

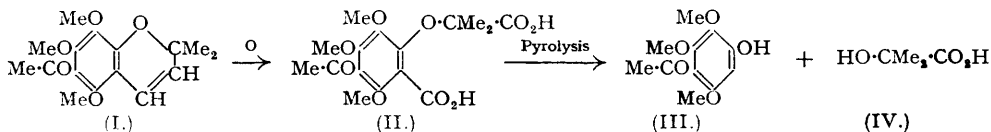
405. The Constitution of Evodione.

By S. E. WRIGHT.

Evodione, a colourless crystalline ketone isolated from the volatile oil of *Evodia Elleryana* has been further investigated. Degradation experiments here recorded indicate it to be 5 : 7 : 8-trimethoxy-6-acetyl-2 : 2-dimethyl-1 : 2-benzopyran. Ultra-violet absorption spectra data support the evidence.

PREVIOUS work on evodione has shown that its molecular formula is $C_{16}H_{20}O_5$, and that one ketonic and three methoxyl groups are present (Jones and Wright, *University of Queensland Chem. Papers*, 1946, No. 27). When evodione is subjected to catalytic hydrogenation, a dihydro-derivative $C_{16}H_{20}O_5$ is obtained, characterised by its *semicarbazone*, *2 : 4-dinitrophenylhydrazone*, and *benzylidene* derivative. Oxidation with permanganate in cold acetone, gives a dibasic acid, $C_{16}H_{22}O_9$. Since this acid is formed without loss of carbon atoms it appears that a ring structure has been ruptured, most probably at the double bond revealed by hydrogenation, for the dihydro-derivative is not attacked by permanganate in acetone. When this dibasic acid is heated just above its melting point, decomposition occurs to give carbon dioxide, traces of acetic acid, a white crystalline sublimate identified as α -hydroxyisobutyric acid, and a glassy amorphous residue. This solid residue on extraction with sodium carbonate yields a liquid phenol which on methylation is converted into 2 : 3 : 4 : 6-tetramethoxyacetophenone, identified by comparison of its *2 : 4-dinitrophenylhydrazone* with that of an authentic sample prepared by synthesis. The solubility of this phenol in sodium carbonate indicates that the free phenolic group is in the *p*-position to the carbonyl. After removal of the carbonate-soluble material, the residue on extraction with sodium hydroxide solution gives a second liquid phenol. This phenol on methylation and subsequent treatment with acetyl chloride in the presence of aluminium chloride is converted into 2 : 3 : 4 : 6-tetramethoxyacetophenone.

These reactions are explained satisfactorily if evodione is regarded as 5 : 7 : 8-trimethoxy-6-acetyl-2 : 2-dimethyl-1 : 2-benzopyran (I), oxidation yielding the dibasic acid (II) which on

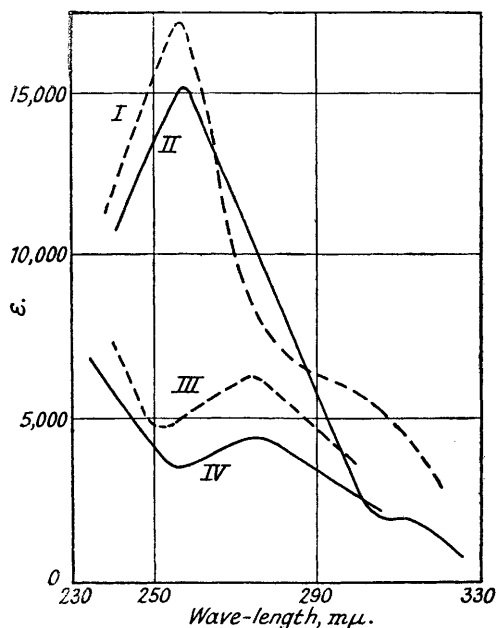


pyrolysis gives 4-hydroxy-2 : 3 : 6-trimethoxyacetophenone (III) and α -hydroxyisobutyric acid (IV). The second phenol obtained after pyrolysis is presumably 2 : 3 : 5-trimethoxyphenol, being derived most probably from (III) by deacetylation.

