The constituents of the flowers of Matricaria chamomilla / by Frederick Belding Power and Henry Browning, Jun.

CCXI.—*The Constituents of the Flowers of* Matricaria Chamomilla.

By Frederick Belding Power and Henry Browning, jun.

The flower-heads of the composite plant *Matricaria Chamomilla*, Linné, commonly designated as the "German Chamomile," are used to a considerable extent medicinally, and possess properties similar to those of the so-called Roman or English chamomile (from *Anthemis nobilis*, Linné). They are recognised by most of the national Pharmacopœias, but not by the British.

The older investigations of *Matricaria* flowers have indicated, besides a relatively small proportion of essential oil, the presence

of only the common constituents of plants, or, in addition thereto, the very indefinite products termed "anthemic acid" and "anthemidin," which need not be further considered here.

Klobb, Garnier, and Ehrwein (*Bull. Soc. chim.*, 1910, [iv], **7**, 946) isolated from the flowers of *Matricaria* a hydrocarbon (m. p. 52—54°), to which they assigned the formula $C_{29}H_{60}$. Klobb (*Ann. chim. Phys.*, 1911, [viii], **24**, 410) subsequently obtained from the same source a product melting at 120—131°, which gave the colour reaction of the phytosterols, and was regarded by him as a mixture of substances of this class. It was stated to yield an acetylated product, melting at 150—175°, from which two bromo-derivatives, melting at 158—165° and 115—118° respectively, were obtained.

Inasmuch as the present authors have recently investigated the constituents of the flowers of *Anthemis nobilis* (this vol., p. 1829), it was deemed of interest, for the purpose of comparison, also to subject the flowers of *Matricaria Chamomilla* to a complete chemical examination. The results of the present research are summarised at the end of this paper.

Experimental.

The material employed for this investigation consisted of a good quality of commercial "German Chamomile Flowers" from *Matricaria Chamomilla*, Linné.

Fifteen grams of the ground material were extracted with Prollius' fluid, and the resulting product tested with the usual alkaloid reagents, but only very slight reactions were obtained.

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

Petroleum (b. p. 35—50°)	extracted	0·63 gram	=	3·15 per cent.
Ether	,,	0·98 ,,	=	4·90 ,, ,,
Chloroform	,,	0·20 ,,	=	1·00 ,, ,,
Ethyl acetate	,,	1·02 ,,	=	5·10 ,, ,,
Alcohol	,,	3·10 ,,	=	15·50 ,, ,,
	Total	5·93 grams	=	29·65 per cent.

For the purpose of a complete examination, 22·23 kilograms of the ground flowers were completely extracted with hot alcohol, when, after the removal of the greater part of the solvent, 8·53 kilograms of a soft, green extract were obtained.

The entire amount of the alcoholic extract was mixed with a little water and distilled in a current of steam, when 23 grams of an essential oil were obtained, which possessed the characteristic, deep blue colour. The oil distilled over a wide range of tempera-

ture, the whole of the distillate being blue, with the exception of a small fraction of high boiling point (250—270°/15 mm.), which was a dark green, viscous liquid. The blue oil gave the colour reaction for furfuraldehyde, and, on keeping for some time, deposited a very small amount of a crystalline substance, which was collected. This substance melted at 110°, developed a coumarin-like odour on heating, and its solution in concentrated sulphuric acid showed a blue fluorescence. It evidently consisted of umbelliferone methyl ether, which was subsequently obtained in much larger amount, as described below. A portion of the essential oil, in ethereal solution, was shaken with aqueous sodium carbonate, when a trace of substance was removed, which, when crystallised from dilute alcohol, melted at 61°, and was evidently a fatty acid. On subsequently shaking the ethereal solution with 10 per cent. sulphuric acid, nothing definite was obtained. The oil which had been subjected to this treatment was heated for several hours with an alcoholic solution of potassium hydroxide, when only a small amount of dark coloured, acidic material was obtained, whilst the distilled neutral portion was of a much more brilliant blue colour than the original oil. This blue colour remained unchanged when the oil, in alcoholic solution, was treated with sodium.

