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THE CONSTITUENTS
OF
LEPTANDRA

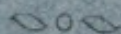
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CCVI.—*The Constituents of Leptandra.*

By FREDERICK BELDING POWER and HAROLD ROGERSON.

UNDER the title of "leptandra," the Pharmacopœia of the United States recognises the dried rhizome and roots of *Veronica virginica*, Linné (*Leptandra virginica*, Nuttall), a plant which is indigenous to the greater part of North America. The above-mentioned underground portion of the plant is used medicinally, and the crude resinous material obtained therefrom is one of the products to which the name "leptandrin" has been assigned.

The first chemical examination of "leptandra" appears to have been that recorded by E. S. Wayne (*Proc. Amer. Pharm. Assoc.*, 1856, p. 34), who stated that, besides essential oil, bitter extractive, tannin, gum, and resin, it contains a crystalline, bitter substance,

which separated from the ethereal solution in needles. This substance, although not further characterised, was considered to represent the active principle of the drug, and for it the name "leptandrin" has since been proposed. The same investigator (*Amer. J. Pharm.*, 1859, **31**, 557) also observed the presence of "a saccharine principle having the properties of mannite." It was subsequently indicated by F. F. Mayer (*Amer. J. Pharm.*, 1863, **35**, 298), and more recently by J. U. Lloyd (*Proc. Amer. Pharm. Assoc.*, 1880, **28**, 421), that the bitter principle of the drug is a glucoside, although no definite substance of this class had actually been isolated. Steinmann (*Amer. J. Pharm.*, 1887, **59**, 229) states that he obtained the bitter principle in crystals of a pale lemon-yellow colour, but they yielded no dextrose when boiled with dilute sulphuric acid, and their solution gave no precipitate with the usual alkaloid reagents.

It will be apparent from the brief review of the literature given above that, with the exception of the recorded presence of mannitol, nothing of a very definite nature has up to the present been known respecting the constituents of "leptandra." It was therefore deemed of interest to subject it to a complete examination, and the results are embodied in the present communication.

EXPERIMENTAL.

The material employed for this investigation consisted of a good quality of commercial "leptandra," which conformed in its characters to the description given of the latter in the United States Pharmacopœia.

A small portion (10 grams) of the material was first tested for an alkaloid, but the reactions were so slight as to indicate the presence of not more than traces of such a substance.

Twenty grams of the ground material were successively extracted in a Soxhlet apparatus with various solvents, when the following amounts of extract, dried at 100°, were obtained:

Petroleum (b. p. 35—50°)	extracted	0.11 gram	=	0.55 per cent.
Ether	"	0.56 "	=	2.80 "
Chloroform	"	1.00 "	=	5.00 "
Ethyl acetate	"	0.65 "	=	3.25 "
Alcohol	"	2.95 "	=	14.75 "

Total 5.27 grams = 26.35 per cent.

For the purpose of a complete examination, a quantity (55.56 kilograms) of the ground material was extracted by continuous percolation with hot alcohol. After the removal of the greater portion of the alcohol, a viscid, dark-coloured extract was obtained, amounting to 19.79 kilograms.

Distillation of the Extract with Steam. Separation of an Essential Oil.

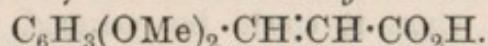
A quantity (2 kilograms) of the above-mentioned extract was mixed with water, and steam passed through the mixture for several hours. The distillate, which amounted to about 6 litres, contained some oily drops floating on the surface. It was thoroughly extracted with ether, the ethereal liquid being dried and the solvent removed, when 0.9 gram of an essential oil was obtained. The yield of the latter was thus equivalent to 0.16 per cent. of the weight of the drug. This essential oil, when distilled under diminished pressure, passed over between 120° and 160°/25 mm. It was a dark brown, mobile liquid, possessing a strong, persistent odour, and gave no coloration with ferric chloride.

Non-volatile Constituents of the Extract.

