[Contribution from the Chemistry Department of the University of Bristol]

THE CONSTITUTION OF CATECHIN

VI. THE PRODUCTION OF MACLURIN FROM ACACATECHIN

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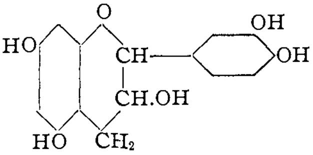
The constitution of acacatechin has been established by Nierenstein both analytically and synthetically. His investigations[1] have been constantly criticized by Freudenberg and his collaborators,[2] who for the last four years[3] have supported the catechin formula I of Perkin and Yoshitake.[4] Freudenberg, Orthner and Fikentscher[5] have, however, recently come to the conclusion that this formula is untenable, with the result that they now only consider the alternative formulas II, III and IV for catechin.



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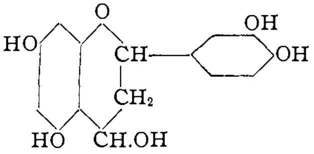

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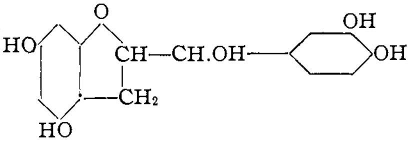

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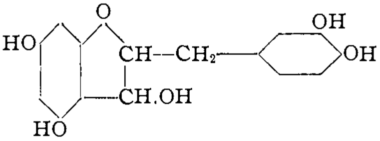
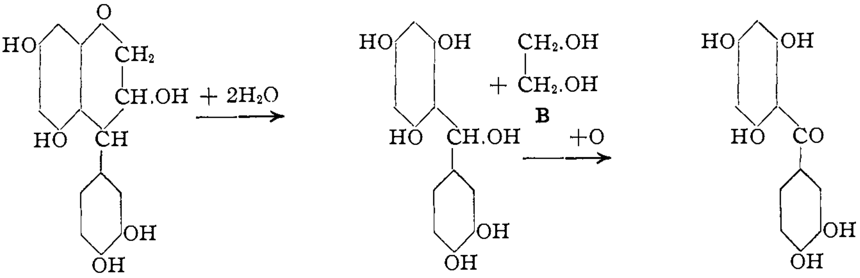


IV

All these formulas (I, II,. III, IV) are, however, obviously untenable since acacatechin yields maclurin to the extent of 86% of the calculated amount when reacted upon by *Penicillium Solitum.* On the other hand, the production of maclurin (VI) from acacatechin (V) is in perfect agreement with the constitution of acacatechin as established by Nierenstein



V A VI

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[1] Nierenstein, (a) *J. Chem. Soc.*, **117**, 971, (b) 1151 (1920); (c) **119**, 164 (1921); (d) **121**, 604 (1920).

[2] (a) Freudenberg, *Ber.*, **54**, 1938 (1921). (b) Freudenberg and Cohn, *Ber.*, **56**, 2127 (1923).

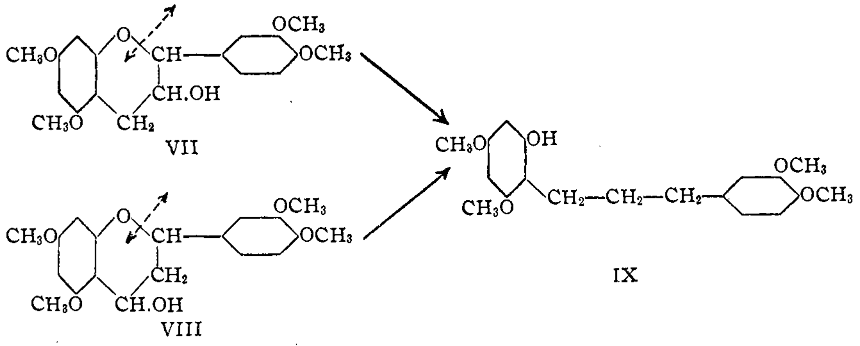
[3] Freudenberg, (a) *Ber.*, **53**, 1416 (1920); (b) *Z. angew. Chem.*, **34**, 27 (1921).

[4] Perkin and Yoshitake, *J. Chem. Soc.*, **81**, 1172 (1902).

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

As will be seen the production of maclurin (VI) from acacatechin (V) requires the intermediate formation of leucomaclurin (A) and glycol (B), both of which we have, however, failed to isolate. This is probably due to the strong oxidizing properties of the living fungus, which lead to the complete destruction of the glycol (B) and the oxidation of the leucomaclurin (A) to maclurin (VI).

