C}_{16}\text{H}_{24}\text{O}_3$ , does not agree in its properties with any acid of this formula which has heretofore been recorded, it is evidently a new compound, but the amount obtained was too small to permit of its further examination. It may, however, be concluded that the oxidation of caulosapogenin with potassium permanganate effects a far-reaching degradation of the molecule.

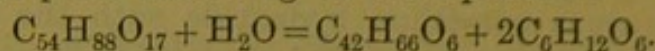
*Examination of the Sugar yielded by the Hydrolysis of Caulosaponin.*

The aqueous acid liquid resulting from the hydrolysis of the glucoside caulosaponin, as above described, was exactly neutralised with sodium carbonate, and evaporated to dryness under diminished pressure. The residue was then digested with hot alcohol, the mixture filtered, and the filtrate concentrated, when a viscid syrup was obtained. The latter yielded *d*-phenylglucosazone, which, after crystallisation from dilute pyridine, melted and decomposed at  $212^{\circ}$ .

The above results have thus shown that caulosaponin is resolved on hydrolysis into caulosapogenin and dextrose. A known quantity of the glucoside, when hydrolysed by dilute hydrochloric acid in



the presence of alcohol, and the alcohol subsequently removed, yielded 64.1 per cent. of its weight of caulosapogenin ( $C_{54}H_{88}O_{17}$ , requires  $C_{42}H_{66}O_6 = 66.1$  per cent.). The hydrolysis of caulosaponin therefore takes place according to the equation:



The amyl-alcoholic liquid, from which the caulosaponin had been separated by treatment with ether, as above described, was brought on to purified sawdust, the mixture thoroughly dried, and then extracted successively in a large Soxhlet apparatus with light petroleum, ether, chloroform, ethyl acetate, and alcohol.

*Petroleum Extract of the Amorphous Material (B).*

This was a dark coloured, fatty product, amounting to 49 grams. It was hydrolysed by heating for a short time with an alcoholic solution of potassium hydroxide, after which the alcohol was removed, water added, and the alkaline mixture extracted with ether. The ethereal liquid was washed, dried, and the solvent removed, when 11 grams of a viscid residue were obtained.

*Isolation of a Phytosterol,  $C_{27}H_{46}O$ .*

The above-mentioned residue of unsaponifiable material was digested with cold alcohol, which removed a quantity of gummy matter, leaving a crystalline solid undissolved. The latter was collected, and, after several crystallisations from ethyl acetate, was obtained in colourless leaflets, melting at  $153^\circ$ . The substance gave the colour reaction of the phytosterols, and evidently belonged to that class of compounds:

0.0918 \* gave 0.2812  $CO_2$  and 0.1002  $H_2O$ . C = 83.5; H = 12.1.

$C_{27}H_{46}O$  requires C = 83.9; H = 11.9 per cent.

*Examination of the Fatty Acids.*

The aqueous alkaline liquid which had been extracted with ether for the removal of the unsaponifiable material, as above described, was acidified with dilute sulphuric acid, and again extracted with ether. After the removal of the solvent, the residual fatty acids were converted into their lead salts, and the latter treated with ether. The soluble portion, when decomposed by hydrochloric acid, yielded 18 grams of liquid acids, whilst the insoluble portion gave about 5 grams of solid acids.

*The Liquid Acids.*—These acids were distilled under diminished

\* Dried at  $110^\circ$ .



pressure, and passed over at 210—245°/15 mm. as a pale yellow oil. An analysis and a determination of the neutralisation and iodine values gave the following results:

0.1176 gave 0.3310 CO<sub>2</sub> and 0.1264 H<sub>2</sub>O. C=76.8; H=11.9.

Neutralisation value=199.1; Iodine value=159.

C<sub>18</sub>H<sub>34</sub>O<sub>2</sub> requires C=76.6; H=12.1 per cent. N.V.=198.9;  
I.V.=90.1.

C<sub>18</sub>H<sub>32</sub>O<sub>2</sub> requires C=77.1; H=11.4 per cent. N.V.=200.4;  
I.V.=181.4.

It would appear from these results that the liquid acids consisted of a mixture of oleic and linolic acids.

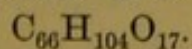
*The Solid Acids.*—These acids were converted into the methyl ester, and the latter separated by distillation under diminished pressure into two fractions, one of which was collected at 200—205°, and the other above 205°/20 mm. The first fraction yielded, on hydrolysis, a product which melted at 55—56°, and had a neutralisation value of 214; it evidently consisted of a mixture of palmitic and stearic acids. The fraction of ester distilling above 205°/20 mm. gave, on hydrolysis, an acid which separated from hot ethyl acetate in small leaflets, melting at 75—76°, and was identified as cerotic acid (Found, C=78.6; H=13.3. Calc., C=78.8; H=13.1 per cent.).

