Summary

1. Of the alcoholic derivatives of aromatic hydrocarbons, only those in which the hydroxyl is on the carbon atom adjacent to the ring condense with benzene in the presence of aluminum chloride.

2. The saturated aliphatic alcohols up to and including amyl alcohol do not react with benzene in the presence of aluminum chloride to form alkylbenzenes.

3. Allyl alcohol condenses with benzene to give a fair yield (16%) of allylbenzene: $CH_2{=}CHCH_2OH + C_6H_6 \longrightarrow CH_2{=}CHCH_2C_6H_5 + H_2O$.

4. Unsaturation on the carbon atom, adjacent to the alcoholic group, increases the reactivity of the hydroxyl toward the dehydrating effect of aluminum chloride.

EAST LANSING, MICHIGAN

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF BRISTOL]

THE CONSTITUTION OF CATECHIN. IX. SOME NEW DISINTEGRATION PRODUCTS OF ACACATECHIN

BY M. NIERENSTEIN

RECEIVED MARCH 9, 1926 PUBLISHED JULY 6, 1926

Various formulas have been suggested by Freudenberg and his collaborators for catechin including Formula I, which was considered untenable[1] in 1924, but is now regarded as the correct formula for epicatechin[2] and catechin[3] respectively, since cyanidin chloride (II) may be reduced to epicatechin. It is beyond the limits of the present communication to discuss the validity of this formula of cyanidin chloride and reference must be made to (1) Willstätter and Mallison,[4] from whom it will become evident that the formula of cyanidin chloride is based on very slender evidence and (2) to Willstätter, Zechmeister and Kindler[5] as well as to the work of Pratt and Robinson[6] from which it will also become evident that so far no convincing synthesis of cyanidin chloride has been accomplished by these workers since the synthetic products obtained by them have been shown only to be similar to but not convincingly identical with cyanidin chloride. As the matter stands at present there is as much evidence in favor of Formula IV for cyanidin chloride as for Formula II[7] and the production of catechin from cyanidin chloride may well be quoted in favor of the author's formula (V) for acacatechin.

---

[1] Freudenberg, Orthner and Fikentscher, *Ann.*, **436**, 290 (1924).

[2] Freudenberg, Fikentscher, Harder and Schmidt, *Ann.*, **444**, 135 (1925).

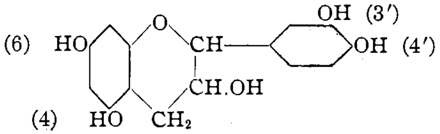
[3] Freudenberg, Carrara and Cohn, *Ann.*, **446**, 87 (1925).

[4] Willstätter and Mallison, *Ann.*, **408**, 24 (1915).

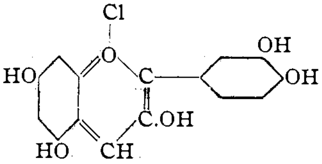
[5] Willstätter, Zechmeister and Kindler, *Ber.*, **57**, 1944 (1924).

[6] Pratt and Robinson, *J. Chem. Soc.*, **127**, 172 (1925).

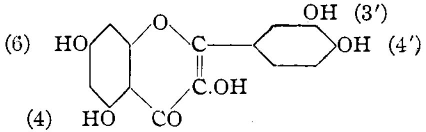
[7] Compare Ref. 4, p. 23.



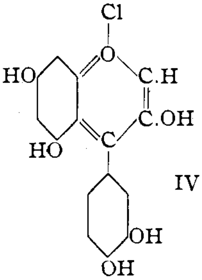
I



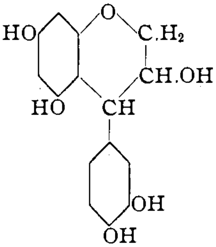
II



III



IV



V

In further support of their Formula I for catechin Freudenberg and his collaborators[8] also state that the pentamethylether of Substance II, which had been prepared according to the method of Pratt and Robinson,[9] may be reduced to a substance melting at 114–116° and that this reduction product is in every respect identical with pentamethyl-epicatechin. Experience which has accumulated in this Laboratory during the last fourteen years makes it hard to understand these results, as only the following two *optically inactive* pentamethylethers have so far been met by us: pentamethyl-acacatechin, m. p. 107°, which is described in the present communication and pentamethyl-iso-acacatechin, m. p. 127°, previously communicated.[10]

In view of these considerations the author's opinion as to the constitution of acacatechin, which is supported by a series of observations recorded in the present communication remains unaltered.

In Part VII of this series[11] it was mentioned that all attempts to reduce quercetin (III) to acacatechin have only yielded negative results and it was therefore thought desirable to attempt the oxidation of acacatechin as on the basis of the Freudenberg formula for catechin (I) the production of quercetin might be anticipated. The scheme adopted was the following:

---

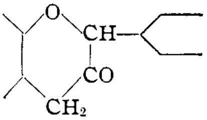
[8] Ref. 2, p. 142.

[9] Ref. 6, p. 171.

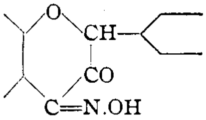
[10] Nierenstein, *Ber.*, **56**, 1879 (1923).

[11] Nierenstein, THIS JOURNAL, **46**, 2794 (1924).

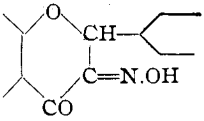
4,6,3′,4′-tetramethyl-acacatechin was to be oxidized to the ketone (VI) from which the isonitroso derivative (VII), which would yield 4,6,3′,4′-tetramethyl-quercetin on hydrolysis, was to be prepared.



VI



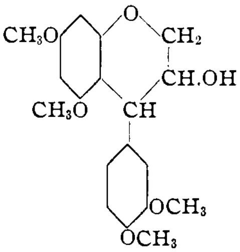
VII



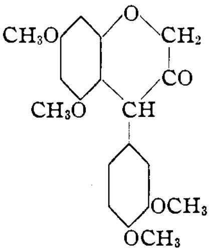
VIII

No difficulties were met in the preparation of the ketone and the isonitroso derivative, but no 4,6,3′,4′-tetramethyl-quercetin was obtained on hydrolysis. This is not consistent with Formula I for catechin, especially if one considers that the isomeric isonitroso derivative (VIII) is known to yield 4,6,3′,4′-tetramethyl-quercetin.[12]

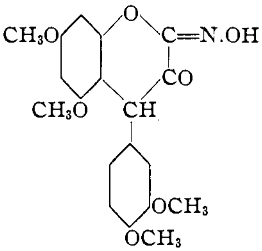
As will be realized, the reaction proceeds according to the Formulas IX, X, XI, XII and XIII, with the result that not tetramethyl-quercetin, but 2-hydroxy-4,6,3′,4′-tetramethoxy-3-phenylcoumarin (XIII) is produced. During these reactions both the α-diketonic (XII) and the enolic (XIII) forms can be isolated, which is not the case in the flavonol syntheses of Kostanecki. The α-diketone (XII) is, however, best prepared by the oxidation of the ketone (X) with neutral permanganate in acetone solution.



