

241. *Piperettine from Piper nigrum ; its Isolation, Identification, and Synthesis.*

By F. S. SPRING and JAMES STARK.

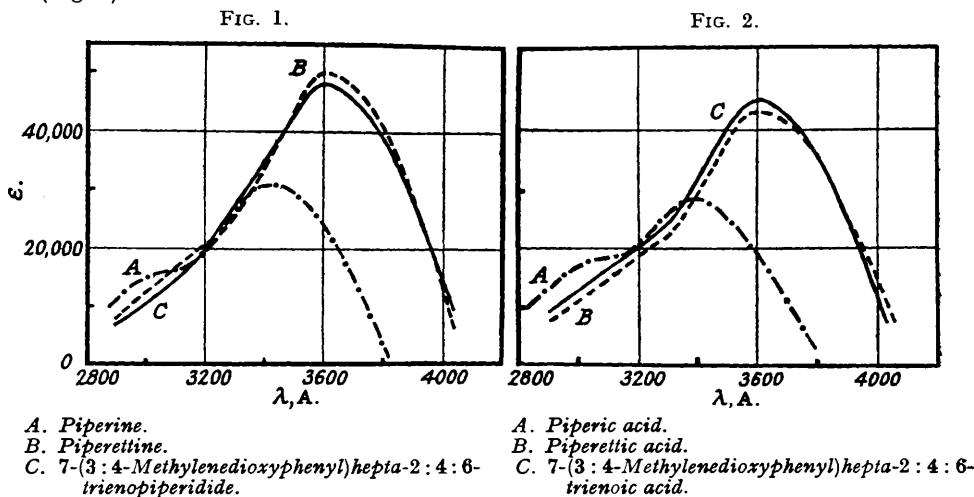
After the removal of piperine from extracts of *Piper nigrum* a second component, *piperettine*, has been isolated. Hydrolysis of piperettine, which is yellow, gives a mixture of piperidine and a yellow acid, piperetic acid, which has been identified by its reactions and by synthesis as 7-(3 : 4-methylenedioxyphenyl)hepta-2 : 4 : 6-trienoic acid* (I; R = H). Piperettine is thus the piperide (II), a conclusion confirmed by synthesis.

EXTRACTION of the dried fruits of *Piper nigrum* with alcohol gives an extract which on concentration deposits piperine (m. p. 129—130°). It was observed in the laboratories of Messrs. T. and H. Smith, Ltd., Edinburgh, that after isolation of subsequent crops of less pure piperine the solution deposits an amorphous powder, m. p. 100—112°, which appeared to differ from piperine. An examination of this material has now shown that it contains a relatively

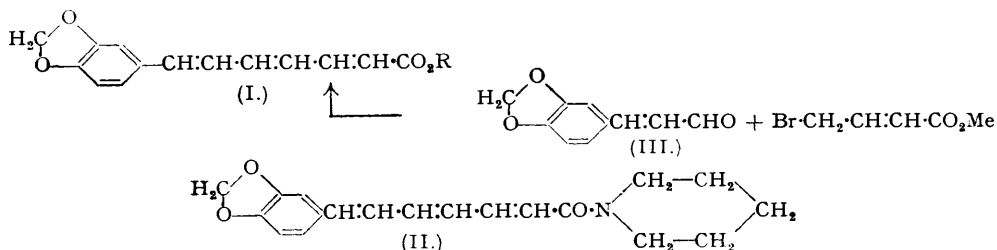
* Geneva nomenclature is used in this paper. ED.

large proportion of piperine together with a second compound to which the name *piperettine* has been given. The separation of the mixture was effected by a chromatographic method and also by crystallisation. The crystallisation procedure involved the mechanical separation of two different types of crystalline aggregates which are deposited simultaneously on slow cooling of an ethyl acetate mother-liquor obtained from the solid, m. p. 100—112°, after the removal of a crop of piperine. Using alumina as adsorbent, it was observed that piperine is less strongly adsorbed than piperettine.

Piperettine, $C_{19}H_{21}O_3N$, m. p. 146°, separates from ethyl acetate in yellow rods possessing a pronounced green sheen. It has properties very similar to those of piperine. It is nearly insoluble in both dilute acids and alkalis and with concentrated sulphuric acid gives a blood-red colour. It gives a positive reaction in the Labat test for the methylenedioxy-group. The ultra-violet absorption spectrum of piperettine in alcohol solution shows a broad band with a maximum at 3640 Å., whereas piperine exhibits a similar broad band with a maximum at 3450 Å. (Fig. 1).