After the distillation of the extract with steam, as above described, there remained in the distillation flask a dark-coloured, aqueous liquid (A), and a quantity of a dark brown resin (B). These products, when cold, were separated by filtration, and the resin repeatedly washed with hot water until nothing further was removed, the washings being added to the aqueous liquid.

Examination of the Aqueous Liquid (A).

Isolation of 3:4-Dimethoxycinnamic Acid,



The aqueous liquid was repeatedly extracted with ether, and the combined ethereal extracts evaporated to a small volume. On cooling, a quantity (5.0 grams) of a crystalline substance separated. This was removed by filtration, dried, and recrystallised from water, when it separated in yellow needles, melting at about 170°, but after repeated crystallisation from absolute alcohol it was obtained in large, colourless needles, melting at 180—181°. (Found, C=63.4; H=5.9; OMe=29.2. Calc., C=63.5; H=5.8; OMe=29.8 per cent.)

The substance was found to be an acid, and is seen to agree in its characters and composition with 3:4-dimethoxycinnamic acid, $\text{C}_6\text{H}_3(\text{OMe})_2\cdot\text{CH}:\text{CH}\cdot\text{CO}_2\text{H}$. When mixed with a portion of the latter, as obtained by the methylation of ferulic acid (Trans., 1907, 91, 893), the melting point was unchanged. Further confirmation of the identity of the acid was obtained by the preparation of its methyl ester, which separated from absolute alcohol in small prisms, melting at 64°. So far as known to us, this is the first

instance in which 3:4-dimethoxycinnamic acid has been observed to occur in nature.

The ethereal liquid from which the above-described acid had been separated was diluted somewhat, and then shaken with successive portions of aqueous ammonium carbonate. On acidifying the alkaline liquids, a solid substance was precipitated, which was likewise found to consist of 3:4-dimethoxycinnamic acid. The total amount of this acid obtained from 2 kilograms of the original alcoholic extract was 12.0 grams, and was thus equivalent to about 0.2 per cent. of the weight of the drug.

The ethereal liquid was subsequently shaken with a solution of sodium carbonate, which, however, removed nothing. It was then treated with a 10 per cent. solution of sodium hydroxide, when a quantity of resinous material was removed, but from which nothing definite could be isolated. On finally evaporating the ether, only a small amount of a yellow, amorphous product was obtained.

The original aqueous liquid (A), which had been extracted with ether as above described, was thoroughly shaken with successive portions of amyl alcohol. These liquids were then united, washed repeatedly with water, and concentrated under diminished pressure to a small volume, when, on cooling, a considerable quantity of a light brown, amorphous product separated. After removing the amyl alcohol as completely as possible, the entire amount of this product was dissolved in alcohol, and the solution poured into a large volume of water. The precipitate thus produced was collected, washed, and dried, when it could be reduced to a brown powder, but all attempts to obtain it in a crystalline state were unsuccessful. It amounted to 90 grams, or 1.6 per cent. of the weight of drug employed.

The above-described product possessed an intensely bitter and nauseous taste. It was readily soluble in alcohol, but very sparingly so in water, even on boiling. Although the very dilute aqueous solution frothed strongly on agitation, the substance appeared to possess otherwise none of the characters of the saponins, and it was not sternutatory.

In order to obtain some further information respecting the character of the above-described product, a quantity (10 grams) of it was heated with 1000 c.c. of 2 per cent. aqueous sulphuric acid for about four hours, when, on cooling, a hard, black, resinous mass separated. The liquid was then distilled in a current of steam, the distillate extracted with ether, and the ethereal liquid shaken with a solution of sodium carbonate. On acidifying the alkaline liquid, again extracting with ether, and removing the solvent, a

small amount of an acid was obtained, which, on crystallising from water, separated in leaflets, melting at 131—133°. This acid yielded benzaldehyde on oxidation, and was identified as cinnamic acid. The ethereal liquid which had been extracted with alkali was finally evaporated, but it yielded only a trace of a deep yellow oil.