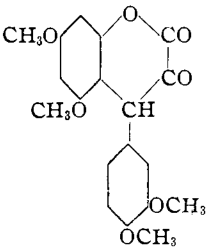
IX



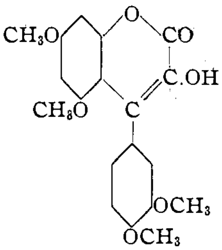
X



XI



XII



XIII

The constitution of 2-hydroxy-4,6,3′,4′-tetramethoxy-3-phenylcoumarin (XIII) becomes still more evident from the fact that the ketone (X) obtained from the oxidation of tetramethyl-acacatechin (IX) is in every re-

---

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

spect identical with the same substance previously synthesized by the action of diazomethane on 2,4,6,3′,4′-pentamethoxy-α,α-diphenyl-acetyl chloride with subsequent closure of the ring.[13] This was proved by the direct comparison of the two substances entailing the repetition of the synthesis of the ketone owing to the lack of the original material prepared in 1921.

Attempts to oxidize the α-diketone with neutral permanganate to a pyruvic acid or a maclurin derivative[14] have been disappointing as the products obtained were 6-hydroxy-2,4,3′,4′-tetramethoxy-α,α-diphenylacetic[15] and formic acids. The production of the latter substance is, however, of some interest as it emphasizes the absence of a phenyl group in the 1-position as required by Formula I for catechin. In this connection it is also interesting to note that Gauthier[16] has already recorded the production of formic acid from catechin and that this was not confirmed by Miller.[17]

The production of 6-hydroxy-2,4,3′,4′-tetramethoxy-α,α-diphenylacetic acid by the action of neutral permanganate on the α-diketone seemed to some extent contradictory to the fact that only dimethylphloroglucinol and veratric acid are produced by the oxidation of tetramethyl-acacatechin with permanganate in alkaline solution.[18] A quantitative study of this reaction has, however, shown that 6-hydroxy-2,4,3′,4′-tetramethoxy-α,α-diphenylacetic acid is produced under these conditions and that the dimethylphloroglucinol and veratric acid are only secondary oxidation products which are formed from the diphenylacetic acid derivative. That this is the case was confirmed by the action of alkali and potassium permanganate on 2,4,6,3′,4′-pentamethoxy-α,α-diphenylacetic acid and pentamethyl-maclurin, respectively, when trimethylphloroglucinol and veratric acid were obtained. In this connection it might be mentioned that the formation of these disintegration products from pentamethyl-maclurin corresponds to the production of phloroglucinol and protocatechuic acid from maclurin.[19]

From these observations it may be concluded that the fission of the chroman nucleus precedes oxidation and this was confirmed as follows. Pentamethyl-acacatechin (XIV) was reacted on with alcoholic potassium hydroxide and methyl iodide or dimethyl sulfate, respectively, when Substance XV was obtained. This latter substance yielded 2,4,6,3′,4′-pentamethoxy-α,α-diphenylacetic acid (XVI) on oxidation. Substance XV was also synthesized according to Formulas XVII, XVIII and XIX.

[13] Nierenstein, *J. Chem. Soc.*, **119**, 167 (1921).

[14] Compare Hazleton and Nierenstein, THIS JOURNAL, **46**, 2100 (1924).

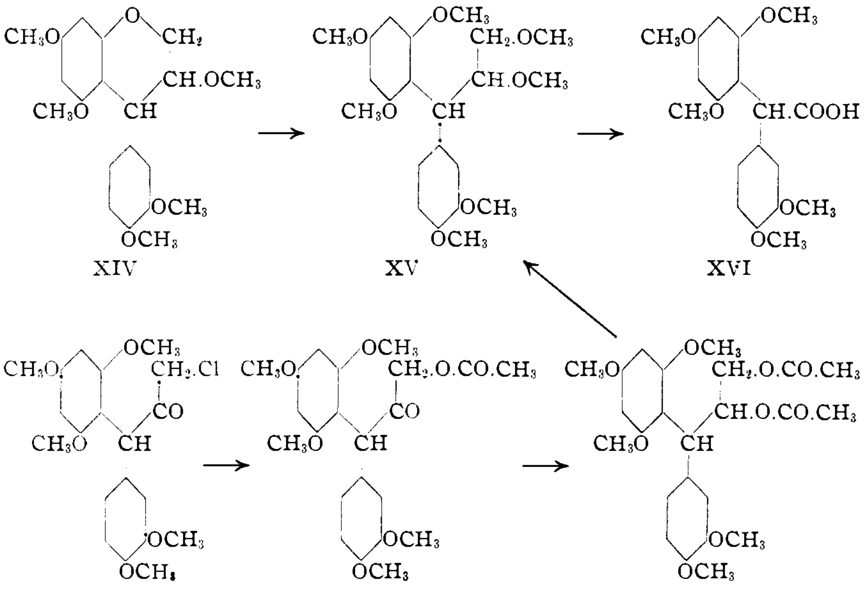
[15] Nierenstein, *J. Chem. Soc.*, **117**, 1154 (1920).

[16] Gauthier, *Bull. soc. chim.*, [ii] **30**, 567 (1878).

[17] Miller, *Ann.*, **220**, 115 (1883).

[18] (a) Perkin, *J. Chem. Soc.*, **87**, 400 (1905). (b) Nierenstein, *ibid.*, **121**, 610 (1922).

[19] Hlasiwetz and Pfaundler, *Ann.*, **127**, 352 (1863).



XIV XV XVI XVII XVIII XIX

The work on catechin published from this Laboratory has been constantly criticized by Freudenberg and his collaborators. Some of the older criticisms have been dealt with in previous communications[20] but reference must be made to a recent publication by Freudenberg and Purrmann.[21] These authors have come to the conclusion that acacatechin (m. p., 204–205°) is a mixture consisting of *dl*-catechin, *l*-catechin and *l*-epicatechin. These contentions are based (1) on the statement that Freudenberg[22] has examined an original specimen of acacatechin sent him by A. G. Perkin, the receipt of which had been acknowledged by Freudenberg, Böhme and Beckendorf[23] and (2) that the melting point 152–153°, found by Perkin[24] for natural and by Nierenstein[25] for synthetic tetramethyl-acacatechin is not correct, since *dl*-tetramethyl-acacatechin melts at 142° and not at 152–153°, the latter melting point being that of tetramethyl-*l*-epicatechin. It must therefore be noted: (1) that the material received by Freudenberg, Böhme and Beckendorf, who state: "wir danken Hrn. A. G. Perkin für die Übersendung einer Probe seines Kath" was not acacatechin but the cutch used by Perkin in his work on acacatechin; (2) that the ether ex-

---

[20] Ref. 15, p. 1156. Ref. 18b, p. 607. Nierenstein, *Ber.*, **55**, 3831 (1922). Ref. 14, p. 2101.

[21] Freudenberg and Purrmann, *Ann.*, **437**, 278 (1924).

[22] Freudenberg, *Ber.*, **55**, 1938 (1922).

[23] Freudenberg, Böhme and Beckendorf, *Ber.*, **54**, 1205 (1921).

[24] Ref. 18a, p. 404.