Hydrolysis of piperettine using alcoholic potassium hydroxide gives a mixture of piperidine and *piperettic acid*, $C_{14}H_{12}O_4$. Piperettic acid, which forms golden-yellow needles from ethanol and gives a positive reaction in the Labat test for the methylenedioxy-group, was characterised by the formation of a *methyl ester*. In alcoholic solution piperettic acid exhibits an absorption maximum at 3600 Å., whereas piperic acid exhibits a maximum at 3400 Å. (Fig. 2). The reactions outlined above suggested that piperettic acid is a vinylogue (I; R = H) of piperic acid and that piperettine is the corresponding piperidide (II). These deductions have been confirmed by synthesis.



Treatment of piperonylideneacetaldehyde (III) with methyl γ -bromocrotonate in the presence of zinc gave in poor yield *methyl 7-(3:4-methylenedioxyphenyl)hepta-2:4:6-trienoate** (I; R = Me), hydrolysis of which yielded the *acid* (I; R = H) which proved to be identical with piperettic acid; the ultra-violet absorption spectrum of the synthetic acid is shown in Fig. 2. Condensation of the acid chloride from (I; R = H) with piperidine gives 7-(3:4-methylenedioxyphenyl)hepta-2:4:6-trienopiperidide (II) which is identical with piperettine.

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EXPERIMENTAL.

Piperettine.—After the separation of piperine from an alcoholic extract of the crushed fruits of *Piper nigrum*, the mother-liquor deposited an amorphous yellow powder, m. p. 100—112°.

(a) A solution of the solid, m. p. 100—112° (6.9 g.), in boiling ethyl acetate (11 c.c.) was cooled during approx. 1 hour to 30°. The crystalline solid (1.3 g.; m. p. 117—127°) was collected by decantation and recrystallised twice from ethyl acetate to give piperine (0.9 g.), m. p. 129° undepressed when mixed with an authentic specimen. The decanted mother-liquor when kept for several hours at room temperature deposited two forms of crystalline aggregates: large, semi-transparent, leaf-shaped, pale yellow clusters, and almost spherical, opaque, wart-like deposits. These forms were separated mechanically, recrystallisation of the leaf-shaped clusters (2.25 g.) from ethyl acetate yielding piperine as highly refracting rods, m. p. 129° undepressed when mixed with an authentic specimen. Recrystallisation of the opaque spheroids (1.35 g.) from ethyl acetate gave *piperettine* as highly refracting, yellow blades with a green tinge, m. p. 146—149° (Found: C, 73.6, 73.5, 73.4; H, 7.1, 6.9, 6.9; N, 4.7, 4.5. $C_{19}H_{21}O_3N$ requires C, 73.3; H, 6.8; N, 4.5%). *Piperettine* crystallises from alcohol as rosettes of needles. It is freely soluble in the cold in chloroform, acetone, or glacial acetic acid and sparingly soluble in cold alcohol, ethyl acetate, benzene, or ether, but insoluble in light petroleum, water, dilute acids, or alkalis. It is sparingly soluble in concentrated hydrochloric acid to give a bright yellow solution. *Piperettine* gives a positive reaction in the Labat test for the methylenedioxy-group, the colour changes being red → brown → olive-green → emerald-green, whereas with piperine the corresponding colour sequence is reddish-brown → brown → green → blue.

(b) A solution of the solid, m. p. 100—112° (10 g.), from *Piper nigrum* in benzene-light petroleum (b. p. 40—60°) (3 : 1; 200 c.c.) was filtered through a column of alumina (Brockmann II; 30 × 5 cm.). The chromatogram was developed by washing with benzene-light petroleum, and then it consisted of a colourless lower zone *A* (ca. 1 cm.) above which was a dark yellow band (ca. 1 cm.) (zone *B*) separated from the principal coloured zone *D* by a colourless zone *C* (4 cm.). Zone *D* (16 cm.) was pale yellow at the foot, the colour deepening in intensity towards the top of the column. Above the principal band was a colourless zone *E* (6 cm.) above which again, and at the head of the column, were two very narrow brown bands (zone *F*). The chromatogram was eluted by continued washing with benzene-light petroleum, benzene, and benzene-alcohol, to give the fractions shown in the table.