#### *Ethereal Extract of the Amorphous Material (B).*

##### *Isolation of Citrullol, C<sub>28</sub>H<sub>45</sub>O<sub>2</sub>(OH)<sub>3</sub>.*

The ethereal extract was a greyish-white powder, and amounted to 71 grams. It was dissolved in hot alcohol, and the solution kept for some time, when a small quantity of a sparingly soluble substance slowly separated. The latter was collected and crystallised from a mixture of pyridine and alcohol, when it was obtained in colourless leaflets, melting and decomposing at about 275—280°. The substance gave the colour reactions of ipuranol and allied alcohols, and yielded an acetyl derivative melting at 169—170°. These properties, together with an analysis of the substance (Found, C=71.9; H=10.4. Calc., C=72.4; H=10.3 per cent.), proved its identity with citrullol, C<sub>28</sub>H<sub>48</sub>O<sub>5</sub> (compare T., 1910, **97**, 102; and P., 1912, **28**, 318).

##### *Isolation of a New Crystalline Glucoside, Caulophyllosaponin,*



The alcoholic liquid remaining after the separation of the above-described citrullol was heated on a water-bath, and water gradually



added until turbidity ensued, when a crystalline solid separated on cooling. Some difficulty was experienced in purifying this substance, owing to the presence of small quantities of citrullol and caulosaponin, but after a process of fractional crystallisation from dilute alcohol it was obtained in colourless, silky needles, melting and decomposing at 250—260°. The substance was glucosidic and anhydrous. It was analysed, with the following results:

0.1129 gave 0.2803 CO<sub>2</sub> and 0.0916 H<sub>2</sub>O. C=67.7; H=9.0.

0.1050 ,, 0.2611 CO<sub>2</sub> ,, 0.0880 H<sub>2</sub>O. C=67.8; H=9.3.

C<sub>66</sub>H<sub>104</sub>O<sub>17</sub> requires C=67.8; H=8.9 per cent.

These results, together with the data subsequently obtained by an examination of the hydrolytic products of the glucoside, showed it to possess the formula C<sub>66</sub>H<sub>104</sub>O<sub>17</sub>. As no glucoside of this formula has hitherto been recorded, it is proposed to designate the above-described compound *caulophyllosaponin*, with reference to the source from which it has been obtained, and the fact that it has the properties of a saponin. For its complete examination, the amount obtained from the total (8.28 kilograms) original alcoholic extract of the drug was employed.

*Caulophyllosaponin*, C<sub>66</sub>H<sub>104</sub>O<sub>17</sub>, is extremely soluble in alcohol, sparingly so in ether, and insoluble in water. It dissolves in solutions of the alkali hydroxides, and possesses phenolic properties. A solution of the substance in water containing a little alcohol yields, on agitation, an abundant and persistent froth. When the substance is dissolved in acetic anhydride, a little chloroform added, and subsequently a few drops of concentrated sulphuric acid, a purplish-red colour is produced, quite analogous to that yielded under the same conditions by caulosaponin.

The specific rotatory power of *caulophyllosaponin* was determined, with the following result:

0.1600, made up to 20 c.c. with absolute alcohol, gave  $\alpha_D + 0^\circ 31'$  in a 2-dcm. tube, whence  $[\alpha]_D + 32.3^\circ$ .

*Deca-acetylcaulophyllosaponin*, C<sub>66</sub>H<sub>94</sub>O<sub>17</sub>(CO·CH<sub>3</sub>)<sub>10</sub>.—This derivative of *caulophyllosaponin* was prepared by heating it for some time with acetic anhydride, removing the greater part of the latter by distillation, and then pouring the residue into water. An amorphous, white solid was thus deposited, which was extremely soluble in organic solvents, and could not be crystallised. It was first dried in a vacuum desiccator over sulphuric acid and solid potassium hydroxide, and then at 110°, when it melted at 155—160°:

0.1503 gave 0.3565 CO<sub>2</sub> and 0.1074 H<sub>2</sub>O. C=64.7; H=7.9.

C<sub>86</sub>H<sub>124</sub>O<sub>27</sub> requires C=65.0; H=7.8 per cent.



