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Trisaspidin, Trisdesaspidin and Trisflavaspidic Acid, Three New Three-Ring Phloroglucinol Derivatives from *Dryopteris austriaca*

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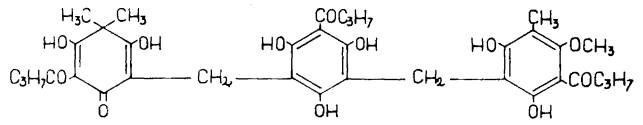
From the Finnish *Dryopteris austriaca* fern three new phloroglucinol derivatives have been isolated, each composed of three rings linked by methylene bridges. These compounds are called trisaspidin (I), trisdesaspidin (II) and trisflavaspidic acid (III) and they can be derived from the well-known two-ring compounds aspidin (IV), desaspidin (V) or flavaspidic acid (VI), respectively, by adding a butyrylphloroglucinol unit between the two rings of the dimeric compounds. In addition, filixic acid BBB (VII), a component of the homologous mixture of filixic acids so far isolated only from *Dryopteris filix mas*, has now been shown to occur in *Dryopteris austriaca* also.

Hitherto, filixic acid has been the only known *Dryopteris* phloroglucinol derivative composed of three rings. The filixic acid isolated from *Dryopteris filix mas* rhizomes has been shown to be a mixture of three homologues.[1] One of the main components, filixic acid BBB (VII), which has previously been isolated from the homologous mixture by the authors,[1] has now unexpectedly also been found in *Dryopteris austriaca*. The filixic acid BBB from *Dryopteris austriaca* has a melting point of 172—174° and is in every respect identical with the filixic acid BBB isolated from *Dryopteris filix mas*. The other filixic acid homologues [1] proved to be totally lacking in *Dryopteris austriaca*.

In addition to filixic acid BBB, three hitherto unknown phloroglucinol derivatives were detected in *Dryopteris austriaca* and were isolated from this species. The molecular weights of these new compounds were about 650, thus indicating a three-ring structure like that of the filixic acids, which up to now have been the sole known three-ring phloroglucinol derivatives in *Dryopteris* ferns. On the basis of the results obtained by elementary analyses and alkaline cleavages of the new compounds, their structures could be resolved. It appeared that the structures could be derived from filixic acid BBB by replacing one butyrylfilicinic acid nucleus by ψ-aspidinol (= butyryl-3-methylphloroglucinol-2-methyl ether),[2,3] desaspidinol (= butyrylphloroglucinol-4-methyl ether) [3,4]



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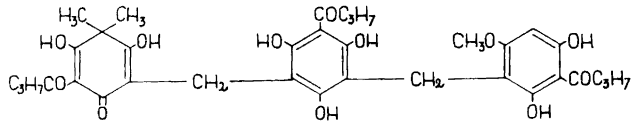

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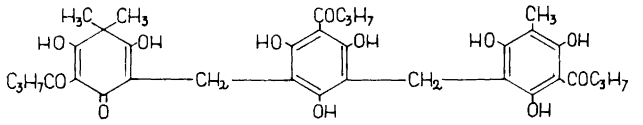

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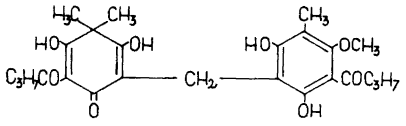

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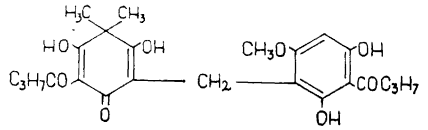

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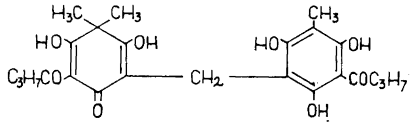

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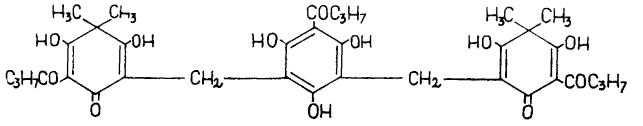
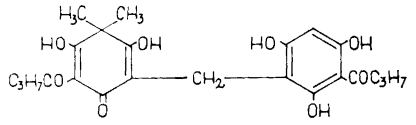


VII



VIII

or butyryl-3-methylphloroglucinol,[5,6] respectively. Because they also can be derived from the well-known two-ring compounds aspidin (IV),[7] desaspidin (V) [8,9] or flavaspidic acid (VI),[10,11] respectively, by enlarging these molecules with a butyrylphloroglucinol [6] unit situated between the two rings of the dimeric compounds, the following names are proposed for the new compounds: trisaspidin (I), trisdesaspidin (II) and trisflavaspidic acid (III).