Fraction.	Zone.	Solvent.	Wt. of fraction, g.		
I	<i>A</i>	Benzene-light petroleum (b. p. 40—60°) (3 : 1),	7.6 l.	0.34	Gummy solid
		Benzene-light petroleum (b. p. 40—60°) (5 : 1),			
		Benzene			
II	<i>B</i>	Benzene	2.1 l.	0.39	Cryst., yellow, m. p. 127—130°
	Benzene	1.8 l.			
III	<i>C</i>	Benzene	1.5 l.	1.72	Cryst.
IV	First quarter of zone <i>D</i>	Benzene	1.5 l.	1.75	Brown resinous solid
V	Second quarter of zone <i>D</i>	Benzene	1.5 l.	1.70	Brown resin
VI	Third quarter of zone <i>D</i>	Benzene	1.5 l.	1.65	Clear brown resin
VII	Fourth quarter of zone <i>D</i>	Benzene	3.5 l.	1.0	Brown resin
VIII	<i>E</i>	Benzene-alcohol (99 : 1) 400 c.c. }		0.10	Resin
		Benzene-alcohol (98 : 2) 500 c.c. }			
IX	<i>F</i>	Benzene-alcohol (95 : 5) 600 c.c.		0.50	Resin
X	—	Benzene-alcohol (1 : 1) 600 c.c.		0.05	Dark brown resin

Fraction I was recrystallised from ethyl acetate to yield piperine as pale yellow rods, m. p. 127—130° undepressed when mixed with an authentic specimen. Similar treatment of fraction II gave piperine as almost colourless rods, m. p. 128—130° undepressed when mixed with an authentic specimen. Crystallisation of fractions III and IV gave slightly less pure piperine. The resinous fraction V was dissolved in hot ethyl acetate; the solution deposited piperine as leaf-shaped aggregates (0.6 g.), m. p. 124—128°. On storage, the mother liquor deposited a crystalline crop, m. p. 130—142°, which after recrystallisation from the same solvent gave prisms, m. p. 138—146° (0.12 g.) not depressed when mixed with the specimen of piperettine described above. Fraction VI crystallised from ethyl acetate and after two recrystallisations from the same solvent gave piperettine (0.1 g.) as pale yellow-green prisms, m. p. 142—146°, undepressed when mixed with the specimen described above; on storage, the mother-liquor deposited a mixture of piperine and piperettine which was resolved by mechanical means. Fraction VII was crystallised from ethyl acetate and then thrice from ethanol, to give piperettine as pale yellow, highly refracting needles, m. p. 141—147°. Fractions VIII and X did not yield crystalline material. Fraction IX crystallised from ethyl acetate and after recrystallisation from the same solvent gave piperettine (17 mg.) as pale yellow prisms, m. p. 144—147°.

The crude piperettine crops obtained from fractions V, VI, VII, and IX were combined and recrystallised from ethyl acetate to give piperettine (210 mg.) as pale yellow prisms, m. p. 145°. Similarly the crops of piperine obtained from fractions I—VI were combined and recrystallised from ethyl acetate to yield piperine (2.0 g.) as highly refracting rods, m. p. 128—129°.

Piperetic Acid.—A solution of piperettine (2.0 g.) in ethanolic potassium hydroxide (30 c.c.; 20%)

was heated under reflux for 6 hours. The crystalline potassium salt which separated during this period was collected, washed with ethanol, dried (dry wt. 1.6 g.), and dissolved in hot water (1600 c.c.). The solution was acidified with hydrochloric acid [1.2 c.c. (*d* 1.16) in 4 c.c. of water]. The voluminous yellow precipitate was collected, washed with water, dried (1.3 g.), and thrice crystallised from ethanol, to yield *piperetic acid* as golden-yellow needles, m. p. 223—224° (Found: C, 68.7; H, 5.1. $C_{14}H_{13}O_4$ requires C, 68.9; H, 4.9%). The *methyl ester*, prepared by the action of diazomethane on a suspension of the acid in ether, separates from ethanol as brittle, orange-yellow needles, m. p. 174° (Found: C, 69.8; H, 5.3. $C_{15}H_{14}O_4$ requires C, 69.8; H, 5.4%).

