It was unnecessary to use recrystallized 5,6-dimethoxy-2-(2-hydroxy-3-methylbenzyl)benzoic acid as the acid purified by precipitation from 10% sodium carbonate solution melted only slightly lower than the recrystallized product.

1,2 - Dimethoxy - 5 - hydroxy - 6 - methyl - 8 - bromo - 9,10 - dihydro - 9 - keto-anthracene. VI.—A solution of 6.2 g. of 5,6-dimethoxy-2-(2-hydroxy-3-methyl-5-bromobenzyl)benzoic acid in 60 cc. of concd. sulfuric acid was allowed to stand at room temperature for ten minutes. It was then poured slowly into 400 cc. of water containing ice while the mixture was stirred. The anthrone separated at once as a heavy, yellow precipitate; yield, 5.4 g., or 91%. A suitable solvent for recrystallization was not found; hence, the crude compound was oxidized directly to the corresponding anthraquinone for identification.

1,2-Dimethoxy-5-hydroxy-6-methyl-8-bromo-anthraquinone. VII.—A solution of 1 g. of crude 1,2-dimethoxy-5-hydroxy-6-methyl-8-bromo-9,10-dihydro-9-keto-anthracene in 10 cc. of glacial acetic acid was oxidized by adding 0.55 g. of chromium trioxide in 5 cc. of glacial acetic acid. From the solution, 0.25 g. of the anthraquinone separated. Recrystallization from glacial acetic acid gave yellow needles; m. p., 193–193.5°. The substance dissolved in sulfuric acid giving a deep blue solution.

Anal. Subs., 0.1556: AgBr, 0.0772. Calc. for $C_{17}H_{13}O_5Br$: Br, 21.19. Found: 21.11.

Summary

1. Aromatic aldehyde acids condense with various *p*-bromophenols by means of sulfuric acid to give substituted phthalides where condensation has taken place *ortho* to the hydroxyl group.

2. The phthalides thus produced are readily reduced with zinc and sodium hydroxide to benzyl-benzoic acids which can be converted to anthraquinones. The procedure outlined gives a method suitable for the synthesis of various natural products and polyhydroxy-methylanthraquinones.

URBANA, ILLINOIS

[CONTRIBUTION FROM THE UNIVERSITY OF BRISTOL]

THE CONSTITUTION OF CATECHIN. VII. 4,5,7,3',4'-PENTAHYDROXY-FLAVAN

BY M. NIERENSTEIN

RECEIVED JULY 11, 1924 PUBLISHED DECEMBER 13, 1924

Of the many formulas that have been suggested for catechin,[1] Formulas I and III are still under consideration. These formulas have been proposed by A. G. Perkin[2] and they both represent catechin as a reduction product of quercetin (II).

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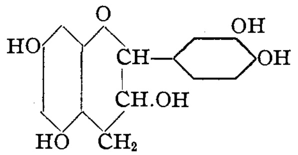
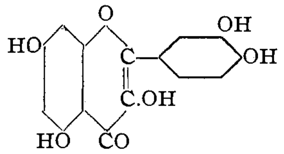
[1] (a) Freudenberg, Böhme and Purrmann, *Ber.*, **55,** 1734 (1922). (b) Drumm, *Sci. Proc. Roy. Dublin Soc.*, **36,** 45 (1923). (c) Freudenberg, Orthner and Fikentscher, *Ann.*, **436,** 286 (1924).

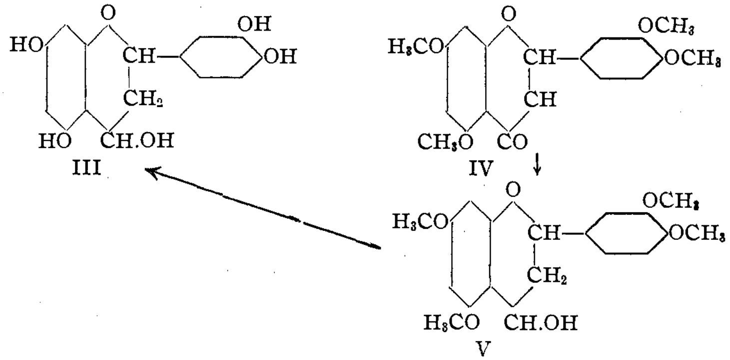
[2] Perkin, *J. Chem. Soc.*, **81,** 1172 (1902); **87,** 405 (1905).