After subjecting the alcoholic extract to distillation with steam, as above described, there remained in the distillation flask a dark brown, aqueous liquid (*A*), together with some fatty material, which separated on the surface, and a comparatively small amount of soft, brown resin, which was deposited. The fatty and resinous material were separately washed with hot water, then united, and constitute the product subsequently described as the resin (*B*), whilst the washings, after concentration, were added to the main portion of the aqueous liquid.

Examination of the Aqueous Liquid (A).

The above-mentioned aqueous liquid was concentrated under diminished pressure, and then extracted many times with ether. Both before and after this treatment it gave slight reactions with the usual alkaloid reagents. The ethereal liquid was therefore first shaken with a 5 per cent. aqueous solution of hydrogen chloride, but this removed only traces of indefinite material, and it was subsequently extracted with aqueous ammonium carbonate, sodium carbonate, and potassium hydroxide. The ammonium carbonate extract, on acidification, deposited a quantity of tarry material, which was only partly soluble in ether. The dissolved portion, after removal of the solvent, was converted into the methyl

ester, and the product distilled in a current of steam, the volatile and non-volatile portions being then treated for their separation into phenolic and non-phenolic esters. The volatile phenolic ester possessed the odour of methyl salicylate, and, after hydrolysis, yielded 0·04 gram of an acid, which crystallised in fine, colourless needles, melting at 150—151°. This acid gave a violet coloration with ferric chloride, and as no depression of the melting point ensued when mixed with salicylic acid, there was no doubt of its identity with the latter substance. The volatile, non-phenolic ester yielded on hydrolysis a small amount of acid, which was fractionally precipitated in the form of its silver salts. The latter, on ignition, gave, respectively, 44·6, 43·7, and 43·8 Ag, the first fraction of salt having undergone slight reduction. $C_8H_{15}O_2Ag$ requires Ag = 43·0 per cent. It therefore seems probable that the volatile, non-phenolic acid consisted chiefly of an octoic acid. The portion of the esterified product which was not volatile in steam yielded nothing definite.

Isolation of Apigenin, $C_{15}H_{10}O_5$.

The above-mentioned sodium carbonate extract of the ethereal liquid was acidified, when a pale yellow substance, mixed with some tarry material, was deposited. This precipitate was collected, washed with water, and dried, when it amounted to 17·3 grams. After several separations from a mixture of alcohol and ethyl acetate, the substance was obtained as a pale yellow powder, melting at 344—347°. (Found, C = 66·0; H = 3·9. $C_{15}H_{10}O_5$ requires C = 66·7; H = 3·7 per cent.)

The substance was evidently apigenin, and its identity was further confirmed by the preparation of its acetyl (m. p. 176—178°) and benzoyl (m. p. 208°) derivatives.

The aqueous, acid liquid from which the crude apigenin had been separated, as above described, was extracted many times with ether. This removed about 0·4 gram of a substance, which, after several crystallisations from dilute alcohol, was obtained in fine, colourless needles, melting at 237—239°. On heating the substance it sublimed, and developed a coumarin-like odour. Its solution in concentrated sulphuric acid showed a strong blue fluorescence, and with ferric chloride a distinct green colour was produced. The aqueous solution of the substance possessed a slight blue fluorescence, which was not perceptible on the addition of alkali, owing to the production of a deep yellow colour. The above-described characters of the substance rendered it probable that it consisted of a mixture of umbelliferone (m. p. 225°) with

a dihydroxycoumarin, such as daphnetin or æsculetin, since the latter compounds, which melt at 253—256° and about 270° respectively, are known to give a yellow colour with alkalis and a green coloration with ferric chloride. An analysis of the substance, and a determination of the molecular weight by the microscopic method, gave the following results:

0·0842 * gave 0·2000 CO_2 and 0·0323 H_2O. C = 64·8; H = 4·3.

0·0424 * in 5 c.c. of alcohol, using benzil as the standard, was between 0·045 and 0·047 mol. Mean M.W. = 183.

Umbelliferone, $C_9H_6O_3$, requires C = 66·7; H = 3·7 per cent. M.W. = 162.

Dihydroxycoumarin, $C_9H_6O_4$, requires C = 60·7; H = 3·4 per cent. M.W. = 178.

The remainder of the substance was acetylated, and the product crystallised from water in three fractions, which possessed the following characters:

(1) M. p. 137°. Mean M.W. (in acetone solution by the microscopic method) = 207.