In the technical isolation of desaspidin and flavaspidic acid from *Dryopteris austriaca*, the extract, previously freed from fatty material, was successively extracted to yield, in the first stage, aspidin, albaspidin [13] and phloropyron;[14] in the second stage, desaspidin and para-aspidin;[15] and in the third stage, finally, flavaspidic acid. The residue obtained after separation of desaspidin from the second extract was used as source for trisaspidin and trisdesaspidin. In addition to these compounds filixic acid BBB was also isolated at this stage. The corresponding residue after isolation of flavaspidic acid produced the third new compound under discussion, trisflavaspidic acid.

Trisaspidin. The residue obtained after separation of desaspidin was concentrated with respect to trisaspidin and filixic acid BBB. The concentrate was dissolved in cyclohexane and column chromatography on silica gel carried out. By using a mixture of cyclohexane and chloroform as solvent, two main fractions were obtained. The first fraction, recrystallized from ethyl acetate, yielded yellow crystals melting at 172—174°. This compound was identified as filixic acid BBB. Of the other filixic acid homologues, not even traces could be detected in *Dryopteris austriaca*. The second chromatographic fraction produced a new compound melting at 156—159°. By alkaline cleavage of the new compound butyrylfilicinic acid, butyrylphloroglucinol, butyryl-3-methylphloroglucinol and ψ-aspidinol were identified [12] (Fig. 1). On the basis of these results structure (I) was proposed for the new compound, which was called

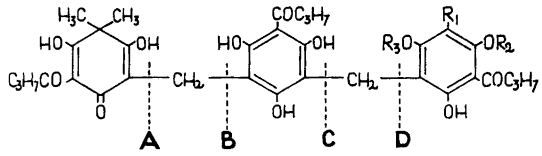


Fig. 1. The one-ring compounds produced by alkaline cleavage of trisaspidin, trisdesaspidin and trisflavaspidic acid.

Cleavages at points marked A—D.

Compound	A	B	C	D	A + C or B + D	B + C
Trisaspidin $R_1=R_2=CH_3$; $R_3=H$	Butyryl-filicinic acid	Butyryl-methyl-filicinic acid *	Methyl-ψ-aspidinol *	ψ-Aspidinol	Butyryl-3-methyl-phloro-glucinol	Butyryl-phloro-glucinol
Trisdesaspidin $R_1=R_2=H$; $R_3=CH_3$	—»—	—»—	Aspidinol	Desaspid-inol	—»—	—»—
Trisflavaspidic acid $R_1=CH_3$; $R_2=R_3=H$	—»—	—»—	Butyryl-3,5-dime-thylphloro-glucinol *	Butyryl-3-methyl-phloro-glucinol	—»—	—»—

* Not identified.

trisaspidin. Structure (I) was in good agreement with the results of elementary analysis as well as with the molecular weight determination, and was further confirmed by synthesis.

The synthesis of trisaspidin was performed in two stages. Butyrylfilicinic acid and butyrylphloroglucinol were first allowed to condense with formaldehyde to form norflavaspidic acid (VIII), which was then condensed with ψ-aspidinol and formaldehyde to yield trisaspidin. The synthesis of norflavaspidic acid proceeded with a poor yield, the main products formed being the symmetrical albaspidin and methylene-bis-butyrylphloroglucinol, from which norflavaspidic acid could be separated only with difficulty. This was chiefly due to the fact that norflavaspidic acid, which is not a naturally occurring phloroglucinol derivative, was mostly obtained as an oil containing various impurities. Only when a high degree of purity was reached could norflavaspidic acid be brought to crystallize from hexane, and then had a melting point of 119—121°.

In the synthesis of trisaspidin starting from norflavaspidic acid, ψ-aspidinol and formaldehyde, an excess of ψ-aspidinol proved to be advisable. In this way the condensation of norflavaspidic acid with formaldehyde to form methylene-bis-norflavaspidic acid could be depressed to a minimum and the yield of trisaspidin correspondingly increased, owing to the fact that ψ-aspidinol showed very little tendency to condense with formaldehyde. Thus the synthesis yielded chiefly trisaspidin and unreacted ψ-aspidinol. The latter was easy to remove on account of its solubility in methanol, in which trisaspidin was very slightly soluble. Recrystallizations from mixtures of acetone and methanol and from acetone only yielded pure trisaspidin melting at 155—158°.