I



II



III IV V

Many attempts made in this Laboratory to reduce quercetin (II) to 3,5,7,3′4′-pentahydroxy-flavan (I) have led only to negative results, but as Formula I has now been withdrawn[3] the main interest in preparing this substance is lost. On the other hand 4,5,7,3′4′-pentahydroxy-flavan (III) was easily prepared: 5,7,3′4′-tetramethoxy-flavanone (IV) was reduced to 4-hydroxy-5,7,3′,4′,-tetramethoxy-flavan (V) which on demethylation with hydriodic acid gave 4,5,7,3′,4′-pentahydroxy-flavan (III).

Already the fact that 4,5,7,3′,4′-pentahydroxy-flavan (III) resists boiling with hydriodic acid shows that it differs fundamentally from catechin, which is completely decomposed when boiled with hydriodic acid. 4,5,7,3′,4′-Pentahydroxy-flavan (III) resembles in this respect quercetin (II), which is also recovered from tetramethyl-quercetin on boiling with hydriodic acid.[4] It also resembles quercetin in that it does not give the phloroglucinol test with pine-wood and hydrochloric acid, which is a specific test for catechin.[5] These, however, are not the only differences between 4,5,7,3′,4′-pentahydroxy-flavan (III) and catechin, as will be seen from the experimental part of this paper. There remains not the slightest doubt that 4,5,7,3′,4′-pentahydroxy-flavan (III) has nothing whatever to do with authentic catechin, which is in perfect agreement with our knowledge of catechin.[6]

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[3] Ref. 1 c, p. 290.

[4] Kostanecki, Lampe and Tambor, *Ber.*, **37**, 1402 (1904).

[5] Perkin and Everest, "The Natural Organic Colouring Matters," Longmans, Green & Co., 1918, p. 464.

[6] Nierenstein, *J. Chem. Soc.*, 117, 971 (1920).

Since Formula I has been withdrawn by Freudenberg, Orthner and Fikentscher and Formula III is now shown not to represent authentic catechin, it must be pointed out that the hypothesis that the catechins are intermediary between the flavones, the anthocyanins and the tannins[7] has also become untenable. It is therefore to be regretted that prominence has been given in botanical circles[8] to Freudenberg's hypothesis.

Experimental Part

4-Hydroxy-5,7,3′,4′-tetramethoxy-flavan (V).—A solution of 8 g. of 5,7,3′,4′-tetramethoxy-flavanone[9] (IV) in 1000 cc. of 80% alcohol is heated on a boiling water-bath for eight hours with 500 g. of zinc dust and 50 cc. of a 25% solution of potassium hydroxide in water. The filtered solution is evaporated to dryness and the solid left extracted with hot water, when the potassium salt of 4-hydroxy-5,7,3′,4′-tetramethoxy-flavan dissolves. The filtered aqueous solution is acidified with dil. sulfuric acid and the solid thus obtained crystallized several times from alcohol with the aid of animal charcoal, whereupon colorless, stout needles are obtained;[10] m. p., 159–160°; yield, 67%. The product is also soluble in ethyl acetate and in a large excess of benzene and carbon tetrachloride, from which solutions it crystallizes in small needles that also melt at 159–160°. With ferric chloride the aqueous solution produces a green coloration, identical with that obtained for catechin. Cold potassium hydroxide solution and hydrochloric acid have no effect on the aqueous solution of 4,5,7,3′,4′-pentahydroxy-flavan, whereas catechin gives red decomposition products under these conditions. The addition of ferric chloride to a suspension of 4-hydroxy-5,7,3′,4′-tetramethoxy-flavan in concd. sulfuric acid produces a violet coloration. Chroman, 1-phenyl-chroman and 3-phenyl-chroman[11] also give a faint violet coloration with ferric chloride and concd. sulfuric acid. These observations are of interest in connection with the chemistry of catechin, in view of the importance which has been attached to the fact that both catechin-tetramethyl ether and the coumarans give a violet coloration with ferric chloride and concd. sulfuric acid.[12]