The melting point (140°) of a known specimen of acetylumbelliferone (M.W. = 204) was not depressed by admixture with this fraction, and the substances were apparently identical.

(2) M. p. 130—133°. An analysis of this fraction gave C = 63·8; H = 4·3.

Acetylumbelliferone, $C_{11}H_8O_4$, requires C = 64·7; H = 3·9 per cent.

Diacetyldihydroxycoumarin, $C_{13}H_{10}O_6$, requires C = 59·5; H = 3·8 per cent.

(3) M. p. 115—118°. The mean molecular weight of this fraction, in acetone solution, was 228. $C_{13}H_{10}O_6$ requires M.W. = 262.

These results served to confirm the conclusion that the above-described substance, melting at 237—239°, consisted chiefly of umbelliferone, together with a small proportion of a dihydroxycoumarin.

Isolation of Umbelliferone Methyl Ether.

The ethereal extract of the aqueous liquid, which had been extracted with aqueous sodium carbonate, as above described, was subsequently shaken with aqueous potassium hydroxide, which removed a small amount of a crystalline substance. On finally washing and drying the ethereal liquid, and evaporating the solvent, a much larger amount of the same substance was obtained. This material was recrystallised from dilute alcohol, when it separated in flat needles of a slightly yellowish colour, melting at 115—116°.

* Dried at 110°.

The substance developed a coumarin-like odour on warming, and its solution in concentrated sulphuric acid showed a beautiful blue fluorescence. (Found, C = 68·0; H = 4·6. $C_{10}H_8O_3$ requires C = 68·2; H = 4·5 per cent.)

The above-described substance was thus identified as umbelliferone methyl ether, the occurrence of which in nature appears only once previously to have been observed, namely, in the caryophyllaceous plant *Herniaria hirsuta*, Linné (*Monatsh.*, 1889, **10**, 161). The amount obtained in the present instance in a pure state was 6·3 grams, being thus equivalent to 0·028 per cent. of the weight of *Matricaria* flowers employed.

The aqueous liquid (*A*) which had been extracted with ether was next shaken with several successive portions of warm amyl alcohol. The combined amyl-alcoholic liquids were concentrated under diminished pressure in three stages, the material which separated during this process being in each case collected. All of these products were of a syrupy or gelatinous character, and formed on drying a varnish-like mass, which seemed to be incapable of crystallising. A portion of the material was therefore heated for two hours in dilute alcoholic solution with an amount of hydrogen chloride equal to 5 per cent. of the mixture. A resinous product was thus deposited, which was separated from the dilute alcoholic liquid, and the latter extracted with ether, but practically nothing was removed. The acid liquid was subsequently exactly neutralised with sodium carbonate, evaporated to dryness under diminished pressure, and the residue extracted with alcohol. From the product thus obtained a small amount of an osazone was prepared, which, in the crude state, melted at about 190°. The above-mentioned resinous product was distributed over purified sawdust, and the mixture extracted in a Soxhlet apparatus with ether. A yellowish substance was thus obtained, which, after separation from dilute alcohol, melted and decomposed at 345°. This substance possessed all the characters of apigenin, and its identity as such was confirmed by analysis. (Found, C = 66·3; H = 4·2. $C_{15}H_{10}O_5$ requires C = 66·7; H = 3·7 per cent.)

From these results it may be concluded that apigenin existed in the flowers of *Matricaria* in the form of a glucoside, as well as in the free state, although, in distinction from the flowers of *Anthemis nobilis* (this vol., p. 1833), the glucoside could not be obtained in a crystalline form.

After removal of the amyl alcohol from the aqueous liquid (*A*), a portion of the latter, representing 4 kilograms of the alcoholic extract, was treated with a slight excess of a solution of basic lead

acetate. A voluminous precipitate was thus produced, which was collected, thoroughly washed with water, then suspended in water, and decomposed by hydrogen sulphide. The filtrate from the lead sulphide was concentrated under diminished pressure, but then gave no precipitate with a solution of gelatin, and only a brown coloration with ferric chloride, thus indicating the absence of tannin. A portion of the concentrated liquid was heated with both 5 per cent. hydrochloric acid and aqueous alkali, but nothing definite was obtained by this treatment.