[25] Nierenstein, *J. Chem. Soc.*, 119, 166 (1921).

traction used by Freudenberg in the preparation of acacatechin from cutch gives different results from the ethyl acetate extraction employed by Perkin. This has frequently been observed in this Laboratory with the result that ethyl acetate only is used in the preparation of catechin by us. In agreement with Freudenberg we find that ether extractions of Indian cutches yield mixtures of varying melting points. These catechin preparations, however, can be purified by crystallization from dil. acetic acid. The acacatechin thus obtained melts at 204–205° and gives the following derivatives: penta-acetyl derivative, m. p., 160°; tetramethyl derivative, m. p., 152–153°; and acetyl-tetramethyl derivative, m. p., 136–137°; these are in agreement with the data recorded by Perkin for natural and by Nierenstein for synthetic acacatechin.[26] It must further be noted (3) that the low melting point 142° recorded by Freudenberg and Purrmann for tetramethyl-acacatechin is due to the presence of traces of the heptamethyl derivative XV which is formed when acacatechin is methylated with dimethyl sulfate and alkali. The production of low-melting tetramethyl-acacatechin has also been observed by us, but it has always been found that such low-melting preparations contained varying amounts of the heptamethyl derivative. These preparations melted, however, at 152–153° when freed from the heptamethyl derivative. Finally, (4) it has already been mentioned that during the course of the present investigation it had been found necessary to repeat the synthesis of the ketone X. In view of the criticism of Freudenberg and Purrmann it was thought desirable to reduce the ketone X to tetramethyl-acacatechin as previously described.[27] The tetramethyl-acacatechin, *the synthesis of which has thus been repeated* melted at 152–153° and this melting point was not depressed on admixture with optically-inactive tetramethyl-acacatechin (m. p., 152–153°). The same result was obtained on admixture of the synthetic acetyl-tetramethyl-acacatechin (m. p., 136–137°, as previously recorded) with the natural product. In view of these observations the recommendation of Freudenberg and Purrmann that the synthetic acacatechin should be crossed out from the literature can scarcely be upheld.

Reference must also be made to a recent publication by Ryan and his collaborators[28] who have favored Formula I for catechin since 1916.[29] These authors have repeated the reduction and subsequent methylation

---

[26] In the exhaustive fractionation of extracts from catechin-producing acacias, an account of which will shortly be published, a large number of fractions have been obtained which melt at 204–205°. It would hardly be expected that this melting point would be so consistently reproduced, and that by successive fractions, if it were that of a fortuitous mixture as suggested by Freudenberg.

[27] Ref. 13, p. 168.

[28] Drumm, O'Reilly and Ryan, *Proc. Roy. Irish Acad.*, **37**, 19 (1925).

[29] Ryan and Walsh, *Sci. Proc. Roy. Dublin Soc.*, **15**, 113 (1916). Drumm, McMahon and Ryan, *Proc. Roy. Irish Acad.*, **36**, 149 (1924).

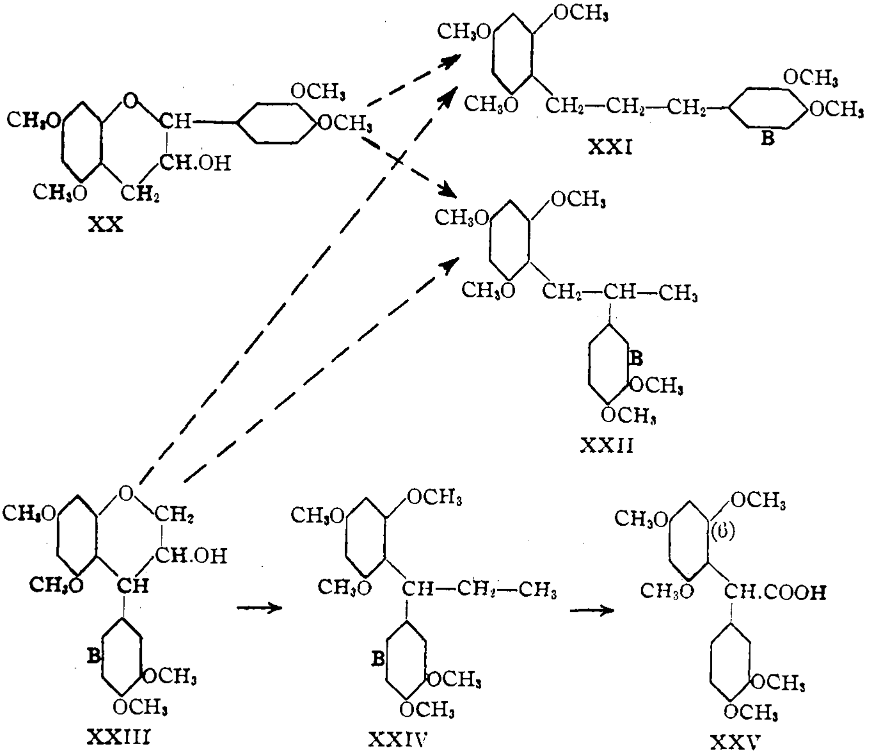
of tetramethyl-gambiercatechin described by Kostanecki and Lampe,[30] and have obtained a product which melted at 87–88°. They have also synthesized 2,4,6,3′,4′-pentamethoxy-α,γ-diphenylpropane (XXI) and 2,4,6,3′,4′-pentamethoxy-α,α-diphenylpropane (XXIV). The following is a summary of the melting points obtained by Drumm, O'Reilly and Ryan as compared with those found by previous workers.

Table I

Melting Points, °C.

	Methylated reduction product	α,α-Deriv.	α,γ-Deriv.
Kostanecki	83–84	...	...
Ryan and Walsh	83–84	...	...
Nierenstein	83–84	83–84	87–88
Freudenberg	87–88	...	87–88
Drumm, O'Reilly and Ryan	87–88	80–81	87–88

As will be realized from this summary the data obtained by Drumm, O'Reilly and Ryan go to show that the methylated reduction product of Kostanecki is identical with 2,4,6,3′,4′-pentamethoxy-α,γ-diphenylpropane



---

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

(XXI) as required by Formula I for catechin[31] and this is still further confirmed by the fact that the melting point of the α,γ-derivative is not depressed on admixture with Kostanecki's methylated reduction product.

These results are bewildering and the whole issue becomes still more confused now that Freudenberg and his collaborators[3] have shown that not only 2,4,6,3′,4′-pentamethoxy-α,γ-diphenylpropane (XXI) but also 2,4,6-3′,4′-pentamethoxy-α,β-diphenylpropane (XXII) may be produced from tetramethyl-catechin (XX, according to Freudenberg).

These observations seem to indicate that the nucleus B in tetramethyl-acacatechin (XXIII) is mobile which leads under various conditions to the production of XXIV, XXII and XXI, respectively, which would thus, perhaps, account for the different results obtained by the various workers. In any case it is evident that very little can be learned as to the constitution of catechin from Kostanecki's methylated reduction product. Far greater importance must be attached to the formation of 2,4,6,3′,4′-pentamethoxy-α,α-diphenylacetic acid (XXV) and 6-hydroxy-2,4,3′,4′-tetramethoxy-α,α-diphenylacetic acid, respectively, as these products have now been obtained under the following different conditions.