The aqueous, acid liquid remaining after the distillation with steam, as above described, was separated from the hard, black, resinous mass, which weighed 5.5 grams, and shaken with ether, the ethereal liquid being subsequently extracted with a solution of ammonium carbonate. On acidifying the alkaline liquid, again extracting with ether, and removing the solvent, about 0.3 gram of a crystalline product was obtained, which was found to consist of a mixture of acids. The ethereal liquid which had been extracted with alkali was finally evaporated, but it yielded only a small amount of a yellow oil, which gave a green coloration with ferric chloride.

After extracting the above-mentioned aqueous, acid liquid with ether, it was treated with barium hydroxide for the removal of the sulphuric acid. The filtered liquid readily reduced Fehling's solution, but no crystalline osazone could be prepared from it.

From the above results it was evident that the bitter, amorphous product, which had been obtained by extracting the original aqueous liquid with amyl alcohol, was of a complex nature, and that not more than a small proportion of it could have been glucosidic. It was, moreover, apparent that the acids which it yielded by treatment with dilute sulphuric acid were present in the form of esters, inasmuch as on heating the product with aqueous sodium hydroxide a similar mixture of acids was obtained, and in better yield. This mixture of acids was found on examination to consist chiefly of *p*-methoxycinnamic acid, together with smaller amounts of cinnamic acid and another compound which could not be identified.

The original aqueous liquid, after being extracted with amyl alcohol as above described, was concentrated somewhat, and treated with a slight excess of a solution of basic lead acetate. A copious brown precipitate was thus produced, which was collected, well washed with water, then suspended in water, decomposed by hydrogen sulphide, and the mixture filtered. The filtrate, when concentrated, was dark reddish-brown, and appeared to contain only tannic and colouring matter.

The liquid from the basic lead acetate precipitate was treated with hydrogen sulphide for the removal of the lead, and the filtered liquid concentrated to a small bulk. To the syrup thus obtained

a large volume of alcohol was added, when a quantity of a crystalline substance was deposited, which was collected, washed with a little alcohol, and dried. The liquid from which this crystalline substance had been separated was deprived of alcohol, and evaporated to the consistency of a syrup. It evidently contained a large amount of a sugar, since it readily reduced Fehling's solution, and yielded *d*-phenylglucosazone, melting at 209—211°.

Isolation of d-Mannitol.

The crystalline substance above described, which amounted to 120 grams, or 2.14 per cent. of the weight of the drug, was recrystallised from alcohol, when it separated in needles, melting at 165—166°, and proved to be *d*-mannitol. (Found, C=39.5; H=7.8. Calc., C=39.6; H=7.7 per cent.)

Further confirmation of the identity of the above-described substance with mannitol was obtained by the formation of its acetyl and benzoyl derivatives.

On heating a little of the substance with acetic anhydride, a product was obtained which, when crystallised from absolute alcohol, separated in octahedra, melting at 122—124°, and consisted of the hexa-acetyl derivative of mannitol.

Another portion of the substance was benzoylated by the Schotten-Baumann method, as employed by Panormoff (*J. Russ. Phys. Chem. Soc.*, 1891, **23**, 375), when a product was obtained which was soluble in chloroform, but, on the removal of the solvent, formed a syrup. On dissolving this, however, in a small volume of ether, it yielded a mass of needle-shaped crystals, which melted at 149°, and after recrystallisation from a mixture of ethyl acetate and alcohol, or from acetic anhydride, the melting point remained unchanged. (Found, C=71.3; H=4.9. Calc., C=71.4; H=4.7 per cent.)

This substance is thus seen to be hexabenzoylmannitol, $C_6H_8O_6(CO \cdot C_6H_5)_6$, the melting point of which has been given as 149° by Skraup (*Monatsh.*, 1889, **10**, 389) and by Panormoff (*loc. cit.*), but was incorrectly recorded by Stohmann, Rodatz, and Herzberg (*J. pr. Chem.*, 1887, [ii], **36**, 354) as 124—125°.