The filtrate from the precipitate produced by basic lead acetate was subsequently treated with hydrogen sulphide for the removal of the excess of lead, again filtered, and then concentrated under diminished pressure. The syrupy liquid so obtained (1173 grams) evidently contained a quantity of sugar, since it readily yielded *d*-phenylglucosazone, melting at 208°.

A portion of the syrupy liquid was acetylated, and from the resulting product a very small amount of a crystalline substance was isolated, which, after recrystallisation from a mixture of alcohol and ethyl acetate, separated in colourless needles, melting at 284—288°. The amount of this substance was too small to permit of its further examination. The uncrystallisable portion of the acetylated product was subsequently hydrolysed by heating with dilute sulphuric acid in a current of steam, and the acid removed by means of baryta. As the liquid so obtained was lævorotatory, it indicated the sugar to consist, to a predominating extent, of lævulose.

Inasmuch as the above-mentioned syrupy liquid gave decided reactions with the usual alkaloid reagents, a portion of it was made alkaline by sodium carbonate, and subsequently extracted with both ether and chloroform, but only traces of indefinite, amorphous material were removed by these solvents.

Isolation of Choline, $C_5H_{15}O_2N$.

A quantity (480 grams) of the above-mentioned syrupy liquid was repeatedly treated with alcohol until a product was obtained which was soluble in nearly absolute alcohol. To the alcoholic solution of this product an alcoholic solution of mercuric chloride was added, the resulting precipitate being collected, and dissolved as completely as possible in hot water. The mercury was then removed from the aqueous liquid by means of hydrogen sulphide, the mixture filtered, and the filtrate, after being nearly neutralised with sodium carbonate, evaporated to dryness under diminished pressure. The residue thus obtained was extracted with alcohol, the solvent evaporated, and the residual substance dissolved in

water. To this aqueous solution, acidified with sulphuric acid, a solution of phosphotungstic acid was added, the resulting precipitate being collected, decomposed by aqueous barium hydroxide, and the mixture filtered. After the removal of the excess of barium by carbon dioxide, the filtrate was slightly acidified with hydrochloric acid, and evaporated to dryness under diminished pressure. This residue was repeatedly treated with absolute alcohol until, on the evaporation of the solvent, a product was obtained which dissolved completely in cold absolute alcohol. From one half of this solution a platinichloride was prepared, which, after crystallisation from water, melted and decomposed at 255°, and amounted to about 0·4 gram. The salt was dried at 110° and analysed. (Found, C=19·5; H=4·8; Pt=31·5. $(C_5H_{14}ONCl)_2PtCl_4$ requires C=19·5; H=4·5; Pt=31·7 per cent.)

These results established the presence of choline in *Matricaria* flowers. The amount obtained, in the form of the pure platinichloride, was equivalent to about 0·007 per cent. of the weight of flowers employed. No evidence could be obtained of the presence of any basic substance other than choline.

Examination of the Resin (B).

The combined fatty and resinous material, which had been separated from the aqueous liquid (*A*) after distillation of the original alcoholic extract with steam, was distributed over purified sawdust, and the thoroughly dried mixture then extracted successively in a large Soxhlet apparatus with various solvents. The material from 4 kilograms of the original alcoholic extract yielded the following amounts of the respective products, dried at 100°:

Petroleum (b. p. 35—50°) extracted	350·0	grams.
Ether ,,	98·0	,,
Chloroform ,,	12·5	,,
Ethyl acetate ,,	23·0	,,
Alcohol ,,	130·0	,,
Total	613·5	grams.

Petroleum Extract of the Resin.

This extract, after the removal of the solvent, was heated with an alcoholic solution of potassium hydroxide, the greater part of the alcohol then removed, water added, and the mixture thoroughly extracted with ether. On concentrating the ethereal extract, a considerable amount of crystalline material separated, which was collected, and by the subsequent complete evaporation of the ether a further amount of substance was obtained. In order to ascertain

whether the last-mentioned product contained a fatty alcohol, it was subjected to treatment with phthalic anhydride, but with a negative result. The phthalic anhydride having then been removed from the material, the latter was subsequently dissolved in a large volume of alcohol.

Isolation of Triacontane, $C_{30}H_{62}$.

