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CHICORIC ACID (DICAFFEYLTARTIC ACID): ITS ISOLATION FROM CHICORY (*CHICORIUM INTYBUS*) AND SYNTHESIS

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Abstract—The isolation from the aqueous decoction of chicory leaves of a new optically active crystalline substance is described, for which the name chicoric acid is proposed. Experimental evidence indicates its structure as a caffeic diester of laevorotatory tartaric acid, which for the first time was found in nature in its (−)-form. Its synthesis, as well as that of laevorotatory and optically inactive isomers, was effected by the action of the chloride of carbonylcaffeic acid on D(−)-, L(+)- and *meso*-tartaric acids, respectively.

A CHROMATOGRAPHIC examination of the phenolic fractions of several plants[1] was carried out for the purpose of establishing the presence of cynarine and the chromatograms of chicory were found to be particularly interesting. In fact, when developed in 0·1 N hydrochloric acid, for example, they are characterised (as shown in Fig. 1) by the presence of two spots; the lower one, very intense, has an R_F inferior to those of caffeic acid, cynarine and chlorogenic acid. This spot should, therefore, correspond to a substance that is found in considerable quantities in chicory and is only slightly

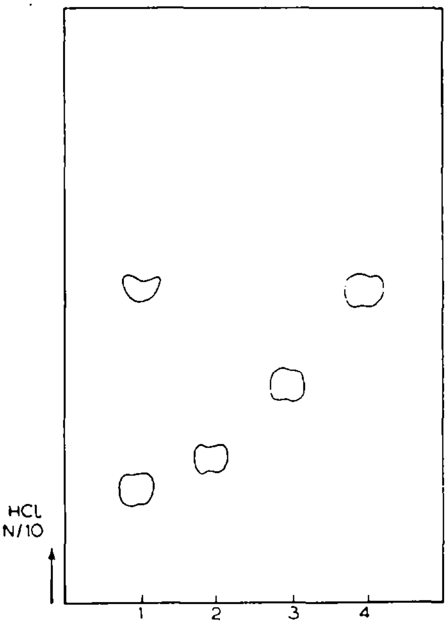

FIG. 1. 1—Solution derived from the lead salts of chicory; 2—caffeic acid; 3—cynarine; 4—chlorogenic acid.

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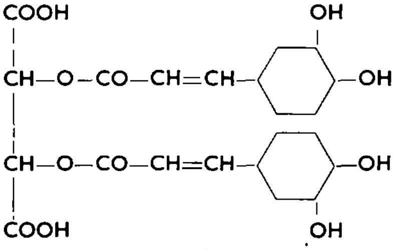
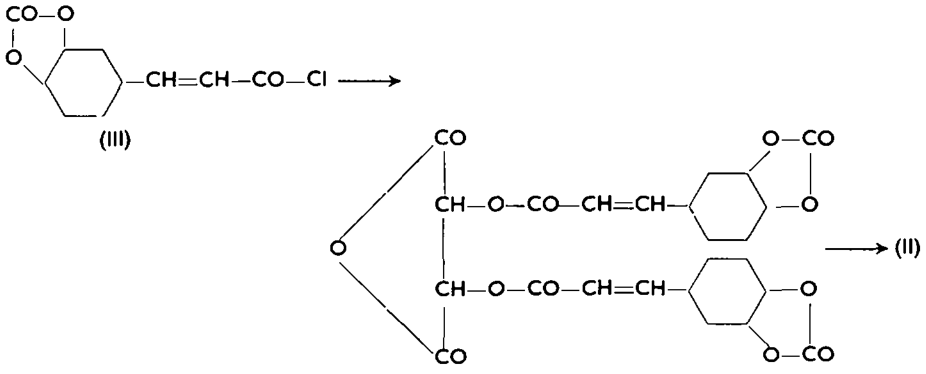
[1] M. L. Scarpati and G. Oriente, *Ann. Chim.* 47, 155 (1957).