The optical rotatory power of hexabenzoylmannitol does not appear to have previously been recorded, and this was therefore determined, with the following result:

0.4238, made up to 20 c.c. with chloroform, gave $\alpha_D + 2^\circ 9'$ in a 2-dcm. tube, whence $[\alpha]_D + 50.7^\circ$.

If the benzoylation of mannitol is conducted in the usual manner, by adding the benzoyl chloride in small quantities at a time, a dibenzoyl derivative, $C_6H_{12}O_6(CO \cdot C_6H_5)_2$, is obtained. This is very

sparingly soluble in the usual organic solvents, and crystallises in small, prismatic needles, which melt at 178—180°. (Found, C=61.0; H=5.8. Calc., C=61.5; H=5.6 per cent.)

0.3410, made up to 20 c.c. with pyridine, gave $\alpha_D + 0^\circ 22'$ in a 2-dcm. tube, whence $[\alpha]_D + 10.7^\circ$.

Dibenzoylmannitol has previously been obtained by Einhorn and Hollandt (*Annalen*, 1898, **301**, 102), who recorded its melting point as 178°. On adding an excess of benzoyl chloride to a hot solution of mannitol in pyridine, according to the method of the last-mentioned investigators, a crystalline substance began to separate at once, which was evidently the dibenzoyl derivative. When, however, the liquid was heated a little longer, a vigorous reaction ensued, which soon subsided, and a perfectly clear solution was obtained. The product was then poured into water and extracted with ether, when a substance was obtained which melted at 149°, and proved to be hexabenzoylmannitol.

Examination of the Resin (B).

This was a dark brown, brittle mass, and amounted to about 350 grams, being thus equivalent to 6.2 per cent. of the drug. It was dissolved in alcohol, mixed with purified sawdust, and the mixture successively extracted in a Soxhlet apparatus with light petroleum (b. p. 35—50°), ether, chloroform, ethyl acetate, and alcohol.

Petroleum Extract of the Resin.

This was a dark brown mass, amounting to 24.5 grams. The extract was dissolved in ether, and the ethereal solution shaken with aqueous ammonium carbonate, which, however, removed only a small amount of resinous material, together with a trace of 3:4-dimethoxycinnamic acid. The ethereal solution was then shaken with aqueous potassium carbonate, and the alkaline liquid acidified, when a quantity of black, tarry material was precipitated. This was distilled several times under diminished pressure, when a product was finally obtained which passed over between 220° and 240°/15 mm. as a light yellow oil, and partly solidified on cooling. The free acids thus obtained amounted to 3.7 grams, and were examined together with the combined acids which will subsequently be described.

After treatment with potassium carbonate, as above described, the ethereal solution was shaken with aqueous potassium hydroxide, which, however, removed nothing. On finally evaporating the ether, a residue was obtained, which was hydrolysed by heating with an alcoholic solution of potassium hydroxide. The alcohol was then

removed, and the cooled, aqueous, alkaline liquid extracted with ether, the ethereal liquid being dried and the solvent evaporated. On dissolving the residue in alcohol, a small quantity of a solid separated, which, when recrystallised from ethyl acetate, melted at 62—65°, and was found to consist of a hydrocarbon and an alcohol, but the amount was too small to permit of their separation.

Isolation of a Phytosterol, Verosterol, $C_{27}H_{46}O, H_2O$.

The alcoholic filtrate from the above-mentioned solid was concentrated to a small bulk, when, after two or three days, a quantity of a crystalline substance separated. This was collected, washed, and recrystallised from a mixture of ethyl acetate and dilute alcohol, when it separated in flat needles, melting at 135—136°, and gave the colour reactions of the phytosterols:

0.2500, on heating at 110°, lost 0.0126 H_2O . $H_2O = 5.0$.