A qualitative test for the 2:2-dimethylbenzpyran nucleus has been developed (Bell, Robertson, and Subramanian, *J.*, 1936, 627), and depends upon the formation of acetone when the material is hydrolysed by refluxing with concentrated aqueous or alcoholic potassium hydroxide. Evodione, however, resists hydrolysis with either aqueous or alcoholic potassium hydroxide and is recovered unchanged after refluxing with boiling 25% alcoholic potassium hydroxide for 8 hours. Attempts to hydrolyse it with 33% alcoholic potassium hydroxide at 15 lbs. pressure for 2 hours also failed.

The decomposition of the dibasic acid (II) to give α -hydroxyisobutyric acid resembles that undergone by nicouic acid and tephrosindicarboxylic acid (Clark, *J. Amer. Chem. Soc.*, 1932, 54, 3000), and supports the presence of the *gem*-dimethylbenzpyran ring in evodione. The behaviour of evodione on oxidation with acetone-permanganate is similar to that of the methyl ether of

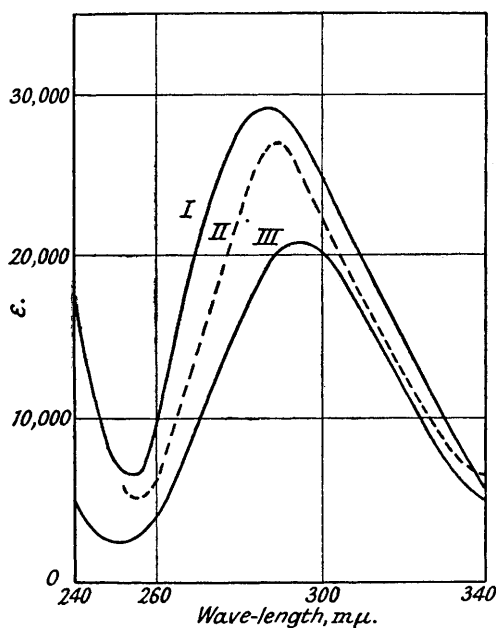
FIG. 1.



- (I) *Evodionol methyl ether* (5:7-dimethoxy-6-acetyl-2:2-dimethyl-1:2-benzpyran).*
- (II) *Evodione*.
- (III) *Dihydroevodionol methyl ether* (5:7-dimethoxy-6-acetyl-2:2-dimethylchroman).*
- (IV) *Dihydroevodione*.

* Lahey, *loc. cit.*

FIG. 2.



- (I) *Benzylidene-evodione*.
- (II) *Benzylidene-evodionol methyl ether*.*
- (III) *Benzylidenedihydroevodione*.

* Lahey, *loc. cit.*

evodionol, a phenolic ketone isolated from the volatile oil of *Evodia littoralis* and shown to be 7-hydroxy-5-methoxy-6-acetyl-2:2-dimethyl-1:2-benzpyran (Lahey, *Univ. Queensland Chem. Papers*, 1942, No. 20); this gave a dibasic acid similar to (II) but lacking a methoxyl group in the position adjacent to the side chain. When this acid was esterified with methyl alcohol in the presence of sulphuric acid, decarboxylation occurred with loss of the nuclear carboxyl group. When the dibasic acid (II) obtained from evodione is esterified with methyl alcohol and sulphuric acid no decarboxylation occurs but a *monomethyl ester*, $C_{17}H_{22}O_9, H_2O$, is obtained. Complete esterification is accomplished by using diazomethane, giving a *dimethyl ester*, $C_{18}H_{24}O_9$. It would appear that the extra methoxyl group present in the dibasic acid from evodione stabilises the nuclear carboxyl group, but steric effects prevent it from being esterified unless diazomethane is used.

Further evidence of the close relationship between evodionol and evodione was obtained by a comparison of the ultra-violet absorption spectra of closely related derivatives of each compound (Figs. 1 and 2).

Absorption data for solutions in alcohol.

	λ max., $\mu\mu$.	ϵ max.	λ min., $\mu\mu$.	ϵ min.
Evodione	257 ~310	15,500 2,100	—	—
Dihydroevodione	272	4,690	254	3200
Benzylidene-evodione	288	29,000	255	6100
Benzylidenedihydroevodione	296	21,000	251	2100

EXPERIMENTAL.