The ethanolic filtrate and washings obtained after removal of potassium piperettate were combined and evaporated to dryness under slightly reduced pressure. The receiver was cooled in ice-salt. The distillate, which was strongly basic, was saturated with hydrogen chloride and evaporated to dryness, to give a colourless solid (0.6 g.) which on crystallisation from ethanol gave piperidine hydrochloride as needles, m. p. 244° alone or mixed with an authentic specimen. The picrate was obtained from water as fine yellow needles, m. p. 150° undepressed when mixed with a specimen of piperidine picrate. A specimen of the hydrochloride was shaken with dilute aqueous sodium hydroxide with an excess of benzenesulphonyl chloride for 1 hour. The benzenesulphonopiperidide which separated crystallised from ethanol as colourless prismatic needles, m. p. 91° alone or mixed with an authentic specimen.

Methyl 7-(3:4-Methylenedioxyphenyl)hepta-2:4:6-trienoate (Methyl Piperettate).—A solution of piperonylideneacetaldehyde (m. p. 84°; 7.5 g.) in dry thiophen-free benzene (35 c.c.) was treated, with stirring, with zinc shavings (2.8 g.) and methyl γ -bromocrotonate (7.6 g.). The reaction was initiated by the addition of a trace of iodine and by gentle warming. When the first vigorous reaction had subsided (10—15 minutes) the mixture was heated under reflux for 2 hours, during which a brown gelatinous solid separated and the mixture was diluted with benzene (10 c.c.). After cooling to room temperature the mixture was again diluted with benzene (100 c.c.), and the liquid and suspended solid were decanted from zinc and washed with 3*N*-hydrochloric acid (60 c.c.). The benzene layer was washed successively with water, aqueous sodium carbonate, and water and then dried (Na_2SO_4). Evaporation of the solution gave a sticky brownish-orange residue which yielded a solid after trituration with ether (15 c.c.). The solid (0.9 g.; m. p. 170°) was collected and washed with ether (5 c.c.). A second crop (0.1 g.) of the same material was obtained by slow evaporation of the ethereal solutions. Recrystallisation of the combined solids from benzene gave *methyl 7-(3:4-methylenedioxyphenyl)hepta-2:4:6-trienoate* as yellow prismatic needles, m. p. 174° undepressed when mixed with the specimen of methyl piperettate described above (Found: C, 69.7; H, 5.7. $C_{15}H_{14}O_4$ requires C, 69.8; H, 5.4%).

7-(3:4-Methylenedioxyphenyl)hepta-2:4:6-trienoic (Piperetic) Acid.—A solution of the foregoing ester (0.25 g.) in absolute ethanol (23 c.c.) containing potassium hydroxide (2.0 g.) was heated under reflux. A potassium salt gradually separated as small plates. After 3 hours the cooled mixture was filtered and the potassium salt washed with ethanol and crystallised from water, giving buff-coloured needles. The acid (0.24 g.) obtained from solution of the salt in hot water (800 c.c.) by 3*N*-hydrochloric acid was washed with water and crystallised from ethanol, to yield *7-(3:4-methylenedioxyphenyl)hepta-2:4:6-trienoic acid* as golden-yellow needles, m. p. 224° alone or mixed with a sample of piperetic acid (Found: C, 68.8; H, 4.8. $C_{14}H_{12}O_4$ requires C, 68.9; H, 4.9%).

7-(3:4-Methylenedioxyphenyl)hepta-2:4:6-trienopiperidide.—A suspension of the foregoing acid (0.4 g.) in dry benzene (20 c.c.) and thionyl chloride (3 c.c.) was heated under reflux, gradually dissolving with liberation of hydrogen chloride and sulphur dioxide. After 4 hours the clear orange-coloured solution was evaporated under reduced pressure at <30°. The orange-coloured residue, in dry benzene (10 c.c.), was treated with piperidine (1.5 c.c.) in dry benzene (5 c.c.). After 18 hours at room temperature, the separated piperidine hydrochloride (0.2 g.) was collected and washed with benzene. The benzene filtrate and washings were combined, diluted with approx. 50 c.c. of benzene, and washed thrice with 3*N*-hydrochloric acid and then successively with water, aqueous sodium carbonate, and water. The dried (Na_2SO_4) solution was evaporated and the yellow solid residue (0.45 g.) crystallised from ethanol (charcoal), to give *7-(3:4-methylenedioxyphenyl)hepta-2:4:6-trienopiperidide* as clusters of pale yellow needles, m. p. 146° undepressed when mixed with a sample of piperettine (Found: C, 73.2; H, 6.5; N, 4.3. $C_{19}H_{21}O_3N$ requires C, 73.3; H, 6.8; N, 4.5%).

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THE ROYAL TECHNICAL COLLEGE, GLASGOW.

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