The alcoholic solution of the substance which had been treated with phthalic anhydride, as above described, was concentrated, and the portions of material which successively separated during this operation were separately collected. The first three of these fractions were oily, but after being distilled under a pressure of 14 mm. they were found to crystallise. This material was crystallised several times from ethyl acetate, and proved to be identical with that which had separated from the above-mentioned ethereal liquid. The substance was finally obtained in colourless, pearly leaflets, melting at 63—65°, and was identified as triacontane. (Found, C = 84·9; H = 14·9. Calc., C = 85·3; H = 14·7 per cent.)

The amount of this hydrocarbon obtained in a pure state was 19 grams, being thus equivalent to about 0·16 per cent. of the weight of *Matricaria* flowers employed.

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

The more soluble products from the above-mentioned alcoholic solution consisted chiefly of a crystalline substance, together with some oily material. The solid was separated, crystallised several times from petroleum of high boiling point, and finally from dilute alcohol. It was thus obtained in colourless leaflets, melting at 132—134°, which gave the colour reaction of the phytosterols:

0·0945, on heating at 105°, lost 0·0039 H_2O. $H_2O = 4·1$.

0·0906 * gave 0·2797 CO_2 and 0·0972 H_2O. C = 84·2; H = 11·9.

$C_{27}H_{46}O,H_2O$ requires $H_2O = 4·5$ per cent.

$C_{27}H_{46}O$ requires C = 83·9; H = 11·9 per cent.

This substance was thus identified as a phytosterol. A portion of it was converted into an acetyl derivative, which, after crystallisation from a mixture of alcohol and ethyl acetate, separated in glistening leaflets, melting at 122—123°. (Found, C = 81·1; H = 11·2. $C_{27}H_{45}O{\cdot}CO{\cdot}CH_3$ requires C = 81·3; H = 11·2 per cent.)

Examination of the Fatty Acids.

The alkaline, aqueous liquid resulting from the hydrolysis of the petroleum extract of the resin, which had been extracted with

* Anhydrous substance.

ether for the removal of the unsaponifiable material, was acidified and again extracted with ether. The fatty acids thus obtained were converted into their ethyl esters, and the latter distilled in a current of steam. A small amount of volatile esters was thus obtained, which possessed an agreeable, fruity odour, but when redistilled they passed over indefinitely between 100° and 250°, and thus consisted of a complex mixture.

The main portion of the esterified product, which was not volatile in steam, was distilled several times under diminished pressure, when it finally passed over between 200° and 260°/12 mm., and amounted to 140 grams. These esters were hydrolysed, and the acids so obtained separated into liquid and solid portions by conversion into their lead salts, and treatment of the latter with ether.

The Liquid Acids.—These acids distilled between 200° and 240°/14 mm., and amounted to 25 grams. They had an iodine value of 132·6, and, on analysis, gave C = 76·7; H = 11·5.

$C_{18}H_{34}O_2$ requires C = 76·6; H = 12·1 per cent. I.V. = 90·1.
$C_{18}H_{32}O_2$ „ C = 77·1; H = 11·4 „ „ I.V. = 181·4.

The above results indicate the liquid acids to have consisted of a mixture of oleic and linolic acids in about equal proportions.

The Solid Acids.—These acids, when distilled under diminished pressure, passed over between 230° and 260°/15 mm. By fractional crystallisation, about 1 gram of an acid was obtained, which melted at 77—78°, and had a neutralisation value of 135·4. This was identified as cerotic acid. (Found, C = 79·1; H = 13·4. $C_{27}H_{54}O_2$ requires C = 79·0; H = 13·2 per cent. N.V. = 136·8.)

The principal portion of solid acid was separated by crystallisation into two fractions, which possessed the following characters:

(1) M. p. 54—55°. C = 75·2; H = 12·5. N.V. = 213·4.
(2) M. p. 55—56°. C = 75·5; H = 12·6. N.V. = 207·1.

$C_{16}H_{32}O_2$ requires C = 75·0; H = 12·5 per cent. N.V. = 219·1.
$C_{18}H_{36}O_2$ „ C = 76·1; H = 12·7 „ „ N.V. = 197.5.