0.1230 * gave 0.3764 CO_2 and 0.1360 H_2O . $C = 83.5$; $H = 12.3$.

$C_{27}H_{46}O, H_2O$ requires $H_2O = 4.5$ per cent.

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

A determination of its optical rotatory power gave the following result:

0.2374,* made up to 20 c.c. with chloroform, gave $\alpha_D - 0^\circ 47'$ in a 2-dcm. tube, whence $[\alpha]_D - 33.0^\circ$.

A small amount of the phytosterol was converted into its acetate, which separated from acetic anhydride in flat needles, melting at 119—120°.

The above-described phytosterol evidently represents a member of this class of substances which is widely distributed in nature, and compounds possessing practically the same physical characters have previously been obtained in these laboratories from various sources, such as olive bark, wild cherry bark, and jalap (Trans., 1908, **93**, 909; 1909, **95**, 246; *J. Amer. Chem. Soc.*, 1910, **32**, 87; compare also Menozzi and Moreschi, *Atti R. Accad. Lincei*, 1910, [v], **19**, i, 187). In view of these facts, and in order to distinguish the above-described phytosterol from sitosterol, which differs by the higher melting point of its acetate (*Monatsh.*, 1897, **18**, 551), it would appear desirable to assign to it a specific name. It is therefore proposed to designate it *verosterol*, with reference to the generic name of the plant, *Veronica*, from which it has now been obtained.

Identification of the Fatty Acids.

The alkaline liquid, which had been extracted with ether as above described, was acidified, and the liberated fatty acids collected,

* Anhydrous substance,

dried, and distilled under diminished pressure, when they passed over between 220° and $250^{\circ}/15$ mm. as a pale yellow oil. The acids thus obtained, which amounted to 4.2 grams, were mixed with the previously mentioned portion of acids present in the free state, and the whole converted into their lead salts, the latter being then digested with ether, when a portion was dissolved. Both the soluble and insoluble portions were decomposed by hydrochloric acid, and the regenerated fatty acids purified by distillation under diminished pressure. The soluble portion of the lead salts yielded 4.2 grams of liquid acids, whilst the insoluble portion gave 3.3 grams of solid acids.

The Liquid Acids.—These acids, when distilled under diminished pressure, passed over between 215° and $235^{\circ}/15$ mm. as a yellow oil. An analysis and a determination of the constants gave the following results:

0.1738 gave 0.4842 CO_2 and 0.1788 H_2O . $\text{C}=76.0$; $\text{H}=11.4$.

0.3788 absorbed 0.4872 iodine. Iodine value = 128.6.

0.1540 neutralised 0.0307 KOH. Neutralisation value = 199.3.

$\text{C}_{18}\text{H}_{34}\text{O}_2$ requires $\text{C}=76.6$; $\text{H}=12.1$ per cent. Iodine value = 90.1;
Neutralisation value = 198.9.

$\text{C}_{18}\text{H}_{32}\text{O}_2$ requires $\text{C}=77.1$; $\text{H}=11.4$ per cent. Iodine value = 181.4;
Neutralisation value = 200.4.

It is evident from the above results that the liquid acids consisted of a mixture of oleic and linolic acids.

The Solid Acids.—These acids, after being again distilled under diminished pressure, were crystallised twice from ethyl acetate, when they melted at $54-56^{\circ}$:

0.1512 gave 0.4190 CO_2 and 0.1728 H_2O . $\text{C}=75.6$; $\text{H}=12.7$.

0.2864 neutralised 0.0590 KOH. Neutralisation value = 206.

$\text{C}_{16}\text{H}_{32}\text{O}_2$ requires $\text{C}=75.0$; $\text{H}=12.5$ per cent.

Neutralisation value = 219.1.

$\text{C}_{18}\text{H}_{36}\text{O}_2$ requires $\text{C}=76.1$; $\text{H}=12.7$ per cent.

Neutralisation value = 197.5.