6-Hydroxy-2,4,3′,4′-tetramethoxy-α,α-diphenylacetic acid.—(1) By the reduction of tetramethyl-acacatechin and oxidation.[15] (2) By the oxidation of the α-diketone (XII) described in the present communication. (3) By the oxidation of tetramethyl-acacatechin with permanganate in alkaline solution, also described in the present communication.

2,4,6,3′,4′-Pentamethoxy-α,α-diphenylacetic acid.—(1) By the reduction of tetramethyl-acacatechin, methylation and oxidation.[32] (2) By the fission of the chroman nucleus, preparation of the heptamethyl derivative (XV) and oxidation, described in the present communication.

From these results one is forced to assume that 2,4,6,3′,4′-pentamethoxy-α,α-diphenylpropane is the *normal* disintegration product, especially if one also considers that acacatechin is known to yield maclurin.[33]

In this connection reference must also be made to the fact that 2-hydroxy-4,6,3′,4′-tetramethoxy-3-phenylcoumarin (XXVI) yields on demethylation with hydriodic acid the same product that has been obtained by Ciamician and Silber[34] by the action of hydriodic acid on 4,6,3′,4′-tetra-acetoxy-3-phenylcoumarin (XXVII). Although it has so far not been possible to elucidate the constitution of Substance XXVIII an interesting link has been established between Substances XXVI and XXVII, the latter of which is obtained by the action of acetic anhydride on maclurin. This again emphasizes the α,α-diphenylpropane structure of acacatechin.

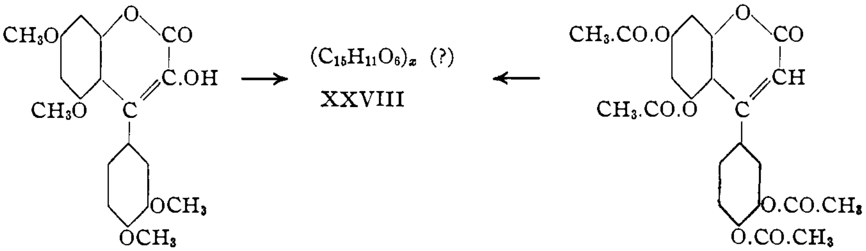
---

[31] Compare Freudenberg, *Ber.*, **53**, 1416 (1920).

[32] Nierenstein, *J. Chem. Soc.*, **117**, 977 (1920).

[33] Ref. 14, p. 2101.

[34] Ciamician and Silber, *Ber.*, **27**, 1630 (1894).



XXVI $\longrightarrow$ $(C_{15}H_{11}O_6)_x$ (?) XXVIII $\longleftarrow$ XXVII

Experimental Part

The acetone used in these experiments was refluxed for some time with alkali and potassium permanganate and then distilled. The "neutral permanganate" solution consisted of 850 cc. of *N* potassium permanganate solution and 15 g. of magnesium sulfate dissolved in 150 cc. of water.

4,6,3′,4′-Tetramethoxy-3-phenylchroman-2-one (X).—To a boiling solution of 10 g. of tetramethyl-acacatechin in 100 cc. of acetone is added 130 cc. of "neutral permanganate" and the solution is heated for two hours. The filtered solution, to which are added the acetone washings of the manganese oxide, deposits on standing a small quantity of Substance X, but the main bulk (68%, average of four experiments) is obtained on concentration to about 50 cc. As already stated the product thus obtained is in every respect identical with synthetic 4,6,3′,4′-tetramethoxy-3-phenylchroman-2-one (X), previously described.[13]

Anal. Subs., 7.24 mg.: CO_2, 17.60; H_2O, 3.93. Calcd. for $C_{19}H_{20}O_6$: C, 66.27; H, 5.81. Found: C, 66.29; H, 6.07.

The phenylhydrazone already described[13] and the *p*-bromophenylhydrazone were also prepared from both substances and they were also found to be identical. The *p-bromophenylhydrazone* crystallizes from glacial acetic acid in brown, thick needles, which melt at 257–259°, with decomposition.

Anal. Subs., 8.10 mg.: N, 0.361 cc. (21°, 752 mm.). Calcd. for $C_{25}H_{25}O_5N_2Br$: N, 5.45. Found: 5.12.

The filtrate from the crude product (X) leaves on evaporation an oily residue which on standing solidifies to a yellow solid. The latter is a mixture and consists of unchanged tetramethyl-acacatechin, 4,6,3′,4′-tetramethoxy-3-phenylchroman-2-one (X), 4,6,3′,4′-tetramethoxy-3-phenylchroman-1,2-dione (XII), 2-hydroxy-4,6,3′,4′-tetramethoxy-3-phenylcoumarin (XIII), 6-hydroxy-2,4,3′,4′-tetramethoxy-α,α-diphenylacetic acid and some resinous by-product.

The separation of these substances may be carried out as follows. The solid is dissolved in ether and the ethereal solution shaken with aqueous sodium bicarbonate, saturated with carbon dioxide. The aqueous solution thus obtained yields 6-hydroxy-2,4,3′,4′-tetramethoxy-α,α-diphenylacetic acid (7.2%, average of three experiments) on acidification, extraction with ether and evaporation of the solvent. The ethereal solution left after separation of the aqueous solution containing the sodium salt of the α,α-diphenylacetic acid derivative is evaporated to dryness at room temperature and the remaining solid dried over phosphorus pentoxide. The product is then powdered, mixed with an excess of sand, and extracted in a small Soxhlet in turn with (1) chloroform, which extracts mainly 4,6,3′,4′-tetramethoxy-3-phenylchroman-1,2-dione (4.1%, average of two experiments), (2) benzene, which removes to a large extent 2-hydroxy-4,6,3′,4′-tetramethoxy-3-phenylcoumarin (2.8%, average of two experiments), (3) ether and (4) alcohol, which extract mixtures, consisting of unchanged tetramethylacacatechin (2.7%, average of three experiments), 4,6,3′,4′-tetramethoxy-3-phenylchroman-2-one (2.1%, average of three experiments) and the resinous by-product (4%, average of two experiments).

Isonitroso-4,6,3′,4′-tetramethoxy-3-phenylchroman-2-one (XI).—A solution of 2 g. of the ketone (X) in 50 cc. alcohol, mixed with 3 g. of amyl nitrite and 12 cc. of concd. hydrochloric acid is heated for one hour and then poured into water. The solid thus obtained is dissolved in alkali, the solution filtered and acidified with acetic acid, when a faintly yellow solid is obtained. The latter crystallizes from benzene in sheath-like plates which melt at 116°. The product is soluble in the usual organic solvents and also slightly in water. Alkali produces a yellow solution, which becomes colorless on acidification. Yield, 88%, average of five experiments.

Anal. Subs., 7.47 mg.: N, 0.241 cc. (21°, 763 mm.). Calcd. for $C_{19}H_{19}O_7N$: N, 3.75. Found: 3.76.