Melting points are uncorrected.

Dihydroevodione.—Evodione (1.46 g.) was hydrogenated in alcohol at 2 atm. pressure using Adams's platinum oxide catalyst (absorbed 116 c.c., N.T.P.); a colourless *product* was obtained which crystallised from light petroleum in needles, m. p. 63° (Found: C, 65.5; H, 7.5; OMe, 31.8. $C_{16}H_{22}O_8$ requires C, 65.3; H, 7.54; 3OMe, 32.3%).

Dihydroevodione 2:4-dinitrophenylhydrazone, crystallised from alcohol in yellow needles, m. p. 162° (Found: N, 11.9. $C_{22}H_{26}O_8N_4$ requires N, 11.3%).

Dihydroevodione semicarbazone. Dihydroevodione (0.2 g.), dissolved in alcohol (2 c.c.) and pyridine (1 c.c.), was treated with semicarbazide hydrochloride (0.2 g.) dissolved in hot water (5 c.c.). The solution was evaporated on a water-bath to dryness, and the solid *product* recrystallised from dilute alcohol; m. p. 178—179° (Found: N, 12.1. $C_{17}H_{25}O_8N_3$ requires N, 11.96%).

Benzylidenedihydroevodione. Dihydroevodione (0.2 g.) was dissolved in alcohol (10 c.c.) and treated with benzaldehyde (0.2 g.) and 4% sodium hydroxide solution (8 c.c.). The mixture was shaken for 1 hour and then left overnight. Pale yellow plates separated which were recrystallised from alcohol; the *compound* had m. p. 103° (Found: C, 72.5; H, 7.0. $C_{23}H_{26}O_8$ requires C, 72.23; H, 6.85%).

Oxidation of Evodione.—Evodione (5 g.) dissolved in dry acetone (200 c.c.) was treated with potassium permanganate at room temperature with mechanical stirring until no more permanganate was reduced (12 g. used in approximately 12 hours). Water was added and the excess of permanganate reduced with a little sodium sulphite. The sludge of manganese dioxide was filtered off and washed with hot water. The filtrate and washings were combined and evaporated under reduced pressure to small volume. The solution was then acidified and extracted thrice with ether. When the ether was removed a colourless crystalline *acid* (II) was obtained and recrystallised from ether or water. It melted at 178° (decomp.). Yield 3.75 g. (Found: C, 54.0; H, 5.7; OMe, 26.4; equiv. by titration, 180; equiv. by silver salt, 179. $C_{16}H_{20}O_8$ requires C, 53.93; H, 5.6; OMe, 26.1%; equiv., 178, dibasic).

Esterification of the Dibasic Acid.—(a) *With methyl alcohol-sulphuric acid*. The dibasic acid (II) (0.6 g.) was dissolved in methyl alcohol (30 c.c.) and sulphuric acid (1 g.), and the solution refluxed for 8 hours, cooled, diluted with water, and extracted with ether. The ether layer was extracted with sodium carbonate solution, which on acidification and extraction with ether gave a crystalline acid. The acid crystallised from ether—light petroleum in needles, m. p. 95°. Yield 0.4 g. (Found: C, 52.4; H, 6.2; equiv. by titration, 383. $C_{17}H_{22}O_8, H_2O$ requires C, 52.5; H, 6.18%; equiv., 388, monobasic). 0.0776 G. required 0.8 c.c. of $N/2$ -sodium hydroxide for saponification, and the recovered acid recrystallised from ether had m. p. 178°, mixed m. p. with original dibasic acid 178°. When heated in a vacuum at 110° for 4 hours in an Aberhalden drier (concentrated sulphuric acid), 0.0288 g. of the *monomethyl* ester lost 0.013 g. of water (calc. for loss of one mol. of water, 0.0134 g.) The resulting anhydrous *acid* was a viscous liquid which would not crystallise (Found: C, 54.6; H, 6.0. $C_{17}H_{22}O_8$ requires C, 55.1; H, 5.99%).