soluble in water, because of its low R_F value. Its isolation was easily accomplished by several extractions from the chromatographic solution with ether. From the ethereal extracts an amorphous substance is obtained, which crystallises from water in colourless needles, m.p. 206°. It is an acid of considerable strength for which the name chicoric acid is proposed. It is strongly dextrorotatory. Alkaline hydrolysis of chicoric acid in a hydrogen atmosphere gave caffeic acid (76 per cent) (I) and laevotartaric acid. This appears to be the first time that laevotartaric acid has been found in nature. The yield of caffeic acid indicates that chicoric acid is composed of two molecules of caffeic acid and one of laevotartaric acid, and this agrees with the analytical data corresponding with the molecular formula $C_{22}H_{18}O_{12}$, for which the structure (II) is proposed:



(II)

This structure is similar to those of other natural depsides such as chlorogenic acid (3-caffeylquinic acid) and cynarine (1:4-dicaffeylquinic acid),[2] in which the ester link occurs between the carboxyl of caffeic acid and the hydroxyls of hydroxy acid. Methylation of chicoric acid and subsequent hydrolysis gave two molecules of 3:4-dimethoxycinnamic acid, indicating that the four phenolic hydroxyls were free in chicoric acid. The synthesis of the latter was carried out by condensing two molecules of carbonylcaffeic acid chloride (III)[3] with laevotartaric acid.



A preliminary synthesis was carried out by condensing natural dextrorotatory tartaric acid with (III), which gave the antipode of chicoric acid. The ultra-violet and infra-red spectra of the natural product and of the two synthetic antipodes appeared to be identical (Figs. 2 and 3). Crystallisation of a mixture of equal

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[2] L. Panizzi and M. L. Scarpati, *Gazz. Chim. Ital.* **84**, 792 (1954).

[3] L. Panizzi, M. L. Scarpati and R. Scarpati, *Gazz. Chim. Ital.* **84**, 812 (1954).

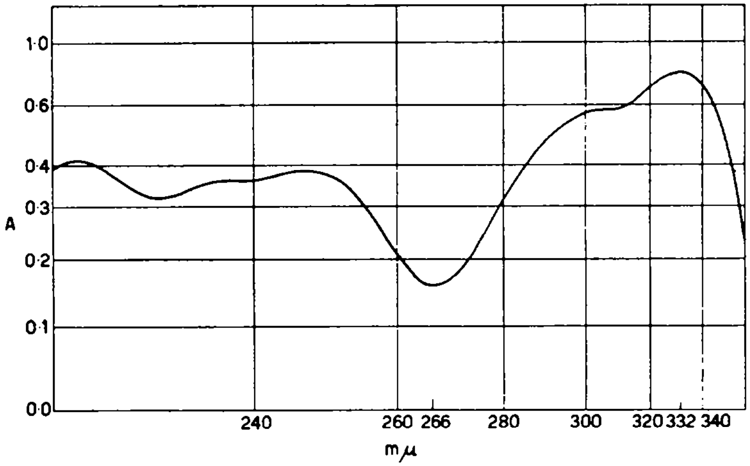

Fig. 2. Ultra-violet spectra: natural chicoric acid. The spectra of the dextro- and laevo-chicoric acids are practically identical.

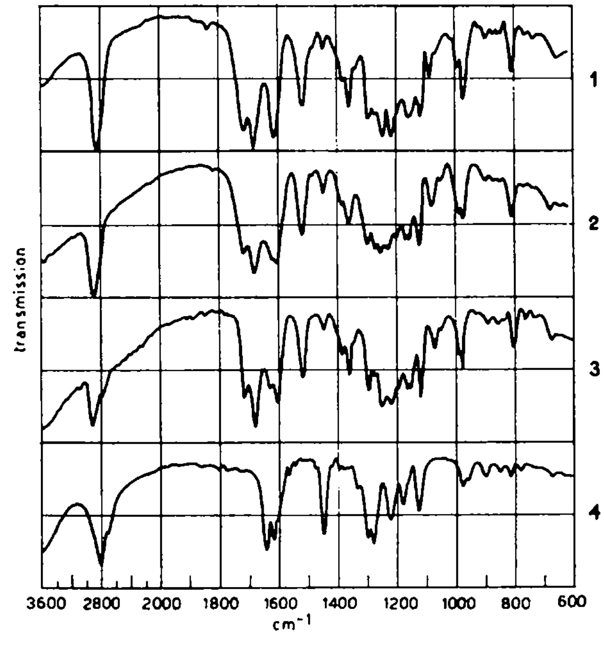

Fig. 3. Infra-red spectra (KBr): 1—dextrochicoric acid (natural); 2—laevochicoric acid (synthetic); 3—dextrochicoric acid (synthetic); 4—caffeic acid.

parts of natural dextrorotatory chicoric acid and synthetic laevorotatory chicoric acid gave *racemic* chicoric acid.