2-Hydroxy-4,6,3′,4′-tetramethoxy-3-phenylcoumarin (XIII).—Three g. of the isonitroso derivative, dissolved in 30 cc. of glacial acetic acid is heated for 45 minutes over a free flame with 30 cc. of 10% sulfuric acid. On standing the flask becomes filled with a yellow solid from which the deep yellow solution is filtered by suction. On crystallization from alcohol, colorless, glittering needles are obtained which melt at 181°. The product is sparingly soluble in methyl and ethyl alcohols and ethyl acetate, but more soluble in glacial acetic acid and quite insoluble in the other organic solvents. It dissolves in cold alkali forming a deep yellow solution which turns saffron-yellow on warming. In concd. sulfuric acid an orange solution is produced which turns yellow on dilution. The alcoholic solution turns deep red on the addition of ferric chloride. Yield, 91%, average of four experiments.

Anal. Subs., 9.61 mg.: CO_2, 22.41; H_2O, 4.31. Calcd. for $C_{19}H_{18}O_7$: C, 63.69; H, 5.02. Found: C, 63.60; H, 5.03.

The ACETYL DERIVATIVE crystallizes from alcohol in small needles; m. p., 153°.

Anal. Subs., 17.42 mg.: CO_2, 40.19; H_2O, 8.08. Calcd. for $C_{21}H_{20}O_8$: C, 63.00; H, 5.00. Found: C, 62.92; H, 5.19.

2,4,6,3′,4′-Pentamethoxy-3-phenylcoumarin is prepared by the action of diazomethane or methyl iodide and silver oxide on the ethereal solution of Substance XIII, but no methylation takes place by the interaction with alkali and dimethyl sulfate in alcoholic solution. The product crystallizes from alcohol in small needles which melt at 146°.

Anal. Subs., 11.53 mg.: CO_2, 27.26; H_2O, 5.62. Calcd. for $C_{20}H_{20}O_7$: C, 64.52; H, 5.38. Found: C, 64.47; H, 5.46.

TABLE II

COMPARISON BETWEEN 2-HYDROXY-4,6,3′,4′-TETRAMETHOXY-3-PHENYLCOUMARIN AND 4,6,3′,4′-TETRAMETHYL-QUERCETIN

	M. p., °C.	Ref.
2-Hydroxy-4,6,3′,4′-tetramethoxy-3-phenylcoumarin	181	..
4,6,3′,4′-Tetramethyl-quercetin	197–198	12
2-Acetoxy-4,6,3′,4′-tetramethoxy-3-phenylcoumarin	153	..
Acetyl-4,6,3′,4′-tetramethyl-quercetin	160–163	35
2,4,6,3′,4′-Pentamethoxy-3-phenylcoumarin	146	..
Pentamethyl-quercetin	148	36
	150–151	37

---

[35] Herzig, *Monatsh.*, **33**, 683 (1912).

[36] Waliaschko, *Arch. Pharm.*, **242**, 225 (1904).

[37] Perkin, *J. Chem. Soc.*, **103**, 1632 (1913).

Mixed melting points of 2,4,6,3′,4′-pentamethoxy-3-phenylcoumarin with authentic pentamethyl-quercetin (m. p., 150°) give depressions of 17° to 21°.

Action of Alkali on 2-Hydroxy-4,6,3′,4′-tetramethoxy-3-phenylcoumarin. (XIII).—Three g. of the substance is heated for ten minutes in a silver dish with 8 g. of powdered sodium hydroxide and a little water. The solid is dissolved in water, and the solution acidified with dil. sulfuric acid, filtered and extracted with ether. The ethereal extract is then shaken with aqueous sodium bicarbonate, saturated with carbon dioxide and the two layers are examined separately.

The *ethereal* layer is dried for some time over anhydrous sodium sulfate and then treated with an excess of diazomethane. The oil left on evaporation of the ether solidifies immediately on inoculation with trimethyl-phloroglucinol; the substance forms long needles from ligroin (b. p., 50–60°) which melt at 52°. This melting point is not depressed on admixture of the substance with authentic trimethyl-phloroglucinol.

The *aqueous* layer is acidified and extracted with ether, which leaves veratric acid (m. p. and mixed m. p., 180°) on evaporation.

Attempt to Demethylate 2-Hydroxy-4,6,3′,4′-tetramethoxy-3-phenylcoumarin. (XIII).—One g. of the substance is heated with 15 cc. of hydriodic acid (d., 1.7) and 3 cc. of acetic anhydride. The product crystallizes from water in faintly yellow needles; m. p., 162–163°. It dissolves in alkali forming a yellow solution and gives a green-yellow coloration with concd. sulfuric acid.

Anal. Subs., 5.40; 8.64 mg.: CO_2, 12.32, 19.70; H_2O, 1.75, lost. Found: C, 62.22, 62.18; H, 3.63.

The analytical data do not agree with those required for 2,4,6,3′,4′-pentahydroxy-3-phenylcoumarin, namely, C, 59.57; H, 3.34. They are, however, in agreement with formula $(C_{15}H_{11}O_6)_x$, which requires further study. They are also in fair agreement with some of the data given by Ciamician and Silber[34] for their product obtained by the action of hydriodic acid on 4,6,3′,4′-tetra-acetoxy-3-phenylcoumarin: C, 62.15, 62.20, 61.86, 61.14; H, 3.67, 3.53, 3.69, 3.87. The melting point given by Ciamician and Silber is, however, 270° and not 162–163°. The substance was, therefore, also prepared according to the method of Ciamician and Silber, when it was found to melt at 162–163°. The identity was also established by the mixed melting point of the two substances which showed no depression. The melting point 270° is apparently a clerical error which should, perhaps, have read 170°. The product was not further investigated.

4,6,3′,4′-Tetramethoxy-3-phenylchroman-1,2-dione (XII).—This product is obtained in small quantities during the oxidation of tetramethyl-acacatechin and the hydrolysis of the isonitroso derivative, but it is best prepared by the oxidation of 4,6,3′,4′-tetramethoxy-3-phenylchroman-2-one.

1. To a solution of 10 g. of 4,6,3′,4′-tetramethoxy-3-phenylchroman-2-one in 100 cc. of acetone is added 130 cc. of "neutral permanganate" and the solution heated for two hours. The solution is filtered, the manganese oxide washed with warm acetone and the solution concentrated to about 25 cc. A small quantity of unchanged 4,6,3′,4′-tetramethoxy-3-phenylchroman-2-one separates on standing in ice. The filtered solution is evaporated to dryness, dissolved in ether and freed from 6-hydroxy-2,4,3′,4′-tetramethoxy-α,α-diphenylacetic acid (22.7%, average of three experiments) as previously described. The solid left on evaporation of the ether consists mainly of 4,6,3′,4′-tetramethoxy-3-phenylchroman-1,2-dione (XII), but it contains also 2-hydroxy-4,6,3′,4′-tetramethoxy-3-phenylcoumarin (XIII) and some resinous by-product. The solid is dissolved in carbon tetrachloride from which the 4,6,3′,4′-tetramethoxy-3-

phenylchroman-1,2-dione crystallizes in long, bright yellow needles, which melt at 134° (16.3%, average of three experiments). A further quantity (5.7%, average of three experiments) of Substance XII is obtained on concentration of the carbon tetrachloride solution. The substance obtained on evaporation to dryness consists of a resinous semisolid, which yields on prolonged treatment with ligroin practically colorless 2-hydroxy-4,6,3′,4′-tetramethoxy-3-phenylcoumarin (47%, average of two experiments).