It would thus appear that both of the above fractions consisted of mixtures of palmitic and stearic acids, but in somewhat different proportions.

Ether Extract of the Resin.

This extract of the resin deposited a comparatively small amount of substance, which was collected, and the ethereal liquid was then shaken successively with aqueous ammonium carbonate, sodium carbonate, and potassium hydroxide. Both the first- and the last-mentioned alkali removed only a small amount of indefinite material. The sodium carbonate extract, however, on acidification,

yielded a further small amount of apigenin, and, on subsequently extracting the filtered acid liquid with ether, a very small amount of a colourless substance was obtained, which crystallised from dilute alcohol in needles, melting at about 216°. This substance appeared to be identical with that obtained in an analogous manner from the ethereal extract of the original aqueous liquid (*A*). After the above-described extraction of the ethereal liquid with alkalis, the ether was evaporated. The residue, which consisted chiefly of amorphous, green material, yielded a further small amount of umbelliferone methyl ether, melting at 115—117°.

Isolation of a Phytosterol Glucoside.

The substance deposited from the ether extract of the resin, as above noted, together with some material of a similar nature which had separated from an emulsion formed on extracting the previously described fatty acids, was brought into a Soxhlet apparatus and extracted with absolute alcohol. The product thus obtained was then separated twice from dilute pyridine, when it formed a nearly colourless, microcrystalline powder, melting and decomposing at about 285°:

0·1051 * gave 0·2795 CO_2 and 0·0983 H_2O. C = 72·5; H = 10·4.

A sitosterol glucoside, $C_{33}H_{56}O_6$, requires C = 72·3; H = 10·2 per cent.

A small portion of the substance was converted into an acetyl derivative, which crystallised in colourless leaflets, melting at 158—160°.

The greater part of the material was hydrolysed in amyl alcohol solution by means of hydrochloric acid (compare T., 1913, **103**, 399). There was thus obtained a reducing sugar and a substance crystallising in lustrous leaflets, melting at 132—133°, which was identified as a phytosterol. (Found, C = 83·7; H = 12·3. $C_{27}H_{46}O$ requires C = 83·9; H = 11·9 per cent.)

It is evident from these results that the above-described substance was a phytosterol glucoside.

Chloroform, Ethyl Acetate, and Alcohol Extracts of the Resin.

The chloroform extract was shaken with aqueous alkalis, but yielded nothing definite. The ethyl acetate and alcohol extracts, when heated with sulphuric acid in aqueous alcohol, gave in each case a small amount of apigenin, together with a sugar from which an osazone, melting in the crude state at about 197°, was prepared. These two extracts therefore appeared to contain a small amount of an apigenin glucoside.

* Dried at 105°.

Summary.

The material employed for this investigation consisted of the flower-heads of *Matricaria Chamomilla*, Linné, commonly known as the German chamomile.

In addition to a deep blue essential oil, which deposited a very small amount of umbelliferone methyl ether, the flowers were found to contain the following compounds: (1) salicylic acid, together with, apparently, an octoic acid; (2) apigenin, $C_{15}H_{10}O_5$; (3) a glucoside of apigenin, which could not be obtained in a crystalline state; (4) umbelliferone methyl ether, $C_{10}H_8O_3$, and a crystalline product (m. p. 237—239°), which possessed the characters of a mixture of umbelliferone and a dihydroxycoumarin; (5) choline, $C_5H_{15}O_2N$; (6) triacontane, $C_{30}H_{62}$; (7) a phytosterol, $C_{27}H_{46}O$; (8) a phytosterol glucoside, $C_{33}H_{56}O_6$; (9) palmitic, stearic, cerotic, oleic, and linolic acids, together with an indefinite mixture of volatile fatty acids. The flowers contained, furthermore, a quantity of sugar, which yielded *d*-phenylglucosazone, melting at 208°. The amount of fatty and resinous material, from which some of the above-mentioned substances were obtained, was equivalent to 5·9 per cent. of the weight of flowers employed.

In comparing the constituents of the flowers of *Matricaria Chamomilla* (German Chamomile) with those of the flowers of *Anthemis nobilis* (Roman or English Chamomile), which have recently been investigated by the present authors (this vol., p. 1829), it may be observed that whilst some of the compounds are common to both, there are also considerable differences.

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