*meso*Chicoric acid was obtained by condensing (III) with *meso*tartaric acid. It differs in physical properties from the antipodes.

EXPERIMENTAL

Extraction of chicoric acid. 1000 g of chicory leaves, roughly chopped, are boiled for 1 to 2 hr in 5 l. of water, with occasional stirring. The decoction, decanted and mixed with the liquid obtained by pressing the leaves, is filtered and precipitated with a 20% solution of neutral lead acetate. The gelatinous yellow lead salts are centrifuged, washed with water by centrifuging, suspended in 300 ml of water and decomposed with hydrogen sulphide. When the precipitation of the lead is completed, the liquid is heated on a steam-bath and filtered hot through a wide Buchner funnel, and the lead sulphide is washed with 50 ml of boiling water. The clear yellow filtrate is concentrated under reduced pressure on a steam-bath to 130 ml.

Two extractions, 80 ml of ether being used for each extraction, are sufficient to remove all of the chicoric acid, as shown by a chromatographic examination of the aqueous solution before and after the extractions.

After evaporation of the ether and drying under reduced pressure, an amorphous product is obtained which is very soluble in water. A 10% aqueous solution gently heated and decolorised with charcoal deposits almost pure chicoric acid as silky needles (0·4–1·1 g), m.p. 206°, [α] +383·5° (*c*, 1·555 in MeOH). (Found: C, 55·69; H, 4·02; equivalent, 231 (potentiometric) and 238 (titration with sodium hydroxide). $C_{22}H_{18}O_{12}$ requires C, 55·70; H, 3·82 per cent; equivalent, 237). The acid is soluble in ethanol, methanol, dioxan and acetone, slightly soluble in ethyl acetate and ether, and insoluble in ligroin, benzene and chloroform. It is very soluble in hot water but only 0·5 per cent soluble at 20°. It yields very soluble sodium salts, a slightly soluble barium salt and an insoluble yellow lead salt. With ferric chloride it gives an intense dark-green colour, and with alkalis a yellow colour, which changes in presence of air.

Alkaline hydrolysis of chicoric acid. Chicoric acid (2 g) is dissolved in 10 ml of boiling water in a flask provided with a reflux condenser. The air in the apparatus is displaced by a current of hydrogen and 30 ml of N sodium hydroxide is added and the mixture is heated for 1 hr. After cooling, 32 ml N hydrochloric acid is added and the acid solution is extracted with ether until the extract no longer gives a green coloration with ferric chloride. After removal of the ether the residue (1·52 g), which crystallises from water in iridescent tablets, m.p. 210°, was identified as caffeic acid (Found: C, 59·95; H, 4·64. Calc. for $C_9H_8O_4$, C, 60·0; H, 4·48 per cent). A mixed m.p. with an authentic specimen of caffeic acid showed no depression. The R_F in various solvents, solubility, crystalline form and ultra-violet and infra-red spectra corresponded to those of caffeic acid. From the acid solution after extraction of caffeic acid, tartaric acid (0·4 g) was obtained and analysed as the acid potassium salt (Found: C, 25·20; H, 3·07. Calc. for $C_4H_5O_6K$: C, 25·51; H, 2·78 per cent). 0·3 g of the acid was converted into pyruvic acid, which was identified as the 2:4-dinitrophenylhydrazone, m.p. 212° (dec.) (Found: N, 20·80. Calc. for $C_9H_8O_6N_4$: N, 20·89 per cent).