Anal. Subs., 10.62 mg.: CO_2, 24.78; H_2O, 4.88. Calcd. for $C_{19}H_{18}O_7$: C, 63.69; H, 5.02. Found: C, 63.64; H, 5.14.

An attempt to condense the α-diketone (XII) with toluene-3,4-diamine gave no definite condensation product, but the interaction with diazomethane in ethereal solution leads to the production of *1,2-methylenedioxy-4,6,3′,4′-tetramethoxy-3-phenylchroman.*[38] This forms faintly yellow needles from dil. alcohol; m. p., 122°; yield, 95%.

Anal. Subs., 10.08 mg.: CO_2, 25.53; H_2O, 5.26. Calcd. for $C_{20}H_{20}O_7$: C, 64.52; H, 5.38. Found: C, 64.47; H, 5.45.

2. The isolation of 4,6,3′,4′-tetramethoxy-3-phenylchroman-1,2-dione (XII) during the oxidation of tetramethyl-acacatechin has already been described under the preparation of Substance X. As regards the isolation of Substance XII formed during hydrolysis of the isonitroso derivative (XI) the following method was found to give the best results. The yellow filtrate obtained from the crude 2-hydroxy-4,6,3′,4′-tetramethoxy-3-phenylcoumarin (XIII) is shaken for some time with carbon tetrachloride and the carefully dried carbon tetrachloride solution diluted with ligroin until a permanent cloudiness is obtained. On standing, a small quantity (about 1.5%, average of two experiments) of the α-diketone crystallizes; m. p., 130–131°. This melting point is raised to 134° on crystallization from carbon tetrachloride.

Interconversion of 4,6,3′,4′-Tetramethoxy-3-phenylchroman-1,2-dione (XII) and 2-Hydroxy-4,6,3′,4′-tetramethoxy-3-phenylcoumarin (XIII).—The interconversion of these desmotropic substances may be observed as follows.

1. The α-diketone crystallizes from carbon tetrachloride in yellow needles; m. p., 134°. When, however, alcohol is added to the carbon tetrachloride solution, not the yellow α-diketone but the colorless enol, melting at 181°, is obtained.

2. The colorless enol may also be crystallized from carbon tetrachloride from which it separates in colorless needles which melt at 181°, but when dry acetone is added to the solution the yellow α-diketone, melting at 134°, is obtained.

3. The yellow α-diketone when dissolved in alcohol gives the colorless enol, melting at 181°.

4. The colorless enol separates from acetone as the yellow α-diketone, melting at 134°.

5. Reference has already been made to the deep red coloration which is obtained by the addition of ferric chloride to the alcoholic solution of the enolic product. This coloration may be used in the following manner to demonstrate the conversion of the α-diketone into the enol. To a solution of the α-diketone in acetone a few drops of ferric chloride are added, when the solution turns faintly red, and this coloration becomes deeper on standing. When, however, a few drops of alcohol are added to the acetone solution the production of the deep red color is instantaneous.

From these results one may conclude that (1) both the ketonic and enolic forms are stable in carbon tetrachloride, (2) alcohol favors the enolic form and (3) acetone favors the ketonic form.

Oxidation of 4,6,3′,4′-Tetramethoxy-3-phenylchroman-1,2-dione (XII).—A solu-

---

[38] Compare Nierenstein, *J. Chem. Soc.*, **107,** 870 (1915). Dean and Nierenstein, *ibid.*, **117,** 803 (1920). Biltz and Paetzold, *Ann.*, **433,** 71 (1923).

tion of 6 g. of the α-diketone in 100 cc. of acetone is oxidized with 100 cc. of "neutral permanganate" for two hours, the mixture filtered and the manganese oxide washed with hot acetone. No solid is formed even on concentration to a small bulk and the solution is concentrated to dryness at room temperature. The solid obtained is triturated with dil. sulfuric acid and dissolved in ether. The ethereal extract is shaken with aqueous sodium bicarbonate saturated with carbon dioxide and the aqueous extract examined separately. In this connection it is interesting to note that the ethereal layer leaves nothing on evaporation, which thus indicates that nothing but acidic disintegration products are obtained.

The aqueous layer is acidified and steam-distilled. The distillate contains formic acid; it reduces silver nitrate and mercuric chloride and precipitates cerium nitrate.[39]

In a second experiment using 6 g. of the α-diketone the formic acid was kindly estimated by Dr. R. C. Menzies,[40] who found 0.5425 g. of formic acid by titration with 0.1 *N* thallium hydroxide using phenolphthalein as indicator. This corresponds to 104.85% as required by calculation. On evaporation of the liquid to dryness in a vacuum over concd. sulfuric acid a crystalline solid was obtained. The analysis of the crude substance gave Tl = 80.97%. The product crystallized from alcohol gave Tl = 82.04%, whereas thallium formate requires 81.95%. An authentic specimen of thallium formate gave Tl = 81.70%. From these experiments one may conclude that traces of some other acid, probably acetic acid which is produced from the acetone[41] are also present, but that formic acid is mainly produced.

The solution left after the formic acid is removed on steam distillation contains 6-hydroxy-2,4,3′,4′-tetramethoxy-α,α-diphenylacetic acid (93%, average of two experiments). For further identification the 6-ethoxy-2,4,3′,4′-tetramethoxy-α,α-diphenylacetic acid, which had previously been obtained only in a very small quantity,[42] was also prepared. It melted at 138°, which is in good agreement with the melting point 137–138° previously recorded.

Oxidation of Tetramethyl-acacatechin (IX) in Alkaline Solution with Potassium Permanganate.—Four experiments were made, using 10 g. of tetramethyl-acacatechin. In two of these experiments the tetramethyl-acacatechin was suspended in alkali and the potassium permanganate added, so that there was always an excess of alkali. In the other two the product was suspended in potassium permanganate and the alkali added, the potassium permanganate thus being in excess. A solution of 40 g. of sodium hydroxide in 250 cc. of water and 1850 cc. of normal potassium permanganate solution was used for each oxidation which was carried out in a boiling water bath for 9½ hours. The following disintegration products were identified.

TABLE III

	Excess of alkali		Excess of $KMnO_4$	
	I, g.	II, g.	III, g.	IV, g.
Dimethyl-phloroglucinol	1.5	0.7	1.8	2.3
6-Hydroxy-2,4,3′,4′-tetramethoxy-α,α-diphenylacetic acid	2.7	3.1	1.9	0.6
Veratric acid	1.8	2.1	2.7	1.7
4,6,3′,4′-Tetramethoxy-3-phenylchroman-2-one	...	0.2	2.8	1.9

---

[39] Compare Rosenthaler, "Der Nachweis organischer Verbindungen," F. Enke, Stuttgart, 1914, p. 27.

[40] Compare Christie and Menzies, *J. Chem. Soc.*, **127**, 2369 (1925).

[41] Compare Evans and Nicoll, THIS JOURNAL, **47**, 2789 (1925).

[42] Ref. 14, p. 2104.

The following is the procedure for the identification of the above mentioned substances.