*Hydrolysis of Caulophyllosaponin.**Formation of Caulophyllosapogenin,  $C_{56}H_{82}O_3(OH)_6$ , and Arabinose.*

The hydrolysis of caulophyllosaponin was affected by heating the latter with a 5 per cent. solution of hydrogen chloride in aqueous alcohol for several hours. The alcohol was then removed in a current of steam, and the hydrolytic product, which had separated from the hot liquid in a crystalline state, was collected, the aqueous liquid being put aside for the subsequent examination of the sugar. The crystalline hydrolytic product was recrystallised from dilute pyridine, when it separated in rhombohedral prisms, which decomposed at about  $315^{\circ}$ :

0.0981 gave 0.2670  $CO_2$  and 0.0862  $H_2O$ . C=74.2; H=9.8.

0.1013 ,, 0.2748  $CO_2$  ,, 0.0900  $H_2O$ . C=74.0; H=9.9.

$C_{56}H_{88}O_9$  requires C=74.3; H=9.7 per cent.

The molecular formula of the above hydrolytic product was established by means of the derivatives described below. It has thus been definitely shown to possess the formula  $C_{56}H_{88}O_9$ , and to contain six hydroxyl groups, two of which are phenolic. As it is a new compound, it is proposed to designate it *caulophyllosapogenin*.

*Caulophyllosapogenin*,  $C_{56}H_{82}O_3(OH)_6$ , possesses physical properties which are very similar to those of the previously described hydrolytic product, caulosapogenin. Both these substances decompose at about  $315^{\circ}$ , and are sparingly soluble in alcohol, but dissolve readily in the latter when containing a little alkali hydroxide. When dissolved in acetic anhydride with a little chloroform, they give a rose-red coloration on the addition of a few drops of concentrated sulphuric acid. Caulophyllosapogenin, unlike caulosapogenin, does not yield a crystalline benzoyl derivative.

*Hexa-acetylcaulophyllosapogenin*,  $C_{56}H_{82}O_9(CO \cdot CH_3)_6$ . — This compound was prepared by heating caulophyllosapogenin for three hours with an excess of acetic anhydride, then removing the greater portion of the latter, and heating the residue with water in a current of steam. An amorphous solid was thus obtained, which melted at  $160-162^{\circ}$ . The substance was extremely soluble in the usual organic solvents, and could not be crystallised, but presumably was homogeneous. An analysis and a determination of its molecular weight gave the following results:

0.0978 gave 0.2517  $CO_2$  and 0.0795  $H_2O$ . C=70.2; H=9.0.

0.9613, in 23.63 benzene, gave  $\Delta t - 0.180^{\circ}$ . M.W.=1130.

$C_{68}H_{100}O_{15}$  requires C=70.6; H=8.7 per cent. M.W.=1156.



*Caulophyllosapogenin Dimethyl Ether*,  $C_{56}H_{86}O_7(O\cdot CH_3)_2$ .—In order to prepare this derivative, caulophyllosapogenin was dissolved in alcohol containing a little potassium hydroxide, and the solution heated with an excess of methyl iodide for several hours. The greater portion of the solvent was then removed, the mixture poured into dilute hydrochloric acid, and the resulting precipitate collected. When crystallised from dilute alcohol, it separated in stellate clusters of small needles, which melted at  $240\text{--}242^\circ$ :

0.0888 gave 0.2436  $CO_2$  and 0.0809  $H_2O$ .  $C=74.8$ ;  $H=10.1$ .

The number of methoxyl groups in the compound was determined by Perkin's modification of Zeisel's method:

0.1547 gave 0.0746 AgI.  $MeO=6.4$ .

$C_{56}H_{86}O_7(O\cdot CH_3)_2$  requires  $C=74.7$ ;  $H=9.9$ ;  $MeO=6.7$  per cent.

*Caulophyllosapogenin dimethyl ether* is readily soluble in alcohol, ether, chloroform, or benzene. Its specific rotatory power was determined with the following result:

0.1222, made up to 20 c.c. with chloroform, gave  $\alpha_D +0^\circ 32'$  in a 2-dcm. tube, whence  $[\alpha]_D +43.6^\circ$ .

*Identification of l-Arabinose, a Hydrolytic Product of  
Caulophyllosapogenin.*

The aqueous liquid obtained in the hydrolysis of caulophyllosapogenin, as above described, was exactly neutralised with sodium carbonate, and evaporated to dryness under diminished pressure. The residue was then digested with hot alcohol, the mixture filtered, and to the hot filtrate an equal volume of ethyl acetate was added, when a syrup was deposited. This was removed, and a further quantity of ethyl acetate added to the hot liquid. On keeping the latter for some time, a crystalline substance separated in small, hard nodules, which melted at  $156^\circ$ , and readily reduced Fehling's solution (Found,  $C=39.9$ ;  $H=6.9$ .  $C_5H_{10}O_5$  requires  $C=40.0$ ;  $H=6.7$  per cent.).

