II.—*Pellitorine, the Pungent Principle of* Anacyclus pyrethrum.

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With one exception, the pungent acid amides of known constitution which occur in nature are alike in containing an aromatic nucleus either in the basic or in the acidic radical. For example, piperine and chavicine (Ott and Eichler, *Ber.*, 1922, **55**, 2653; Ott and Lüdemann, *Ber.*, 1924, **57**, 214) are piperides of piperic acid and its geometrical isomeride, chavicic acid, respectively, and capsaicin has been shown to be a decenovanillylamide by Nelson (*J. Amer. Chem. Soc.*, 1919, **41**, 1115). This characteristic is shared, moreover, by the synthetical pungent amides, which are either derivatives of benzylamine (chiefly vanillylamine) (Nelson, *ibid.*, p. 2121; Ott and Zimmermann, *Annalen*, 1921, **425**, 314; Jones and Pyman, J., 1925, **127**, 2588) or piperides of arylated (chiefly phenylated) aliphatic acids (Scholtz, *Ber.*, 1895, **28**, 1196; Staudinger and Schneider, *Ber.*, 1923, **56**, 699; Staudinger and Müller, *ibid.*, p. 711).

The sole exception to these statements is spilanthol, the pungent principle of para cress, *Spilanthes acmella*, Murr. (*S. oleracea*) (Asahina and Asano, *J. Pharm. Soc. Japan*, 1920, 503), whose dihydroderivative is *n*-deco*iso*butylamide (*ibid.*, 1922, 85). It is therefore a matter of considerable interest to record the isolation of a purely aliphatic, pungent acid amide, pellitorine, from *Anacyclus pyrethrum*, DC., a plant native to North Africa and gathered chiefly in Algeria. The root of this plant is used medicinally under the names *Pyrethri radix* and pellitory root to stimulate the activity of the salivary glands, and an alcoholic extract was formerly prescribed for the alleviation of bronchitis. The powdered root resembles snuff in appearance, and when chewed causes a persistent tingling sensation and partial insensibility of the tongue, accompanied by profuse salivation (Brit. Pharmacopœia, 1914, p. 322; Squire's "Companion" to the B.P., 1916, p. 1112).

The pungent constituent of pellitory root was first examined by Buchheim (*Arch. exp. Path. Pharm.*, 1876, **5**, 455), who isolated a syrup which slowly solidified to a mass of waxy microscopic needles of very low melting point. He named this material "pyrethrin" and classified it as an amide allied to piperine. By hydrolysis he obtained an oily acid and a base, of which the sulphate was erroneously stated to exhibit all the properties of piperidine sulphate. Later, Dunstan and Garnett (J., 1895, **67**, 100) obtained a brown resin which partly crystallised on long standing. They called this product "pellitorine" * and stated, without advancing any real experimental support, that on hydrolysis it gave rise to what appeared to be a pyridine derivative possessing basic properties. In the following year, Schneegans (*Pharm. Zeit.*, 1896, **41**, 668), having used a more laborious process of extraction, recorded the isolation of a somewhat purer specimen of the active principle, which formed colourless needles, m. p. 45°, but no attempt was made to ascertain the constitution of this material.

During the earlier experiments of the present investigation of pellitorine, the method of extraction used by Schneegans was employed, but later it became evident that the simpler procedure of Dunstan and Garnett was equally efficacious when followed by the complex fractional distillation which has been found essential to free the crystalline principle from neutral oily by-products. Earlier workers have commented on the extreme difficulty of eliminating the latter substances. The syrup obtained by evaporating an alcoholic extract of the dried powdered root † was extracted thoroughly with ether, and the ethereal solution was freed from acidic impurities and evaporated. The residual syrup was distilled under highly reduced pressure (0·2—0·5 mm.), and the distillate was subjected to a series of fractionations which are described in detail in the experimental section. Ultimately fractions were obtained which rapidly crystallised in the receiver, and crystallisation of these from light petroleum yielded colourless feathery needles of pure *pellitorine*, m. p. 72°. Considerable quantities remained in the mother-liquor, from which further amounts were obtained by distillation, crystallisation of the solid distillate, and repetition of the process. The yield of pellitorine obtained from 13 kg. of root was 5 g., or 0·04%, but the actual content is probably of the order of 0·06%. Pellitorine is flavourless, but a milligram causes profuse salivation when placed on the tongue. The pungency