These results indicate that the solid acids consisted of a mixture of palmitic and stearic acids in about equal proportions.

Ethereal Extract of the Resin.

During the extraction of the resin with ether a quantity of a sparingly soluble, yellowish-brown substance was deposited, and when the extraction was complete this was collected, washed with ether, and dried, when it was found to weigh 5 grams. It was entirely amorphous, and proved to be similar in character to the product extracted from the original aqueous liquid by amyl alcohol,

which has already been described. On heating with aqueous sodium hydroxide, it yielded *p*-methoxycinnamic acid, which was subsequently obtained in larger amount from the chloroform extract of the resin.

The portion of extract which was more readily soluble in ether consisted of a dark resinous mass, amounting to 95 grams. It was thoroughly examined, but nothing except a small quantity of 3:4-dimethoxycinnamic acid could be isolated from it.

Chloroform Extract of the Resin.

This was a dark-coloured resinous mass, weighing 135 grams. It could easily be reduced to a fine powder, which was tasteless. The chloroform solution of the resin was shaken with aqueous ammonium carbonate, when a small quantity of 3:4-dimethoxycinnamic acid was removed. The liquid was then shaken with a solution of sodium carbonate, but only a small amount of a resinous product was obtained.

Isolation of p-Methoxycinnamic Acid, $\text{OMe} \cdot \text{C}_6\text{H}_4 \cdot \text{CH} : \text{CH} \cdot \text{CO}_2\text{H}$.

After treating the chloroform liquid with the alkaline carbonates, as above described, it was shaken with successive portions of a 10 per cent. solution of sodium hydroxide. These liquids were united and acidified, when a large quantity of a black, resinous product was precipitated. This resinous product was then treated with chloroform, in which it only partly dissolved. The chloroform solution was shaken with aqueous sodium carbonate, and the alkaline liquid acidified, when a crystalline precipitate was obtained. It was thus evident that on shaking the original chloroform liquid with alkali hydroxide, some constituent of it had been hydrolysed. The crystalline precipitate was collected, washed, and dried, when it amounted to 14 grams. By fractional crystallisation from ethyl acetate, it was found to consist of a mixture of 3:4-dimethoxycinnamic acid and an acid which separated in iridescent, prismatic needles. The latter melted at 170° , assuming a "liquid-crystalline" phase, which persisted until the temperature of 181 – 182° was reached, when it passed into the ordinary liquid state. The "crystalline" character of the liquid between 170° and 181° was confirmed by observing it through crossed Nicol's prisms. The last-mentioned acid was analysed. (Found, $\text{C} = 67.3$; $\text{H} = 5.8$; $\text{OMe} = 17.3$. Calc., $\text{C} = 67.4$; $\text{H} = 5.6$; $\text{OMe} = 17.4$ per cent.)

In order further to characterise this acid, its methyl ester was prepared. This was accomplished by boiling a solution of the acid in methyl alcohol with a few drops of concentrated sulphuric acid

for about two hours on the water-bath. The product so obtained was recrystallised from absolute alcohol, when it separated in flat needles, melting at 88—90°.

The above results render it evident that the substance under examination was *p*-methoxycinnamic acid, which appears only once previously to have been observed to occur in nature. In the form of its ethyl ester, it was found by van Romburgh to be the chief constituent of the essential oil of *Kaempferia galanga*, Linné (*Proc. K. Akad. Wetensch. Amsterdam*, 1900, **3**, 38; 1902, **4**, 618; Schimmel's *Bericht*, Oct., 1900, p. 37, and April, 1903, p. 38).

As it appears not to have previously been recorded that *p*-methoxycinnamic acid shows, on heating, a "liquid-crystalline" phase, it was deemed desirable to confirm this observation by means of the synthetically prepared acid. For this purpose a small quantity of *p*-coumaric acid was methylated by means of methyl sulphate, and the product recrystallised from ethyl acetate, when it separated in prismatic needles, melting to the "liquid-crystalline" phase at 170°, and then passing to the ordinary liquid state at 181—182°. A mixture of the naturally-occurring and synthetic acids likewise showed exactly the same behaviour at the same temperatures, and their identity was therefore definitely established.