The criticism of Freudenberg, Böhme and Beckendorff[6] and that of Freudenberg[2a] has previously been dealt with by Nierenstein.[7] Reference however must be made to the comparatively recent publication of Freudenberg and Cohn[2b] where it is claimed that the phenol, hereafter called phenol "A," obtained when reducing catechin-tetramethyl ether (VII or VIII) with metallic sodium and alcohol is 2-hydroxy-4,6,3′,4′-tetramethoxy-α,γ-diphenyl-propane (IX). Freudenberg and Cohn give the melting point of phenol "A" as 89–90°, and they also state that it dissolves in concd. sulfuric acid forming a yellow solution, which in itself is very remarkable. Nierenstein[8] who has obtained the phenol "A" from acacatechin-tetramethyl ether (X) by the same reduction method has assigned to it Formula XI. He gives its melting point as 106°. In support of Formula XI Nierenstein has shown that on methylation with diazomethane 2,4,6,3′,4′-pentamethoxy-α,α-diphenyl-propane (XII) is produced, which he found to be identical in every respect with synthetic 2,4,6,3′,4′-pentamethoxy-α,α-diphenyl-propane. He has also shown that the substance XII is oxidized to 2,4,6,3′,4′-pentamethoxy-diphenylacetic acid (XIII) which yields on methylation with diazomethane the methyl ester (XIV). Both of these substances are, again, in every respect identical with the corresponding synthetic products XIII and XIV.



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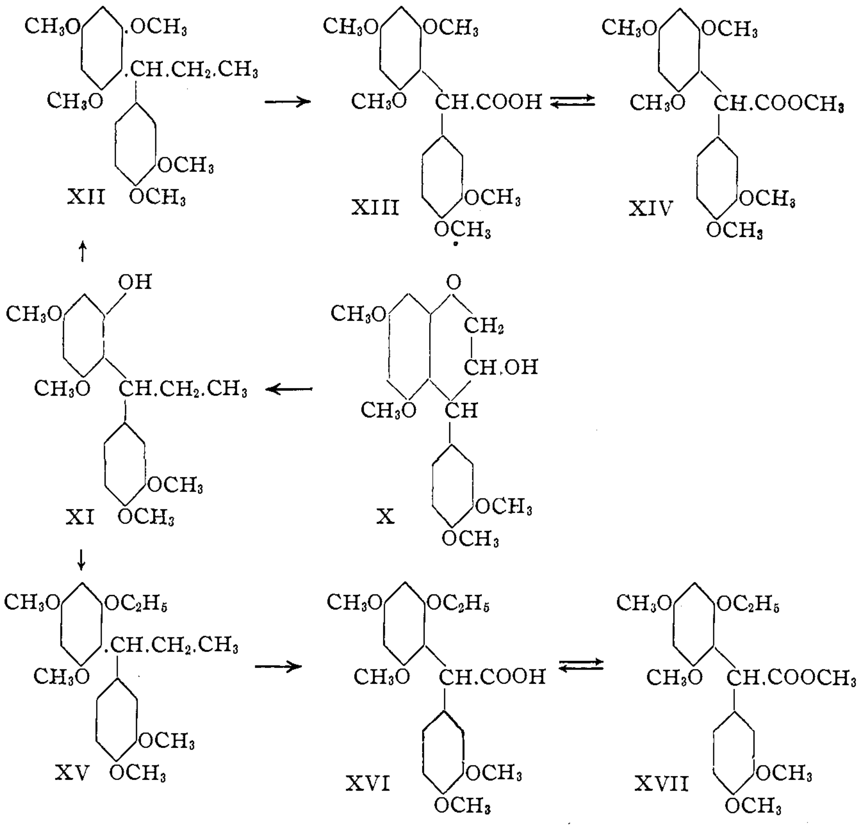
[6] Freudenberg, Böhme and Beckendorff, *Ber.*, **54,** 1204 (1921).

[7] Nierenstein, Ref. 1 b, p. 1156; Ref. 1 d, p. 607; *Ber.*, **55,** 3831 (1922).

[8] Ref. 1 b, p. 1154.



In view of the results of Freudenberg and Cohn we have re-examined a specimen of phenol "A," which had been standing in the laboratory for over three and a half years. We found that it melted vitreously between 100° and 103° and gave no coloration with concd. sulfuric acid. This was independently confirmed by Dr. G. H. Christie of this University who found that it melted vitreously between 100° and 102° and who noted that "with concd. sulfuric acid no color was observed even when warmed to about 100°." As will be seen, our specimen of phenol "A," which seems to have slightly altered on standing, melts appreciably higher than given by Freudenberg and Cohn.