Trisdesaspidin. To isolate trisdesaspidin from the previously mentioned residue after separation of desaspidin from the second technical extract, the residue was dissolved in isopropanol and methanol was added. The precipitate was filtered off and discarded. Dilute hydrochloric acid was added to the filtrate and the precipitate filtered off and dried in a vacuum. The powder so obtained contained trisdesaspidin, together with desaspidin, albaspidin, para-aspidin and filixic acid BBB. Column chromatography on silica gel was carried out with cyclohexane-chloroform (1:1) as solvent. The fractions containing trisdesaspidin were combined and recrystallized from cyclohexane. The melting point of pure trisdesaspidin was 143—146° (decomp.).

Alkaline cleavage of trisdesaspidin yielded butyrylfilicinic acid, butyrylphloroglucinol, butyryl-3-methylphloroglucinol, desaspidinol and aspidinol, all identified by paper chromatography [12] (Fig. 1). On the basis of these results, structure (II) was proposed for trisdesaspidin and further confirmed by synthesis, in which norflavaspidic acid and desaspidinol were condensed with formaldehyde in a dilute alkaline solution. In this case, in contrast to the synthesis of trisaspidin, a great excess of the monomeric compound was not advantageous, because desaspidinol readily condenses with formaldehyde to form methylene-bis-desaspidinol.[3] This symmetrical condensation product turned out to be difficult to remove from the synthetic mixture. On the other hand, when the synthesis was started from equivalent amounts of norflavaspidic acid and desaspidinol, considerable amounts of methylene-bis-norflavaspidic acid were formed. This, too, led to difficulties in the purifica-

tion of trisdesaspidin. The best result was attained by using a slight excess of desaspidinol whereby the synthesis yielded, besides trisdesaspidin and the symmetrical compounds mentioned, minor amounts of desaspidin, albaspidin and unidentified condensation products. To obtain pure trisdesaspidin, fractional crystallizations from cyclohexane and column chromatography on silica gel were carried out. The melting point of synthetic trisdesaspidin, recrystallized from hexane, and the mixed melting point with natural trisdesaspidin were 142—146° (decomp.).

Trisflavaspidic acid. Trisflavaspidic acid was isolated from the residue obtained after the technical separation of flavaspidic acid from *Dryopteris austriaca*. The concentrated and dried residue was dissolved in glacial acetic acid and left at room temperature for some days. The fine crystalline precipitate formed was filtered off and recrystallized from glacial acetic acid and from a mixture of cyclohexane and hexane. Pure trisflavaspidic acid is a yellowish crystalline compound melting with decomposition at 169—174°.

Alkaline cleavage of trisflavaspidic acid yielded butyrylfilicinic acid, butyrylphloroglucinol and butyryl-3-methylphloroglucinol [12] (Fig. 1). Structure (III), based on these decomposition results, was confirmed by synthesis.

The synthesis of trisflavaspidic acid, carried out analogously with the syntheses of trisaspidin and trisdesaspidin, should be started from norflavaspidic acid and butyryl-3-methylphloroglucinol. However, the exceptional readiness with which trisflavaspidic acid was known to crystallize from glacial acetic acid offered a possibility of carrying out the synthesis without the laborious production of norflavaspidic acid. It was to be expected that trisflavaspidic acid would crystallize from the synthetic reaction mixture even though its concentration was somewhat lower and the mixture contained several by-products. This also proved to be true. The synthesis of trisflavaspidic acid was started from butyrylphloroglucinol and butyryl-3-methylphloroglucinol condensed with formaldehyde, and the reaction continued by addition of butyrylfilicinic acid and formaldehyde. The acidified reaction mixture consisted mainly of albaspidin, methylene-bis-butyryl-3-methylphloroglucinol, trisflavaspidic acid, flavaspidic acid, norflavaspidic acid, and undefined condensation products. On dissolving the synthetic mixture in glacial acetic acid fairly pure trisflavaspidic acid was obtained and further recrystallizations yielded trisflavaspidic acid in a pure state, melting at 168—174° (decomp.).