1. The alkaline solution is filtered hot and the manganese oxide is washed several times with hot water, about 800 cc. of water being used. The manganese oxide is carefully dried and exhaustively extracted with ether. The ethereal extract thus obtained contains some unchanged tetramethyl-acacatechin (1.3 g., average of three experiments) and 4,6,3',4'-tetramethoxy-3-phenylchroman-2-one, which are separated from each other by several crystallizations from acetone when the 4,6,3',4'-tetramethoxy-3-phenylchroman-2-one is first obtained.

2. The alkaline filtrate is exhaustively extracted with ether and the ethereal extract dried over anhydrous sodium sulfate. On evaporation of the ether a small quantity of 4,6,3',4'-tetramethoxy-3-phenylchroman-2-one and traces of tetramethyl-acacatechin are obtained.

3. The aqueous alkaline solution is acidified and exhaustively extracted with ether. The ethereal extract is shaken with aqueous sodium bicarbonate saturated with carbon dioxide and separated from the ethereal layer. The latter is dried over anhydrous sodium sulfate and treated with an excess of diazomethane. Trimethyl-phloroglucinol is obtained on evaporation of the ether, from which the amount of dimethyl-phloroglucinol obtained is calculated.

4. The aqueous layer left after the removal of the dimethyl-phloroglucinol is acidified and extracted with ether, dried over anhydrous sodium sulfate and evaporated to dryness. The solid left is dissolved in absolute alcohol[43] and saturated with dry hydrogen chloride, heated for a short time and again treated with hydrogen chloride. This is repeated thrice and the alcohol then removed in a vacuum. The residue is again dissolved in absolute alcohol and once more treated with dry hydrogen chloride. The solid left on evaporation of the alcohol under diminished pressure is redissolved in absolute alcohol, the alcohol distilled in a vacuum and the residue dissolved in about 400 cc. of ether. The ethereal solution is then shaken with 100 cc. of 5% sodium hydroxide solution, any rise of temperature being carefully avoided. The alkaline solution thus obtained yields 6-hydroxy-4,6,3',4'-tetramethoxy-α,α-diphenylacetic acid when warmed, extracted with ether and the ethereal solution evaporated.

5. The ethereal extract obtained on the separation of the 6-hydroxy-4,6,3',4'-tetramethoxy-α,α-diphenylacetic acid leaves a semisolid residue on evaporation of the ether. This solid gives veratric acid when warmed with dil. alkali, subsequent acidification with dil. hydrochloric acid, extraction with ether and evaporation of the ether.

Oxidation of 2,4,6,3',4'-Pentamethoxy-α,α-diphenylacetic acid (XVI) in Alkaline Solution with Potassium Permanganate.—A solution of 25 g. of 2,4,6,3',4'-pentamethoxy-α,α-diphenylacetic acid in 250 cc. of water is oxidized in a boiling water-bath with 25 g. of sodium hydroxide and 850 cc. of normal potassium permanganate solution. The alkaline filtrate to which are added the washings of the manganese oxide yields trimethyl-phloroglucinol on steam distillation; yield of crude material, 10.84 g., or 93.2%. The solution left after the removal of the trimethyl-phloroglucinol is acidified and extracted with ether. The solid obtained on evaporation consists mainly of veratric acid, but it contains traces of 2,4,6,3',4'-pentamethoxy-α,α-diphenylacetic acid. Sharply melting veratric acid (9.7 g., or 76.8%) and 2,4,6,3',4'-pentamethoxy-α,α-diphenylacetic acid (1.3 g.) are obtained on several fractional crystallizations from dil. alcohol.

Action of Potassium Permanganate and Alkali on Pentamethyl-maclurin.—Ten g. of pentamethyl-maclurin is oxidized with 10 g. of sodium hydroxide and 650 cc. of *N*

---

[43] The alcohol was refluxed over calcium oxide, dried over calcium carbide and distilled.

potassium permanganate solution in the manner described in the case of the α,α-acetic acid; yields, 3.7 g. of crude trimethyl-phloroglucinol (72.6%), 4.1 g. of crude veratric acid (74.5%) and 1.2 g. of pentamethyl-maclurin. In this connection it is interesting to note that benzophenone may be converted under the same conditions to benzoic acid. An experiment using 5 g. of benzophenone gave 1.7 g. of benzoic acid.

Pentamethyl-acacatechin (XIV).—Twenty-five g. of acetyl-tetramethyl-acacatechin (m. p., 136–137°) dissolved in methyl alcohol is methylated with 29 g. of dimethyl sulfate and 13 g. of potassium hydroxide. The solid obtained on pouring the mixture into water is dried over phosphorus pentoxide and exhaustively extracted in a Soxhlet apparatus with ligroin (b. p., 80–90°). On concentration of the ligroin solution, fine, silky needles are obtained which melt at 107° and this melting point is not raised on successive crystallizations of the substance from ligroin, chloroform, carbon tetrachloride and dil. alcohol. The solid left after removal of the pentamethyl-acacatechin consists of β,γ,2,4,6,3′,4′-heptamethoxy-α,α-diphenylpropane (XV) and tetramethyl-acacatechin. The average yields in two experiments were: 16.5 g. of pentamethyl-acacatechin, 2.1 g. of tetramethyl-acacatechin and 1.8 g. of β,γ,2,4,6,3′,4′-heptamethoxy-α,α-diphenylpropane.

Anal. Subs., 10.42 mg.: CO_2, 25.36; H_2O, 6.37. Calcd. for $C_{20}H_{24}O_6$: C, 66.66; H, 6.66. Found: C, 66.37; H, 6.84.

β,γ,2,4,6,3′,4′-Heptamethoxy-α,α-diphenylpropane (XV).—This substance can be obtained by the following methods.

1. A solution of 20 g. of pentamethyl-acacatechin in 100 cc. of alcohol is heated on a boiling water-bath for 8–10 hours with 25 cc. of 25% alcoholic potassium hydroxide and 11 g. of methyl iodide. The solution is then poured into water and freed from alcohol by standing in a boiling water-bath. The solid thus obtained is crystallized from alcohol from which it separates in small cubes which melt at 122°. The average yield of two experiments is 87%.

2. Ten g. of pentamethyl-acacatechin, dissolved in 50 cc. of alcohol is heated under the above-mentioned conditions with 25 cc. of 25% alcoholic potassium hydroxide and 12 g. of dimethyl sulfate. The average yield of three experiments is 91%.

3. The product is formed during the preparation of tetramethyl-acacatechin by the action of dimethyl sulfate on acacatechin. Low-melting tetramethyl-acacatechin is freed from it in the following manner. The product dried over phosphorus pentoxide is dissolved in four times its weight of dry carbon tetrachloride; to this solution ligroin is added until a faint cloudiness appears when, on standing, various amounts of the heptamethoxy derivative crystallize. After filtration a fresh amount of ligroin is added when again a small quantity of the heptamethoxy derivative crystallizes. The tetramethyl-acacatechin obtained on evaporation of the carbon tetrachloride crystallizes from alcohol and melts at 152–153°.

4. Reference has already been made to the production of β,γ,2,4,6,3′,4′-heptamethoxy-α,α-diphenylpropane and tetramethyl-acacatechin during the production of pentamethyl-acacatechin from acetyl-tetramethyl-acacatechin. The separation of the two substances is carried out by dissolving in carbon tetrachloride and precipitating with ligroin as already described.