Anal. Subs., 0.1731: CO_2, 0.4173; H_2O, 0.0983. Calc. for $C_{19}H_{22}O_6$: C, 65.9; H, 6.4. Found: C, 65.7; H, 6.4.

4-ACETOXY-5,7,3′,4′-TETRAMETHOXY-FLAVAN crystallizes from alcohol in long needles; m. p., 171°.

Anal. Subs., 0.2025: CO_2, 0.4823; H_2O, 0.1138. Calc. for $C_{21}H_{24}O_7$: C, 64.9; H, 6.2. Found: C, 65.0; H, 6.2.

4,5,7,3′,4′-Pentahydroxy-flavan (III).—Small quantities of 4-hydroxy-5,7,3′,4′-tetramethoxy-flavan (V) are boiled for six hours with an excess of hydriodic acid (d.,

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[7] Freudenberg, (a) *Ber.*, **53**, 1417 (1920); (b) *Z. angew. Chem.*, **34**, 27 (1921).

[8] Jonesco, *Compt. rend.*, **173**, 168 (1921); **174**, 1634 (1922). Noack, *Z. Botanik*, **14**, 17 (1922).

[9] For the preparation of Substance IV the method of Kostanecki and Tambor [*Ber.*, **37**, 793 (1904)] was used. This substance melted at 157–159°, which is slightly lower than the melting point given by Kostanecki and Tambor, who found 159–160°.

[10] As will be noticed, the melting point found for 4-hydroxy-5,7,3′,4′-tetramethoxy-flavan (V) is that given by Kostanecki and Tambor for 5,7,3′,4′-tetramethoxy-flavanone (IV). It must therefore be noted that mixed melting points of the substances IV and V were found to give depressions of 17–31°.

[11] Greenwood and Nierenstein, *J. Chem. Soc.*, 117, 1597 (1920).

[12] Compare (a) Kostanecki and Lampe, *Ber.*, **39**, 4007 (1906). (b) Ref. 7 a, p. 1423. (c) Freudenberg and Orthner, *Ber.*, **55**, 1748 (1922). (d) Ref. 1 c.

1.94) and the cold solution decolorized with dilute thiosulfate solution. The solid thus obtained crystallizes from water in well developed, slightly colored needles that melt at 212–214°. This melting point is not altered on recrystallization. Very remarkable is the fact that all melting points are accompanied by evolution of gas and slight decomposition. 4,5,7,3′,4′-Pentahydroxy-flavan is soluble in water, alcohol and ethyl acetate, slightly soluble in ether but insoluble in carbon tetrachloride.

Anal. Subs., 0.1610 (kept for some time in a desiccator over calcium chloride and then dried in a vacuum at 100° over P_2O_5): 0.0302; 0.2260 (exposed to air and then dried in a vacuum at 100° over P_2O_5): 0.0452. Calc. for $C_{15}H_{14}O_6.4H_2O$: H_2O, 19.9. Found: 18.8, 20.0.

Subs., 0.1308 (dried in a vacuum at 100° over P_2O_5): CO_2. 0.2974; H_2O, 0.0588. Calc. for $C_{15}H_{14}O_6$: C, 62.1; H, 4.8. Found: C, 62.0; H, 5.0.

4,5,7,3′,4′-PENTA-ACETYL-FLAVAN crystallizes from alcohol in needles; m. p., 167°.

Anal. Subs., 0.1314: CO_2, 0.2890; H_2O, 0.0593. Calc. for $C_{25}H_{24}O_{11}$: C, 60.0; H, 4.8. Found: C, 60.0; H, 5.1.