The paper chromatographic behaviour of the *Dryopteris* phloroglucinol derivatives has been studied and reported on by the authors.[12] A method using buffered and formamide-impregnated papers developed with a benzene-chloroform (1:1) solvent has been shown to separate all known phloroglucinol derivatives isolated from *Dryopteris* species. In order to avoid the use of benzene, notorious for its poisonous qualities, the solvent mentioned has later been replaced by a mixture of cyclohexane and chloroform (1:1); this exchange has not appreciably influenced the R_F-values. When this method is used, trisaspidin and trisdesaspidin have the R_F-values shown in Fig. 2. Compared with the corresponding dimeric compounds, aspidin and desaspidin, it appears that a satisfactory separation can be achieved in the pH range 9.1—8.9. On papers buffered to a lower pH value, 8.7—8.5, neither the pair aspidin-trisas-

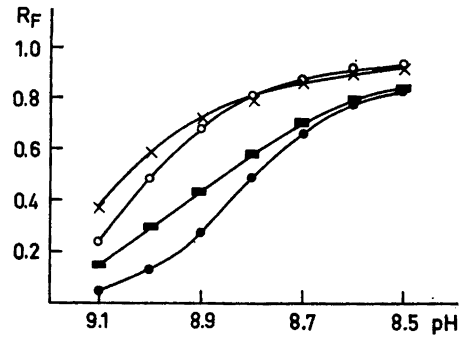


Fig. 2. Variation of the R_F values with the pH of the papers. × Aspidin, O Trisaspidin, ■ Desaspidin, ● Trisdesaspidin.

pidin nor the pair desaspidin-trisdesaspidin can be separated, but the trisaspidin is well separated from the trisdesaspidin (Fig. 2).

For the detection of the spots, tetrazotized di-*o*-anisidine has proved superior to all other reagents tested.[12] With this reagent trisaspidin gives a reddish brown spot readily distinguishable from the yellow one of aspidin. Trisdesaspidin takes on a yellowish brown colour, while desaspidin is purplish red.

For the chromatography of pure samples of trisflavaspidic acid, flavaspidic acid and norflavaspidic acid, papers buffered to pH 4.0 and 5.0 are suitable. On these papers the R_F-values and colours of flavaspidic acid and norflavaspidic acid are virtually identical. This is, however, of little importance, because norflavaspidic acid is not a naturally occurring phloroglucinol derivative in *Dryopteris*, and therefore the possibility of its being confused with flavaspidic acid is negligible. The R_F-value of trisflavaspidic acid is somewhat higher that of flavaspidic acid but the difference is not sufficient to allow a really good separation. But because the colour produced by the reagent mentioned is pale orange in the case of trisflavaspidic acid while flavaspidic acid is greyish purple, a reliable identification can be achieved in spite of the unsatisfactory separation. For the detection of trisflavaspidic acid in impure samples, chromatography on unbuffered papers is recommended, notwithstanding the fact that outstretched spots are obtained. In this way the spots of flavaspidic acid and trisflavaspidic acid partially overlap, but the spot of trisflavaspidic acid is noticeably longer and therefore clearly distinguishable owing to its different colouring.

EXPERIMENTAL

Isolation of filixic acid BBB and trisaspidin. The dried residue obtained after isolation of desaspidin from *Dryopteris austriaca* extract was concentrated in regard to filixic acid BBB and trisaspidin by dissolving the residue in glacial acetic acid. After some weeks a considerable solid mass containing neither filixic acid BBB nor trisaspidin had settled. When the precipitation was complete the mixture was filtered and the filtrate treated with methanol. The voluminous precipitate now formed was filtered off and dried in a vacuum. Paper chromatographic analysis indicated the presence of two main compounds, namely filixic acid BBB and trisaspidin. These were separated by column chromatography on silica gel. Mixtures of cyclohexane and chloroform (1:1) produced practically pure filixic acid BBB as a first fraction. Repeated recrystallizations from ethyl acetate yielded pure filixic acid BBB, melting at 172–174°. (Found: C 64.28; H 6.52. Calc. for $C_{36}H_{44}O_{12}$: C 64.67; H 6.59.)

From the subsequent fractions obtained by continued elution with the cyclohexane-chloroform (1:1) mixture, trisaspidin was obtained together with residual amounts of filixic acid BBB. These fractions were combined and a new chromatographic separation performed under similar conditions. Repetition of the procedure yielded practically pure trisaspidin, which, when recrystallized from acetone, was obtained in a pure state with a melting point of 156–159°. (Found: C 64.65; H 6.71; OCH_3 4.75. Calc. for $C_{36}H_{44}O_{12}$: C 64.67; H 6.59; OCH_3 4.64).