(b) *With diazomethane*. The dibasic acid (II) (0.5 g.) was left overnight with excess of diazomethane in ether. The excess of diazomethane was decomposed with acetic acid, and the ether solution washed with sodium carbonate. When the ether was removed an ester was isolated and recrystallised from ether—light petroleum; m. p. 77.5°. Yield 0.5 g. (Found: C, 56.3; H, 6.3. $C_{18}H_{24}O_8$ requires C, 56.2; H, 6.29%). 0.6 G. of the *dimethyl* ester required 3.1 c.c. of $N/2$ -sodium hydroxide for saponification, and the recovered acid had m. p. 178°, mixed m. p. with original dibasic acid, 178°.

Pyrolysis of the Dibasic Acid.—The dibasic acid (II) (2 g.) was heated in a wide-mouthed test-tube connected by a delivery tube through a liquid-air trap to a vacuum pump. The temperature was maintained just above the m. p. of the acid (180—190°) until no more decomposition was noted. During the heating a sublimate of colourless crystals formed in the delivery tube. This solid was acidic and hygroscopic, had m. p. 78—79°, and gave no melting point depression when mixed with an authentic sample of α -hydroxyisobutyric acid. Traces of acetic acid were collected in the liquid-air trap and identified by qualitative tests. In another experiment, the acid (0.2 g.) was sealed in a tube under high vacuum and heated to 180° until no more gas was evolved. The tube was then connected to a high-vacuum system and the gases distilled off, water vapour being collected in a trap at -40° and a sublimate of carbon dioxide in the liquid-air trap.

The solid residue remaining after pyrolysis was dissolved in ether and extracted with sodium carbonate and then with sodium hydroxide solution. On acidification, the sodium carbonate solution yielded a dark liquid (0.4 g. from 2 g. of acid) which gave a red-brown colour with ferric chloride. This liquid did not crystallise, and was methylated by refluxing with methyl sulphate and anhydrous potassium carbonate in dry acetone. The resulting methylated *product* gave a 2:4-dinitrophenylhydrazone, crystallising from alcohol in orange needles, m. p. 168° (Found: N, 13.0. $C_{18}H_{20}O_8N_4$ requires N 13.3%).

A carbonate-soluble phenol was also obtained when the dibasic acid (0.5 g.) was refluxed with 20 c.c. of quinoline and 1 g. of copper bronze for $\frac{1}{2}$ hour, and when methylated gave the same 2:4-dinitrophenylhydrazone, m. p. 168°. A sample of 1:2:3:5-tetramethoxybenzene was prepared by synthesis from 2:6-dimethoxybenzoquinone (Chapman, Perkin, and Robinson, *J.*, 1927, 3015) and converted into 2:3:4:6-tetramethoxyacetophenone by reaction with aluminium chloride in carbon disulphide solution

(Bargelli and Bini, *Atti R. Accad. Lincei*, 1920, **19**, 595). The 2:4-dinitrophenylhydrazone of this compound melted at 168° and showed no depression with the above 2:4-dinitrophenylhydrazone.

When the sodium hydroxide solution was acidified, a liquid phenol (0.1 g. from 2 g. of acid) was obtained which gave a purplish-brown colour with ferric chloride solution. The liquid was methylated with diazomethane in ether, and the product distilled in a vacuum. The distillate (0.1 g.) proved difficult to crystallise and was therefore dissolved in acetyl chloride (0.2 c.c.), treated with aluminium chloride (1 g.), and cooled in ice-water. After $\frac{1}{2}$ hour the product became semi-solid, and ice-cold water was added. The liquid was then extracted with ether, and the ether solution washed with dilute sodium hydroxide. The ether was removed, and the product distilled in a vacuum and treated with 2:4-dinitrophenylhydrazine sulphate in alcohol to give a 2:4-dinitrophenylhydrazone, m. p. 168° after recrystallisation from alcohol. This gave no depression when mixed with the 2:4-dinitrophenylhydrazone of 2:3:4:6-tetramethoxyacetophenone.

The author wishes to thank Professor T. T. H. Jones for his interest in this work, and the Commonwealth Government Research Fund for a grant.

UNIVERSITY OF QUEENSLAND, AND PHARMACY COLLEGE,
WELLINGTON, NEW ZEALAND.

[Received, December 16th, 1947.]