For further identification we have also prepared the ethyl derivative XV by the action of ethyl iodide and silver oxide on phenol "A." This product melts at 49–50°, as found by Freudenberg and Cohn for their ethyl derivative. We have also oxidized the ethyl derivative XV to the acid XVI, which gave on methylation with diazomethane the corresponding methyl ester XVII, from which the free acid XVI is easily recovered by warming with alkali.

In view of these results and also in view of the fact that maclurin is produced from acacatechin we have deemed it unnecessary to compare our ethyl derivative from phenol "A" with 2-ethoxy-4,6,3′,4′-tetramethoxy-α,γ-diphenyl-propane, which are claimed to be identical by Freudenberg and Cohn. It is obviously impossible for an α,γ-diphenyl-propane derivative to yield a diphenylacetic acid derivative, as demonstrated in the case of the methyl and ethyl derivatives of phenol "A."

In conclusion we summarize the melting points obtained by Freudenberg and by Nierenstein for phenol "A" and its derivatives.

	Freudenberg °C.	Nierenstein °C.
Phenol "A"	89–90	106
Methyl ether	87–88	83–84
Ethyl ether	49–50	49–50

In this connection it must be noted that the melting point 83–84° for the methyl ether has not only been observed by Nierenstein[9] but also by Kostanecki and Lampe[10] and by Ryan and Walsh.[11] Also, the claim put forward by Freudenberg[12] that the melting point 83–84° can be raised to 87–88° on distilling the methyl ether in a vacuum with the aid of a Vollmer pump is not confirmed by us.

Experimental Part

Production of Maclurin (VI) from Acacatechin (V)

It has frequently been noticed in this Laboratory that *dilute* solutions of catechin grow a specific mould and a colored precipitate is produced. The investigation of the precipitate showed it to consist mainly of maclurin, whereas the identification of the mould, for which we are indebted to Miss Grace G. Gilchrist, proved it to be *Penicillium Solitum.* After many trials the following method was found to give the best yield of maclurin.

A solution of 0.72% acacatechin in water to which 5% cane sugar is added is inoculated with *Penicillium Solitum.* The inoculated solution is kept in an incubator at 22° and the first signs of growth become visible after about seven days. After the culture has stood in the incubator for several weeks the felt is removed and the solid formed, collected. The solid gives pure maclurin on extraction with boiling water and purification through the lead salt. The melting point of the anhydrous product (dried at 100° in a vacuum over phosphorus pentoxide) is 220–222°, but it begins to become resinous at 208–210°. The same data were found by us (1) for a purified specimen of maclurin obtained from Schuchardt and

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[9] Ref. 1 a, p. 972. *J. Chem. Soc.*, **117**, 972, 1156 (1920).

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

[11] Ryan and Walsh, *Sci. Proc. Roy. Dublin Soc.*, **15**, 117 (1916).

[12] Ref. 3 a, p. 1417; *Ber.*, **55**, 1941 (1922).

(2) on admixture of maclurin from acacatechin with Schuchardt's maclurin. Hoesch[13] who has synthesized maclurin gives for anhydrous maclurin "Oberhalb 200° Verharzung, gegen 220° dunkelbrauner Schmelzfuess," which is in good agreement with our results.

Anal. Subs. (dried in a vacuum at 100° over P_2O_5), 0.1464: CO_2, 0.3184; H_2O, 0.0531. Calc. for $C_{13}H_{10}O_6$: C, 59.5; H, 3.8. Found: C, 59.3; H, 4.1.

The pentamethyl ether, prepared by the action of an excess of diazomethane on the ethereal suspension of maclurin and crystallized from alcohol melts at 156–157°, which melting point is not depressed on admixture with authentic pentamethyl-maclurin. Kostanecki and Tambor[14] give 157° as the melting point of pentamethyl-maclurin which is in agreement with our results.

Anal. Subs., 0.1626: CO_2, 0.3873; H_2O, 0.0828. Calc. for $C_{18}H_{20}O_6$: C, 65.1; H, 6.0. Found: C, 65.0; H, 5.8.

Ethoxy Derivative of Phenol "A" (XV).—A solution of 0.32 g. of phenol "A" dissolved in 50 cc. of ether is heated on a water-bath for six hours with 1 cc. of ethyl iodide and 3 g. of silver oxide. The filtered solution is evaporated and the residue is crystallized from dil. alcohol in small needles that melt at 49–50°, as found by Freudenberg and Cohn for the ethoxy derivative, prepared by the action of ethyl sulfate on phenol "A." In view of the scarcity of the material and the satisfactory analyses of this substance published by Freudenberg and Cohn no combustion was made.