Alkaline cleavage of trisaspidin. Trisaspidin (50 mg) was dissolved in aqueous sodium hydroxide (5 %, 20 ml), zinc dust (100 mg) was added and the mixture heated on a steam bath for 5 min. The cooled solution was filtered and diluted with water, acidified with dilute sulphuric acid and extracted with ether. The ethereal solution was evaporated to dryness and the residue dissolved in acetone and chromatographed on papers buffered to pH 8.8 and 5.0. On the paper of pH 8.8, treated with tetrazotized di-*o*-anisidine ("fast blue salt B", Merck) reagent, a red-brown spot with the R_F-value 0.66 was obtained, the colour and the R_F value of which were identical with the spot obtained by chromatography of an authentic specimen of *ψ*-aspidinol, m.p. 72–73°. On the paper of pH 5.0 a carmine red spot with the R_F value 0.35 was obtained and it was identical with that of butyrylfilicinic acid, m.p. 98°.

The same decomposition mixture was further chromatographed on unbuffered papers with tetraline-acetic acid-water (10:10:1) solution. Two blue spots identical with butyryl-phloroglucinol, m.p. 185–186°, and butyryl-3-methylphloroglucinol, m.p. 166–167°, were obtained.

Synthesis of norflavaspidic acid. Butyrylfilicinic acid (22.4 g) and butyrylphloroglucinol (19.6 g) were dissolved in potassium hydroxide (1 %, 1.5 l), and formaldehyde (40 %, 7.5 ml) was added. The mixture was kept at room temperature for 1 min and acidified with dilute hydrochloric acid. The precipitate was filtered off, washed with water and dried. The bulk of the albaspidin formed could be removed on account of its insolubility in acetone. The evaporated acetone solution left behind a yellow oil containing methylene-bis-butyrylphloroglucinol, norflavaspidic acid, butyrylfilicinic acid and residual albaspidin. The mixture was dissolved in cold methanol, whereby an insoluble part containing mostly albaspidin was obtained. To the methanol solution an equal volume of water was added and the oily mass gradually depositing from the mixture consisted mostly of norflavaspidic acid and methylene-bis-butyrylphloroglucinol. The bulk of the butyryl-filicinic acid remained in the dilute methanol solution. The dried and powdered mass was then treated with boiling hexane, whereby an insoluble part consisting mainly of methylene-bis-butyrylphloroglucinol and butyrylfilicinic acid was obtained. The hexane solution was kept in a refrigerator for several days, and each day the clear solution was decanted from the amorphous and viscous deposit formed. In this way the norflavaspidic acid remaining in the hexane solution was effectively purified and finally obtained as yellow crystals, which when recrystallized from hexane, melted at 119–121°. The total yield of pure norflavaspidic acid was some hundreds of mg. (Found: C 64.57; H 6.55. Calc. for $C_{23}H_{28}O_8$: C 63.88; H 6.48).

Synthesis of trisaspidin. Norflavaspidic acid (864 mg) was dissolved in potassium hydroxide (1 %, 30 ml) and *ψ*-aspidinol (1.344 g) was dissolved in the same solvent (50 ml). These solutions were combined and formaldehyde (4 %, 3 ml) was added. The mixture was kept at room temperature for 1 min and acidified with dilute hydrochloric acid. The precipitate was filtered off and immediately treated with cold methanol, whereby the unreacted *ψ*-aspidinol was dissolved and practically pure trisaspidin was left behind. Recrystallizations from acetone-methanol mixtures and from acetone yielded pure trisaspidin, m.p. 155–158°. (Found: C 64.66; H 6.74; OCH_3 4.72. Calc. for $C_{36}H_{44}O_{12}$: C 64.67; H 6.59; OCH_3 4.64.)

Isolation of trisdesaspidin. The residue after the technical isolation of desaspidin, described above, was dissolved in isopropanol, and methanol was added gradually until no more precipitation occurred. The mixture was filtered and the filtrate was once more precipitated by addition of dilute hydrochloric acid. The amorphous mass was filtered off and dried in a vacuum. It was chromatographed through a silica gel column, with cyclohexane-chloroform (1:1) as eluant. The first fractions consisted of albaspidin and filixic acid BBB and were followed by fractions of para-aspidin and desaspidin. Trisdesaspidin was then obtained together with the remaining desaspidin and with minor amounts of the other phloroglucinol derivatives mentioned. The best fractions were combined and the

chromatographic procedure was repeated, now yielding trisdesaspidin in sufficiently pure form to be crystallized from cyclohexane and hexane. The melting point of trisdesaspidin after several recrystallizations was 148–152° (decomp.). (Found: C 64.85; H 6.64; OCH_3 4.72. Calc. for $C_{35}H_{42}O_{12}$: C 64.22; H 6.42; OCH_3 4.74).