The chloroform liquid from which the above acids had been isolated was finally evaporated for the removal of the solvent. A resinous product was thus obtained, from which, however, nothing crystalline could be isolated.

Ethyl Acetate and Alcohol Extracts of the Resin.

These extracts were dark, resinous products, amounting to 77.5 and 32.0 grams respectively. They were heated with a 5 per cent. solution of sulphuric acid in aqueous alcohol, but, with the exception of a small quantity of sugar yielding *d*-phenylglucosazone (m. p. 209—210°), nothing definite was obtained.

Summary.

The results of the present investigation may be summarised as follows:

The material employed was commercial "leptandra," consisting of the rhizome and roots of *Veronica virginica*, Linné (*Leptandra virginica*, Nuttall).

An alcoholic extract of this material, when distilled with steam, yielded an amount of essential oil equivalent to 0.16 per cent. of the weight of the drug. This essential oil was a dark brown liquid, which distilled between 120° and 160°/25 mm.

The portion of the extract which was soluble in water contained 3:4-dimethoxycinnamic acid, a quantity of mannitol, amounting to 2.14 per cent. of the weight of the drug, and a sugar which yielded *d*-phenylglucosazone (m. p. 209—211°), together with some tannic and colouring matter. It yielded, furthermore, a quantity of a brown, amorphous product, which possessed an intensely bitter, nauseous taste, and amounted to 1.6 per cent. of the weight of the drug. By the hydrolysis of this product there were obtained, besides resinous material, cinnamic and *p*-methoxycinnamic acids.

The portion of the extract which was insoluble in water consisted chiefly of a dark brown resin, which amounted to 6.2 per cent. of the weight of the drug. From this resin the following substances were obtained: A phytosterol, $C_{27}H_{46}O$ (m. p. 135—136°; $[\alpha]_D -33.0^\circ$), which it is proposed to designate *verosterol*; a mixture of fatty acids, consisting apparently of oleic, linolic, palmitic, and stearic acids; *p*-methoxycinnamic acid, which was present in the form of an ester; and a very small amount of 3:4-dimethoxycinnamic acid, which had probably been occluded by the resin.

It has been observed that *p*-methoxycinnamic acid, when melted, passes into a "liquid-crystalline" phase, which persists until a temperature of 181—182° is reached.

It has not been possible to confirm the statement recorded in the literature that "leptandra" contains a crystalline, bitter glucoside, designated as "leptandrin," to which its activity may be attributed. Steinmann (*Amer. J. Pharm.*, 1887, **59**, 229) obtained from "leptandra," in an amount of about 0.1 per cent., a crystalline, yellow substance, which possessed a very bitter taste, and was found not to be a glucoside, although it was not further characterised. From the method by which this substance was isolated, it appears highly probable that it consisted of 3:4-dimethoxycinnamic acid, contaminated with a little of the above-mentioned, bitter, amorphous product. The fact that an aqueous solution of this product froths strongly on agitation has doubtless led to the statement recorded in the literature that "leptandra" contains saponin.

Some tests with preparations of "leptandra," which were kindly conducted for us by Dr. H. H. Dale, Director of the Wellcome Physiological Research Laboratories, led to the following conclusions.

Both the crude resin and the bitter, amorphous product obtained from the portion of the alcoholic extract which was soluble in water were administered by the mouth to dogs, in doses of 1 gram each, but without any visible effect. The bitter, amorphous product was also tested on the mammal by intravenous injection, and on the isolated mammalian heart, but no characteristic action could be

observed. Although the total alcoholic extract of the drug, when given to a dog in doses of 5 grams, produced vomiting, this may be attributed to its nauseous taste and irritant effect on the stomach rather than to any specific action.

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