β,γ,2,4,6,3′,4′-Heptamethoxy-α,α-diphenylpropane is soluble in the usual organic reagents. The addition of ferric chloride to a suspension of the substance in concd. sulfuric acid does not produce either a reddish or a reddish-violet coloration, which seems to be typical for the 3-phenylchroman nucleus only.[44]

---

[44] Compare Kostanecki and Lampe, *Ber.*, **39**, 4007 (1906). Greenwood and Nierenstein, *J. Chem. Soc.*, **117**, 1597 (1920). Kahil and Nierenstein, THIS JOURNAL, **46**, 2558 (1924).

Anal. Subs., 0.1532: CO_2, 0.3650; H_2O, 0.1034. Calcd. for $C_{22}H_{30}O_7$: C, 65.02; H, 7.41. Found: C, 64.98; H, 7.55.

On oxidation of 3 g. of β,γ,2,4,6,3′,4′-heptamethoxy-α,α-diphenylpropane with 75 cc. of 20% potassium hydroxide solution and an excess of potassium permanganate, 1.6 g. or a 59.7% yield of 2,4,6,3′,4′-pentamethoxy-α,α-diphenylacetic acid (XVI) is produced.

γ-Acetoxy-2,4,6,3′,4′-pentamethoxy-α,α-diphenylpropane-β-one (XVIII).—A solution of 4 g. of 2,4,6,3′,4′-pentamethoxydiphenyl methyl chloromethyl ketone (XVII)[45] dissolved in 75 cc. of alcohol is heated for six hours with 4.5 g. of potassium acetate. The solid obtained on pouring the mixture into water crystallizes from alcohol in silky needles; m. p., 162°. The product is soluble in the usual organic solvents, but not in benzene or chloroform; yield, 95.9%.

Anal. Subs., 0.1343: CO_2, 0.3113; H_2O, 0.0749. Calcd. for $C_{22}H_{26}O_8$: C, 63.27; H, 6.22. Found: C, 63.35; H, 6.25.

β,γ-Diacetoxy-2,4,6,3′,4′-pentamethoxy-α,α-diphenylpropane (XIX).—Four g. of Substance XVIII dissolved in 75 cc. of acetic anhydride is heated with 15 g. of carefully dried zinc dust for seven hours in an oil-bath at 120–130°. The solution is then filtered and the zinc dust washed with hot acetic acid. The acetic anhydride solution and the acetic acid extract are poured into water and the solid is crystallized from a 2 : 1 mixture of alcohol and acetone. Fine needles are obtained which melt at 173°. The product is soluble in the usual organic solvents; yield, 75%.

Anal. Subs., 0.1547: CO_2, 0.3528; H_2O, 0.0905. Calcd. for $C_{24}H_{30}O_9$: C, 62.17; H, 6.47. Found: C, 62.19; H, 6.54.

Conversion of β,γ-Diacetoxy-2,4,6,3′,4′-pentamethoxy-α,α-diphenylpropane (XIX) into β,γ,2,4,6,3′,4′-Heptamethoxy-α,α-diphenylpropane. (XV).—A boiling solution of 2.5 g. of β,γ-diacetoxy-2,4,6,3′,4′-pentamethoxy-α,α-diphenylpropane in alcohol is treated twice with 15 cc. of 25% potassium hydroxide solution and 10 cc. of dimethyl sulfate. The solid obtained on precipitation with water crystallizes from alcohol in small cubes, which melt at 122° after two crystallizations. This melting point is not depressed on admixture with β,γ,2,4,6,3′,4′-heptamethoxy-α,α-diphenylpropane from pentamethyl-acacatechin.

During these investigations, which covered a period of nearly three years, I was assisted by Miss E. O. Hazleton, 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 Dr. G. H. Christie for many valuable suggestions and to the Colston Research Society of the University of Bristol for grants which have covered the expenses of this work.

Summary

1. It is pointed out that the constitution of cyanidin chloride has not been conclusively established and, therefore, its conversion into epicatechin does not throw definite light on the constitution of the latter.

2. Tetramethyl-acacatechin has been converted into 2-hydroxy-4,6,3′,4′-tetramethoxy-3-phenylcoumarin by a method which would have yielded 4,6,3′,4′-tetramethyl-quercetin if acacatechin had been a reduced quercetin derivative as assumed by Freudenberg.

---

[45] Ref. 15, p. 1153.

3. The synthesis of 2-hydroxy-4,6,3′,4′-tetramethoxy-3-phenylcoumarin is described.
4. The synthesis of tetramethyl-acacatechin previously described by the author and since then contested by Freudenberg has been repeated.
5. The chroman nucleus in pentamethyl-acacatechin is shown to undergo fission by the interaction of alkali and methylating reagents when β,γ-2,4,6,3′,4′-heptamethoxy-α,α-diphenylpropane is produced.
6. β,γ,2,4,6,3′,4′-Heptamethoxy-α,α-diphenylpropane has been synthesized.
7. The production of the α,α-diphenylacetic acid derivatives from acacatechin is emphasized, thus showing that the α,α,-diphenylpropane structure is the normal structure of acacatechin.
8. It is shown that 2-hydroxy-4,6,3′,4′-tetramethoxy-3-phenylcoumarin obtained from tetramethyl-acacatechin and 4,6,3′,4′-tetra-acetoxy-3-phenylcoumarin prepared by the action of acetic anhydride on maclurin yield the same substance when reacted on with hydriodic acid.
9. These observations confirm the formula assigned to acacatechin by the author.

BRISTOL, ENGLAND

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF OTAGO]

EXPERIMENTS ON THE SYNTHESIS OF APOFENCHOCAMPHORIC ACID. PREPARATION OF ALPHA, ALPHA-DIMETHYL-GAMMA-CARBOXYADIPIC ACID

BY KENNETH CHARLES ROBERTS

RECEIVED MARCH 10, 1926 PUBLISHED JULY 6, 1926

Recent literature on the dicyclic terpenes contains several references[1] to a dibasic acid of the formula $C_9H_{14}O_4$. This acid is isomeric with apocamphoric acid, and has been named apofenchocamphoric acid. All the papers cited appear to regard it as having the constitution 4,4-dimethylcyclopentane-1,3-dicarboxylic acid but, since the constitutions of the substances from which the acid is obtained can in no case be regarded as definitely established, this tentative structure still remains to be proved. It has been the aim of the present investigation to synthesize 4,4-dimethylcyclopentane-1,3-dicarboxylic acid and thus prove, if possible, its identity with apofenchocamphoric acid.

By analogy with Perkin and Thorpe's synthesis of camphoric acid, it was thought that, if α,α-dimethyl-γ-carboxyadipic acid could be prepared, this could then be readily closed up to a five-carbon ring, and the resulting cyclic keto acid transformed into the required 4,4-dimethylcyclopentane-

---

[1] Nametkin and Chuchrikovaia, *J. Chem. Soc.*, **108**, 701 (1915). Komppa and Roschier, *ibid.*, **112**, 398 (1917); **122**, 1167 (1922). Roschier, *ibid.*, **116**, 408 (1919).