TABLE I

COMPARISONS BETWEEN *dl*-ACACATECHIN, *dl-Iso*-ACACATECHIN AND 4,5,7,3′,4′-PENTA-HYDROXY-FLAVAN AND THEIR RESPECTIVE DERIVATIVES

	M. p. °C.	Mixed m. p. °C.
4,5,7,3′,4′-Pentahydroxy-flavan	212–214	.....
dl-Acacatechin	204–205	175–191
dl-Iso-acacatechin	237–238	209–216
4,5,7,3′,4′-Penta-acetoxy-flavan	167	.....
Penta-acetyl-*dl*-acacatechin	160	137–149
Penta-acetyl-*dl-iso*-acacatechin	171	143–159
4-Hydroxy-5,7,3′,4′-tetramethoxy-flavan	159–160	.....
Tetramethyl-*dl*-acacatechin	152–153	.....
Tetramethyl-*dl-iso*-acacatechin	171–172	.....
4-Acetoxy-5,7,3′,4′-tetramethoxy-flavan	171	.....
Acetyl-tetramethyl-acacatechin	136–137	.....
Acetyl-tetramethyl-*iso*-acacatechin	157–158	.....

Although 4,5,7,3′,4′-pentahydroxy-flavan is obviously not *dl*-acacatechin or *dl-iso*-acacatechin, reference must be made to some of the data found by Freudenberg and his collaborators for their *dl*-catechin and *dl-epi*-catechin and the derivatives they have obtained from them. Some of the melting points found by them seem to show agreement with those observed for 4,5,7,3′,4′-pentahydroxy-flavan and its derivatives.

TABLE II

	M. p. °C.	Reference to Freudenberg and his collaborators M. p. °C.
4,5,7,3′,4′-Pentahydroxy-flavan	212–214	
dl-Catechin		216–218[13] 214–216[14] 204–205[15] 212–214[16]

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[13] *Ber.*, **54**, 1212 (1921).

[14] *Ber.*, **56**, 1192 (1923).

[15] Ref. 13, p. 1188.

[16] Ref. 1 c, p. 276.

Table II (*Concluded*)

	M. p. °C.	Reference to Freudenberg and his collaborators M. p. °C.
dl-Epi-catechin		240[17] 229–232[18] 224–226[16]
4,5,7,3′,4′-Penta-acetoxy-flavan	167	
Penta-acetyl-*dl*-catechin		156[19] 166[14] 164–165[16]
Penta-acetyl-*dl-epi*-catechin		169–172[20] 167[18] 169[16]
4-Hydroxy-5,7,3′,4′-tetramethoxy-flavan	5 9–160	
Tetramethyl-*dl*-catechin		142[16]
Tetramethyl-*dl-epi*-catechin		141–142[16]
4-Acetoxy-5,7,3′,4′-tetramethoxy-flavan	171	
Acetyl-tetramethyl-*dl*-catechin		134–135[16]
Acetyl-tetramethyl-*dl-epi*-catechin		160–161[16]

The identity of the melting point 212–214° for 4,5,7,3′,4′-pentahydroxy-flavan and the *dl*-catechin, also that of 167° for 4,5,7,3′,4′-penta-acetoxy-flavan and of 166° and 167° for penta-acetyl-*dl*-catechin and penta-acetyl-*dl-epi*-catechin is striking.[21] This may, of course, only be coincidental; on the other hand it suggests the possibility that Professor Freudenberg is perhaps after all working with some products of the 4,5,7,3′,4′-pentahydroxy-flavan series. Should this prove to be the case it must be clearly understood that Professor Freudenberg's work does not refer to the catechins present in *Acacia Catechu,* since all comparisons made between 4,5,7,3′,4′-pentahydroxy-flavan and *dl*-acacatechin as well as *dl-iso*-acacatechin were made on the catechins which had been prepared in this Laboratory from authentic *Acacia Catechu* heart-wood. This material was sent to the author by the authorities of the Forest Research

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[17] Ref. 1 a, p. 1742.