The optical rotatory power of the substance was determined with the following result:

0.1702, made up to 25 c.c. with water, gave  $\alpha_D +1^\circ 27'$  in a 2-dcm. tube, whence  $[\alpha]_D +106.5^\circ$ .

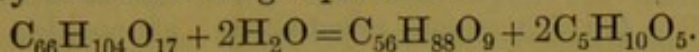
The substance yielded an osazone, which, when crystallised from dilute alcohol, was obtained in brownish-yellow needles, melting at  $160^\circ$  (Found,  $C=62.2$ ;  $H=6.2$ .  $C_{17}H_{20}O_3N_4$  requires  $C=62.2$ ;  $H=6.1$  per cent.).

From the above results it was evident that the sugar formed by the hydrolysis of caulophyllosapogenin is a pentose, agreeing in all its properties with *l*-arabinose. In order further to confirm its



identity, it was compared with a commercial specimen of arabinose. The latter melted at  $156^{\circ}$ , and when mixed with the above-described substance no depression in melting point was observed.

The glucoside caulophyllosaponin,  $C_{66}H_{104}O_{17}$ , is thus seen to be converted by hydrolysis into caulophyllosapogenin,  $C_{56}H_{88}O_9$ , and *l*-arabinose,  $C_5H_{10}O_5$ . A known quantity of the glucoside, when hydrolysed by dilute hydrochloric acid in the presence of alcohol, and the alcohol subsequently removed, yielded 72.6 per cent. of its weight of caulophyllosapogenin ( $C_{66}H_{104}O_{17}$  requires  $C_{56}H_{88}O_9 = 77.4$  per cent.). The hydrolysis of the glucoside is therefore to be represented by the following equation:



*Chloroform, Ethyl Acetate, and Alcohol Extracts of the Amorphous Material (B).*

*Chloroform Extract.*—This was a brittle, black solid, amounting to 10.5 grams. It was glucosidic in character, but no definite compound could be isolated from it.

*Ethyl Acetate Extract.*—This was a greyish-white solid, amounting to 24 grams. It was dissolved in hot alcohol, and the solution kept for some time, when a substance separated in needles, which decomposed at  $250$ — $255^{\circ}$ . This substance was collected, and found to be identical with the previously described glucoside, caulosaponin,  $C_{54}H_{88}O_{17}$  (Found, C=64.0; H=8.6. Calc., C=64.3; H=8.7 per cent.).

The alcoholic liquid remaining after the separation of the above glucoside was heated with dilute hydrochloric acid, when it yielded a small quantity of caulosapogenin,  $C_{42}H_{66}O_6$ , decomposing at  $315^{\circ}$ .

*Alcoholic Extract.*—This was a brittle, black solid, amounting to 12 grams. It was glucosidic in character, and yielded on hydrolysis a small quantity of caulosapogenin,  $C_{42}H_{66}O_6$ , which was identified by means of its benzoyl derivative, melting at  $288^{\circ}$ .

*Summary and Physiological Tests.*

The material employed for this investigation consisted of the rhizome and roots of *Caulophyllum thalictroides* (Linné), Michaux.

A preliminary test showed the presence of an alkaloid, and a relatively small amount of an enzyme was obtained, which slowly hydrolysed amygdalin.

An alcoholic extract of the ground material, when distilled in a current of steam, yielded a small amount of a pale yellow essential oil. From the alcoholic extract, the following definite compounds were isolated: (i) A crystalline alkaloid,  $C_{12}H_{16}ON_2$  (m. p.  $137^{\circ}$ ;