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* We propose to retain this name in preference to the earlier "pyrethrin" in order to avoid possible confusion with the constituents of *Pyrethri flores* ("The Extra Pharmacopœia," 1928, 879), the dried flowers of pyrethrum species which are used in powdered form as insecticides (see Staudinger and Ruzicka, *Helv. Chim. Acta*, 1924, **7**, 177, and other recent papers).

† The commercial alcoholic extract is very much less satisfactory for experimental purposes than the product freshly obtained in the laboratory.

value was 20 as compared with piperine (100), and was determined by diluting an alcoholic solution until the effect of placing one drop on a cover-glass on the tip of the tongue was just perceptible.

Pellitorine is optically inactive, neutral in character, and unsaturated, since it rapidly decolorises permanganate solution. Elementary analyses and the determination of its molecular weight showed that the formula is $C_{14}H_{25}ON$, and the presence of one oxygen atom and one nitrogen atom, and the physiological analogy with piperine, led to the assumption that pellitorine is an acid amide. This view was confirmed by hydrolysis, which took place extremely slowly in boiling alcoholic potash, but was effected more rapidly by heating with dilute hydrochloric acid in a sealed tube. In this way, a crystalline amine hydrochloride, an oily acid, and an oily neutral fraction were obtained.

The neutral fraction contained nitrogen, but as all attempts to crystallise it were unsuccessful and the amount available was small, its further investigation was abandoned.

The basic fraction was shown to be a primary amine by the nitrous acid reaction, and was identified as *iso*butylamine by comparison of the melting points of the hydrochloride, chloroplatinate, and p-*toluenesulphonyl* derivative with those of authentic specimens, by analysis of the first- and last-named derivatives, and by the determination of the melting point of a mixture with authentic *p*-toluenesulphon*iso*butylamide.

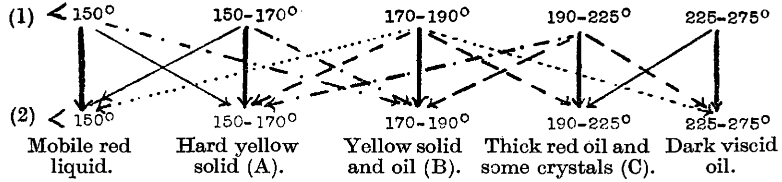
The acid fraction had the characteristic odour of the higher aliphatic acids, was sparingly soluble in water, to which it imparted an acid reaction, and was unsaturated, since it decolorised permanganate solution. In an attempt to purify it by distillation, a small amount of a clear, pale brown oil was collected at 160—200°/0·5 mm., but most of the acid carbonised. This distillate was acidic and unsaturated, but the molecular weight was 271 when determined by titration, a figure considerably higher than that of pellitorine itself. It seemed probable, therefore, that polymerisation or condensation had occurred during the distillation and that the examination of this material would be of little value in arriving at the constitution of pellitorine.

Since the basic portion of the pellitorine molecule is *iso*butylamine, the acidic component must have the formula $C_9H_{15}{\cdot}CO_2H$, and thus lacks four atoms of hydrogen for saturation. Acetylenic linkages being unknown in nature, this deficiency may be accounted for by the presence either of two double bonds or of an alicyclic ring and one double bond, and the choice between these alternatives was made by estimating the amount of hydrogen absorbed during the catalytic reduction of pellitorine. A methyl-alcoholic solution, when shaken with palladised charcoal in an atmosphere of hydrogen, absorbed the volume corresponding to four atoms of hydrogen, and reduction then ceased completely. The tetrahydropellitorine thus prepared was therefore acyclic, and being a deco*iso*butylamide, it was subjected to direct comparison, and found to be identical, with a synthetical specimen of *n*-deco*iso*butylamide. It follows that pellitorine is the *iso*butylamide of a *n*-nonadienecarboxylic acid, but the position of the double bonds must for the present remain indefinite.