[18] Ref. 13, p. 1193.

[19] Ref. 12, p. 1204.

[20] Ref. 1 a, p. 1743.

[21] *dl-Epi*-acacatechin has been prepared in this Laboratory by the action of dilute pyridine. It melts at 230–231° and yields a penta-acetyl derivative that melts at 167°. On admixture of this substance with penta-acetyl-*iso*-acacatechin (m. p., 171°) the melting point of penta-acetyl-*epi*-acacatechin (m. p., 167°) is depressed to 159–162°. The melting point of 4,5,7,3′,4′-penta-acetoxy-flavan (m. p., 167°) is depressed to 122–129° on admixture with penta-acetyl-*epi*-acacatechin. Experiments which will be published at a later date have shown that dilute pyridine epimerizes acacatechin very smoothly. This accounts also for the reason why Professor Freudenberg finds practically the same melting point (167°) for penta-acetyl-*dl*-catechin and penta-acetyl-*dl-epi*-catechin, since he uses pyridine in connection with the acetylation of both *dl*-catechin and *dl-epi*-catechin. It has been found in this Laboratory that penta-acetyl-acacatechin (m. p., 160°) is easily converted into penta-acetyl-*epi*-acacatechin (m. p., 167°) on boiling with acetic acid and pyridine.

Institute of Dehra Dun, India, where it was carefully identified before it was despatched to England. In this connection it is worth while to remember that not only *Acacia Catechu* but also *Acacia Catechuoides* and *Acacia Sundra* are used for the manufacture of cutch, which is one of the main sources of "catechin."[22]

During this investigation I was assisted by Miss E. O. Hazelton, and I wish to thank the Department of Scientific and Industrial Research for a grant which has enabled her to take part in this work. My thanks are also due to the Colston Research Society of this University for a grant which has covered the expenses of this research.

Summary

4,5,7,3',4'-Pentahydroxy-flavan has been prepared and shown to differ in every respect from *dl*-acacatechin and *dl-iso*-acatechin.

BRISTOL, ENGLAND

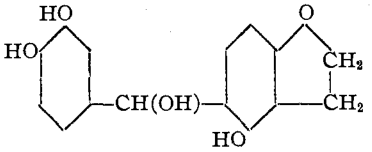
[CONTRIBUTION FROM THE UNIVERSITY OF BRISTOL]

THE CONSTITUTION OF CATECHIN. VIII. α,3,5,3',4'-PENTAHYDROXY-4-BENZYL-1,2-DIHYDROCOUMARONE

BY H. F. DEAN AND M. NIERENSTEIN

RECEIVED JULY 11, 1924 PUBLISHED DECEMBER 13, 1924

The experiments described in the present communication were in progress in 1914, when they were suspended in consequence of the War. At that time, and for some years subsequently, Formula I proposed by Kostanecki and Lampe[1] was generally considered to represent catechin.[2] Consequently, the synthesis of a substance having this formula was attempted.



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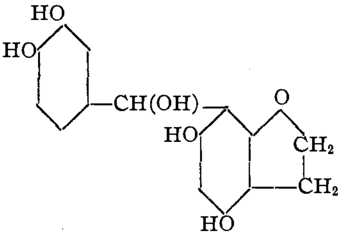

II

Both α,3,5,3',4'-pentahydroxy-4-benzyl-1,2-dihydrocoumarone (I) and its isomer α,3,5,3',4'-pentahydroxy-6-benzyl-1,2-dihydrocoumarone (II) have now been prepared and they have been found to differ in every

[22] In view of what has been said it must be regretted that Professor Freudenberg did not see his way to accept the offer of an exchange of specimens made to him by the author two years ago.

[1] Kostanecki and Lampe, *Ber.*, **40**, 720 (1907).

[2] Compare, for example, Karrer and Widmer, *Helvetica chim. Acta*, **2**, 454 (1919).