$[\alpha]_D - 221.6^\circ$ ), which has been identified as methylcytisine; the *picrate* melts at  $228^\circ$ . (ii) A crystalline glucoside, *caulosaponin*,  $C_{54}H_{88}O_{17} \cdot 4H_2O$  (m. p.  $250-255^\circ$ ), which yields a *deca-acetyl* derivative,  $C_{54}H_{78}O_{17}(CO \cdot CH_3)_{10}$ , melting at  $135-140^\circ$ , and on hydrolysis is resolved into *caulosapogenin*,  $C_{42}H_{66}O_6$  (m. p.  $315^\circ$ ), and dextrose. *Caulosapogenin* yields a *tetra-acetyl* derivative,  $C_{42}H_{62}O_6(CO \cdot CH_3)_4$ , melting at  $120^\circ$ , and a *diacetyl* derivative,  $C_{42}H_{64}O_6(CO \cdot CH_3)_2$ , melting at  $160-162^\circ$ , from which a crystalline *monosodio*-derivative,  $C_{42}H_{63}O_6Na(CO \cdot CH_3)_2$ , was prepared; it yielded, furthermore, a *tetrabenzoyl* derivative,  $C_{42}H_{62}O_6(CO \cdot C_6H_5)_4$ , melting at  $288^\circ$ , and a *monomethyl ether*,  $C_{42}H_{65}O_5(O \cdot CH_3)$ , which melts at  $235^\circ$ . (iii) A new crystalline glucoside, *caulophyllosaponin*,  $C_{66}H_{104}O_{17}$  (m. p.  $250-260^\circ$ ;  $[\alpha]_D + 32.3^\circ$ ), which yields a *deca-acetyl* derivative,  $C_{66}H_{94}O_{17}(CO \cdot CH_3)_{10}$ , melting at  $155-160^\circ$ , and on hydrolysis is resolved into *caulophyllosapogenin*,  $C_{56}H_{88}O_9$  (m. p.  $315^\circ$ ), and arabinose. *Caulophyllosapogenin* yields a *hexa-acetyl* derivative,  $C_{56}H_{82}O_9(CO \cdot CH_3)_6$ , melting at  $160-162^\circ$ , and a *dimethyl ether*,  $C_{56}H_{86}O_7(O \cdot CH_3)_2$ , which melts at  $240-242^\circ$ , and has  $[\alpha]_D + 43.6^\circ$ . (iv) A phytosterol,  $C_{27}H_{46}O$  (m. p.  $153^\circ$ ). (v) Citrullol,  $C_{28}H_{45}O_2(OH)_3$ . (vi) A mixture of fatty acids, consisting of palmitic, stearic, cerotic, oleic and linolic acids. The alcoholic extract also contained a quantity of sugar, which yielded *d*-phenylglucosazone (m. p.  $210^\circ$ ), and a comparatively small amount of resinous material.

The above-mentioned methylcytisine,  $C_{12}H_{16}ON_2$ , represents the alkaloid previously obtained by J. U. Lloyd (*Proc. Amer. Pharm. Assoc.*, 1893, **41**, 115), and designated "*caulophylline*," but he did not succeed in crystallising the base, and its composition was not determined. In view of its present identification, the name "*caulophylline*" should no longer be retained for this alkaloid.

The compound designated by the present authors as *caulosaponin*,  $C_{54}H_{88}O_{17} \cdot 4H_2O$ , is undoubtedly identical with a crystalline glucoside first obtained by J. U. Lloyd ("*Drugs and Medicines of North America*," Vol. II, 1887, p. 151), and termed by him "*leontin*," although the formula deduced from its analysis was not correct. As it has now been completely characterised, it appears desirable that it should receive the new and distinctive name assigned to it.

For the purpose of determining the physiological action of methylcytisine and the two above-mentioned crystalline glucosides, *caulosaponin* and *caulophyllosaponin*, some tests were kindly conducted for us by Dr. P. P. Laidlaw, of the Wellcome Physiological Research Laboratories, to whom our best thanks may here be expressed.

Methylcytisine has been found to be very similar in its action to



cytisine, but not nearly so potent, the latter being at least ten times as active as the former on the blood pressure of the cat (compare Dale and Laidlaw, *J. Pharmacol. and Exp. Therap.*, 1912, 3, 205). In other directions, such as the action on the ganglion cells supplying the eye and heart, methylcytisine is also very much weaker than cytisine. On the frog the difference in potency is not so obvious.

The glucosides, caulosaponin and caulophyllosaponin, showed the behaviour of the class of substances known as saponins. Solutions of these substances in physiological salt solution, although very dilute, were found to be powerfully hæmolytic for washed red blood corpuscles, and were also toxic for isolated, perfused frog's hearts. Whole blood and unwashed red blood corpuscles were unaffected, and both glucosides were without action on the frog's heart *in situ*. This difference in action on tissues in the body and on tissues freed from serum is known to be due to lipoid substances in the serum and tissues, for which substances saponins as a class have a marked affinity. The administration of the two glucosides by the mouth to small cats, in doses of 0.1 gram each, resulted in no symptoms of physiological activity other than a mild purgative action after several hours.

THE WELLCOME CHEMICAL RESEARCH LABORATORIES,  
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