Three observations may be made as the result of this investigation. Firstly, spilanthol and pellitorine are very closely related, differing only in the presence of an extra double bond in the latter, and it is an interesting but not entirely unexpected fact that the plants which yield them are also related, both being members of the order *Compositæ*. Secondly, one double bond at least is necessary for the pungent character of this molecular structure, since *n*-deco*iso*butylamide is not pungent whereas the two unsaturated compounds are both pungent. *n*-Deco*iso*butylamide causes no reaction when placed on the tongue, but, after swallowing, a localised tingling sensation lasting for several minutes is felt on the pillars of the fauces. Thirdly, the suggested identity of pellitorine and piperovatine, the pungent principle of *Piper ovatum* (Dunstan and Garnett, J., 1895, **67**, 94), is erroneous, since the latter substance has the formula $C_{16}H_{21}O_2N$ and melts at 123°.

EXPERIMENTAL.

Isolation of Pellitorine.—Powdered pellitory root (13 kg., in batches of 1·5 kg.) was extracted three times with boiling 95% alcohol, and the combined extracts were evaporated to a thin gum, mixed with clean sand, and extracted repeatedly with boiling ether. During this process the mass was stirred as efficiently as possible, but with each extraction the residue became harder, until finally further working became impossible. The ethereal solution, which contained almost all the pellitorine, was shaken twice with dilute sodium carbonate solution, washed with water, dried with sodium sulphate, and evaporated to small volume. The residue, after being transferred to a Claisen flask and freed from ether under diminished pressure, was distilled at the lowest possible pressure attained by a Hyvac pump. During this operation frothing was extremely troublesome. A pale yellow oil was collected at 150—275°/0·3 mm.; extensive decomposition then set in, and a hard varnish remained in the flask and was discarded. The distillate was submitted to two fractionations at 0·3 mm. pressure with the following results :



▬▬ indicates about 60% of the fraction being distilled.
——— ,, ,, 30% ,, ,, ,,
– – – ,, ,, 15% ,, ,, ,,
—·— ,, ,, 10% ,, ,, ,,
····· ,, ,, 5% ,, ,, ,,

Fraction C was again distilled : 17% was collected at 170—190°/0·3 mm. and solidified (D); the higher fractions were dark-coloured oils. The solid fractions A, B, and D were combined and crystallised repeatedly from light petroleum (b. p. below 40°) by keeping the clear solutions in a refrigerator for some days and washing the deposited crystals with ice-cold solvent. *Pellitorine* forms colourless needles, m. p. 72° (corr.), b. p. 162—165°/0·3 mm., which dissolve very easily in organic solvents but are sparingly soluble in water [Found in material dried at 80° : C, 75·2, 75·0; H, 11·4, 11·3; N, 6·2; *M* in camphor (Rast), 224. $C_{14}H_{25}ON$ requires C, 75·3; H, 11·2; N, 6·3%; *M*, 223]. It is insoluble in dilute hydrochloric acid and sodium hydroxide solutions, but forms a very faintly yellow solution in concentrated sulphuric acid. Decomposition takes place when a specimen is exposed to the air for some time.