2-Ethoxy-4,6,3',4'-tetramethoxy-diphenylacetic Acid (XVI).—To a suspension of 0.288 g. of the ethyl derivative XV in 5 cc. of a 5% solution of potassium hydroxide is added 20 cc. of 0.1 *N* solution of potassium permanganate and the mixture heated on a boiling-water-bath for six hours. The filtered solution is acidified with dil. sulfuric acid containing a little sulfurous acid and the solid so obtained crystallized several times from water, when 0.1742 g. of colorless prismatic needles is obtained, which melt at 137–138°, carbon dioxide being evolved.

Anal. Subs. (dried at 100° in a vacuum over P_2O_5), 0.00457: H_2O, 0.00044. Calc. for $C_{20}H_{24}O_7 + 2H_2O$: H_2O, 8.8. Found: 9.6.

Subs., 0.00413: CO_2, 0.00970; H_2O, 0.00241. Calc. for $C_{20}H_{24}O_7$: C, 63.8; H, 6.4. Found: C, 63.8; H, 6.5.

Methyl 2-Ethoxy-4,6,3',4'-tetramethoxy-diphenylacetate (XVII).—The ester is prepared by the action of an excess of diazomethane on the ethereal suspension of the acid XVI. It crystallizes from benzene in small needles that form wart-like nodules and melt sharply at 64°. The molecular weight determined according to the method of Rast[15] was 417, whereas $C_{21}H_{26}O_7$ requires 390.

Anal. Subs., 0.00785: CO_2, 0.01871; H_2O, 0.00501. Calc. for $C_{21}H_{26}O_7$: C, 64.6; H, 6.7. Found: C, 65.0; H, 7.1.

Conversion of the Methyl Ester XVII into the Free Acid XVI.—When the ester is warmed with dil. alkali it is smoothly converted into the free acid; small needles separate from water; m. p., 137–138°. There was not enough material for either a combustion or a mixed-melting-point determination.

In conclusion we wish to thank the Department of Scientific and Industrial Research and the Colston Research Society of the University of Bristol for the grants used in connection with this work.

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[13] Hoesch and von Zarzecki, *Ber.*, **50**, 467 (1917).

[14] Kostanecki and Tambor, *Ber.*, **39**, 4022 (1906).

[15] Rast, *Ber.*, **55**, 1051 (1922).

Summary

1. Maclurin has been produced from acacatechin.

2. Further evidence is brought forward showing that the fission of the chroman nucleus in acacatechin leads to the formation of an α,α-diphenyl-propane derivative.

3. These observations confirm the formula assigned to acacatechin by Nierenstein.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

ISOXAZOLINE OXIDES
III. TRIPHENYL-ISOXAZOLINE OXIDE

BY E. P. KOHLER AND G. R. BARRETT

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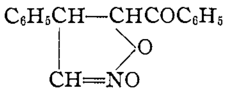
The isoxazoline oxide that was described in the first paper[1] of this series gave a number of products which could be obtained in solid form only with difficulty and could not be distilled. By substituting a phenyl group for the hydrogen atom in the 3 position it was possible, as was shown in the second paper,[2] to obtain oxides with physical properties which are more favorable for manipulation (II). These oxides, however, like the first have a benzoyl group in the 5 position, and it was found that this group to a great degree determines the chemical properties of the substance. It imparts mobility to the hydrogen atoms in the alpha position—hence these oxides easily lose water; it makes enolization possible and therefore complicates the reactions between the oxides and bases; and it reacts with the substances that one would naturally employ in a study of the system, C=NO. For these reasons it was desirable to investigate an oxide that contains no carbonyl group. Triphenyl-isoxazoline oxide, the subject of this paper, is a compound of the desired type (III).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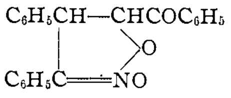
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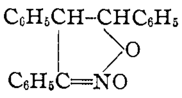
III

This oxide was made by condensing phenyl-nitromethane with nitrostilbene under certain rather narrowly prescribed conditions. It is present in small quantities in the by-products obtained when nitrostilbene is made by the method of Knoevenagel and Walter,[3] doubtless as the result of addition of phenyl-nitromethane to the nitrostilbene already formed and subsequent elimination of nitrous acid.

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[1] Kohler, THIS JOURNAL, **46,** 503 (1924).

[2] Kohler, *ibid.*, **46,** 1733 (1924).

[3] Knoevenagel and Walter, *Ber.*, **37,** 4509 (1904).