Methylation of chicoric acid. A mixture of chicoric acid (0·4 g), finely powdered potassium carbonate (3 g) and freshly distilled dimethyl sulphate (0·6 ml) in acetone (70 ml) was heated under reflux for 7 hr with exclusion of moisture, until the yellow colour of the mixture had faded. After filtration from the solid deposit of salts, and evaporation of the acetone filtrate under reduced pressure, the cold residue was mixed with benzene and shaken three times with 4 ml of 2 N sodium hydroxide to remove the products of incomplete methylation and excess of dimethyl sulphate. The benzene solution was washed with water, dried with anhydrous sodium sulphate and evaporated in a high vacuum until the residue had a constant weight (0·4 g). Since the residue could not be crystallised, 0·368 g was hydrolysed by heating under reflux with ethanol (10 ml) and 30% sodium hydroxide (5 ml) for 4½ hr. After concentration to one-third of the initial volume and acidification with diluted hydrochloric acid (1:1), 0·271 g of 3:4-dimethoxycinnamic acid was obtained (theoretical for two molecules of the acid 0·275 g). Crystallisation from water yielded colourless needles, m.p. 178–179°, which showed no depression when mixed with an authentic specimen of 3:4-dimethoxycinnamic acid (Found: MeO, 29·5. Calc. for $C_{11}H_{12}O_4$: MeO, 29·8 per cent).

Laevorotatory chicoric acid. An intimate mixture of (III) (4·6 g) and (+)-tartaric acid (1·72 g) is heated under reduced pressure in a flask in a silicone bath. Reaction begins at 115° and the mixture fuses with evolution of hydrogen chloride. The temperature of the bath is raised to 135° for 10 min and then cooled. The white solid is heated with 80% acetic acid (90 ml) on a steam-bath until completely dissolved (40 min), and the solution is then evaporated under reduced pressure at 40°. The residue, consisting of chicoric acid and unchanged caffeic and tartaric acids, is heated with water (25 ml) at 50°. The mixture is filtered and the insoluble portion on chromatographic examination appears to be caffeic acid. The filtrate is twice extracted with ether (40 ml), which dissolves chicoric acid and any remaining caffeic acid, leaving tartaric acid in the aqueous layer. The ether layer is separated and evaporated, the residue is mixed with warm water (10 ml) and the pH is adjusted to 6 by addition of sodium hydrogen carbonate. Addition of saturated barium acetate solution precipitates the barium salt of chicoric acid, which is separated by centrifuging and washed with 3% barium acetate solution and then transferred to a separating funnel; 2 N hydrochloric acid (15 ml) and ether (40 ml) are added and the mixture is agitated until the solid has dissolved. The ether layer is removed and the aqueous layer is again extracted with ether (40 ml). The combined extracts are dried with anhydrous sodium sulphate and the ether is evaporated. The residue (2–2·5 g) is dissolved in warm water (20 ml), decolorised with charcoal and filtered. The acid crystallises in masses of tuft-like needles (1·5–1·9 g), m.p. 206°, and is identical with natural chicoric acid in every respect except the sign of the angle of rotation, [α] —384·2° (*c*, 1·075 in MeOH) (Found: C, 55·48; H, 3·99. $C_{22}H_{18}O_{12}$ requires C, 55·70; H, 3·82 per cent).

Racemic chicoric acid. This is obtained as pale-yellow needles by crystallising a mixture of natural dextrorotatory chicoric acid (0·2 g) and synthetic laevorotatory chicoric acid (0·2 g) three times from warm water. It has the same m.p. and R_F as the antipodes, [α] 0° (*c*, 1 in MeOH), but differs in solubility (0·1 per cent by weight in water at 20°).

Dextrorotatory chicoric acid. This is obtained by condensing (III) with (—)-tartaric acid, following the procedure for the laevorotatory acid. It was identical with the natural acid in every respect, [α] +384·6° (*c*, 0·988 in MeOH) (Found: C, 56·08; H, 4·03. $C_{22}H_{18}O_{12}$ requires C, 55·70; H, 3·82 per cent).

meso*Chicoric acid.* The product of condensation of (III) with *meso*tartaric acid, following the usual procedure, is finely powdered and heated on a steam-bath for ½ hr with 30 ml of 80% acetic acid, which dissolves the unreacted starting materials, the condensation product is filtered hot and dissolved in 80% acetic acid (90 ml). The same procedure is then followed as described previously. *meso*Chicoric acid crystallises from water as small lanceolate colourless crystals, m.p. 225°; the solubility in water is

0·11 per cent by weight at 20°; it is optically inactive and the sodium salt is sparingly soluble in water (Found: C, 55·18, 55·09; H, 4·08, 4·17. $C_{22}H_{18}O_{12}$ requires C, 55·70; H, 3·82 per cent).

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