Hydrolysis of Pellitorine.—Isolation of iso*butylamine.* Pellitorine (1 g.) and 2*N*-hydrochloric acid (20 c.c.) were heated in a sealed tube at 150° for 48 hours. There was no increase in pressure in the cooled tube. The products of four experiments were combined and extracted thoroughly with ether (E, see below), and the clear almost colourless acid solution was evaporated to dryness first on the water-bath and then in a desiccator. The residual crystalline *iso*butylamine hydrochloride (1·8 g.) formed colourless needles, m. p. 174° (Walden, Ulich, and Laun, *Z. physikal. Chem.*, 1925, **114**, 290, give m. p. 175·5°), when precipitated from absolute alcoholic solution by means of ether (Found : C, 43·7 ; H, 11·0. Calc. for $C_4H_{11}N,HCl$: C, 43·8 ; H, 11·0%). The chloroplatinate formed irregular plates, decomp. 217°, when prepared in alcoholic solution.

p-*Toluenesulphon*iso*butylamide.* *iso*Butylamine hydrochloride (0·24 g.) obtained from pellitorine, recrystallised *p*-toluenesulphonyl chloride (1·3 g.; 3 mols.), ether (25 c.c.), and 2*N*-sodium hydroxide solution (25 c.c.) were shaken mechanically for 12 hours; the smell of the acid chloride could not then be detected. The ethereal layer was separated, washed with water, dried, and freed from solvent. The residual p-*toluenesulphon*iso*butylamide* crystallised when cold and separated from light petroleum (b. p. 60—80°) in colourless rhombs, m. p. 75—76° (Found: C, 58·2; H, 7·6. $C_{11}H_{17}O_2NS$ requires C, 58·2; H, 7·5%). A specimen prepared in a similar manner from authentic *iso*butylamine formed colourless rhombs, m. p. 75—76° alone or when mixed with the material prepared from pellitorine.

Examination of the ethereal extract E (see above). The ethereal solution was shaken repeatedly with sodium carbonate solution to remove the acidic contents, and was then washed with water, dried, and evaporated. The neutral oily residue (1·6 g.) distilled at 160—190°/0·5 mm.; the clear distillate, which had an odour not unlike that of peaches, contained nitrogen and did not crystallise when kept in a refrigerator for some days. It was not examined further.

The acidic fraction (1·8 g.), which was liberated as a dark oil from the carbonate solution, was perceptibly purified neither by treatment with charcoal nor by repeated precipitation from alkaline solution, and an attempt was made to distil it. Much carbonisation took place, and the distillate (0·5 g.; b. p. 160—200°/0·5 mm.; mol. wt. 271) failed to crystallise. The acid chloride, prepared by means of phosphorus pentachloride in chloroform solution, yielded an oily anilide and an amide; the latter crystallised from very dilute methyl alcohol in colourless plates, m. p. 35°, which dissolved very readily in organic solvents.

Tetrahydropellitorine (n-*Deco*iso*butylamide*).—A solution of pellitorine (0·342 g.) in methyl alcohol (25 c.c.) was run into a suspension of palladised charcoal (from palladous chloride, 0·2 g., and charcoal, 1·5 g.) in methyl alcohol (25 c.c.) which was stirred mechanically in an atmosphere of hydrogen: the absorption of hydrogen (69·6 c.c., corrected to N.T.P.) ceased completely after 3 minutes. The volume of hydrogen required for the addition of 4 atoms of hydrogen to $C_{14}H_{25}ON$ is 68·2 c.c. The solution was filtered from charcoal, the methyl alcohol distilled, and the residual oil dissolved in ether and dried. Removal of the solvent yielded tetrahydropellitorine as a colourless oil which rapidly crystallised in flat needles, m. p. 35° (corr.), very soluble in organic solvents (Found: C, 74·1; H, 12·7. Calc. for $C_{14}H_{29}ON$: C, 74·0; H, 12·8%). This material melted at 36° when mixed with synthetic *n*-deco*iso*butylamide, m. p. 36°; the necessary decoic acid, m. p. 31°, was obtained by the hydrolysis of a carefully fractionated sample of commercial ethyl decoate, and the amide was obtained by the action of *iso*butylamine on the acid chloride in benzene solution.

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