Alkaline cleavage of trisdesaspidin. Trisdesaspidin (50 mg) was dissolved in aqueous sodium hydroxide (5 %, 20 ml), zinc dust (100 mg) was added and the mixture was heated on a steam bath for 5 min. The cooled solution was filtered and diluted with water, acidified with dilute hydrochloric acid and extracted with ether. The ethereal solution was evaporated to dryness and the residue dissolved in acetone and chromatographed on papers buffered to pH 8.8 and 5.0. On the paper of pH 8.8 two purple spots were obtained, the larger one being identical with that of desaspidinol, m.p. 127–128°, and the smaller one with that of aspidinol, m.p. 142–143°. All other spots were exactly the same as obtained in the alkaline cleavage of trisaspidin, excluding ψ-aspidinol: butyrylfilicinic acid, butyrylphloroglucinol and butyryl-3-methylphloroglucinol.

Synthesis of trisdesaspidin. Norflavaspidic acid (864 mg) was dissolved in potassium hydroxide (1 % 30 ml) and desaspidinol (630 mg) was dissolved in the same solvent (25 ml). These solutions were combined and formaldehyde (4 %, 1.9 ml) was added. The mixture was kept at room temperature for 1 min and acidified with dilute hydrochloric acid. The precipitate was filtered off, washed with water and dried. The synthetic mixture was dissolved in cyclohexane and kept in a cool place for fractional crystallization. The first fractions contained most of the methylene-bis-desaspidinol present, while trisdesaspidin together with other condensation products remained in solution. The procedure was repeated several times but the methylene-bis-desaspidinol could not be removed quantitatively in this way. Column chromatography on silica gel was then carried out, with benzene as eluant. The first fractions contained practically pure trisdesaspidin, which, recrystallized from cyclohexane and hexane, yielded pure trisdesaspidin melting at 142–146° (decomp.). (Found: C 63.78; H 6.38. Calc. for $C_{35}H_{42}O_{12}$: C 64.22; H 6.42. Owing to lack of material the methoxy content could not be determined.)

Isolation of trisflavaspidic acid. The residue after the technical isolation of flavaspidic acid was obtained as a dilute methanolic solution from which a concentrate of the residual phloroglucinol derivatives present was obtained by precipitation with dilute hydrochloric acid. The vacuum-dried and powdered amorphous mass was dissolved in glacial acetic acid and the voluminous insoluble part containing no phloroglucinol derivatives was filtered off and discarded. From the acetic acid solution a crystalline precipitate was obtained during a few days at room temperature. Further recrystallizations from the same solvent and crystallizations performed by dissolving the compound in boiling cyclohexane followed by addition of an equal volume of hexane yielded, at 4°, trisflavaspidic acid in a pure state with a melting point of 169–174° (decomp.). (Found: C 63.78; H 6.40. Calc. for $C_{35}H_{42}O_{12}$: C 64.22; H 6.42.)

Alkaline cleavage of trisflavaspidic acid. Trisflavaspidic acid (50 mg) was dissolved in aqueous sodium hydroxide (5 %, 20 ml), zinc dust (100 mg) was added and the mixture was heated on a steam bath for 5 min. The isolation of the decomposition products was performed as described for trisaspidin and trisdesaspidin. Paper chromatography on a paper buffered to pH 5.0 revealed butyrylfilicinic acid. Butyrylphloroglucinol and butyryl-3-methylphloroglucinol were identified by chromatography on an unbuffered paper, with tetraline-acetic acid-water (10:10:1) as solvent.

Synthesis of trisflavaspidic acid. Butyrylphloroglucinol (1.96 g) and butyryl-3-methylphloroglucinol (2.10 g) were dissolved in potassium hydroxide (1 %, 150 ml), and formaldehyde (40 %, 0.75 ml) was added. After 1 min butyrylfilicinic acid (2.24 g) dissolved in potassium hydroxide (1 %, 50 ml) was added, followed by formaldehyde (40 %, 0.75 ml). After 1 min the solution was acidified with dilute hydrochloric acid. The precipitate was filtered off, washed with water and dried. Direct crystallization from glacial acetic acid yielded trisflavaspidic acid as the main compound. Further purification was performed as described for the isolation of the naturally occurring trisflavaspidic acid. The synthetic compound had a melting point and with natural trisflavaspidic acid a mixed melting point of 168–174° (decomp.). (Found: C 63.90; H 6.47. Calc. for $C_{35}H_{42}O_{12}$: C 64.22; H 6.42.)

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