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.

UNIVERSITY OF BRISTOL, ENGLAND

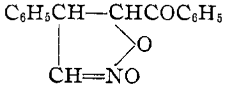
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

ISOXAZOLINE OXIDES
III. TRIPHENYL-ISOXAZOLINE OXIDE

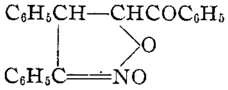
BY E. P. KOHLER AND G. R. BARRETT

RECEIVED JUNE 7, 1924 PUBLISHED SEPTEMBER 5, 1924

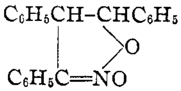
The isoxazoline oxide that was described in the first paper[1] of this series gave a number of products which could be obtained in solid form only with difficulty and could not be distilled. By substituting a phenyl group for the hydrogen atom in the 3 position it was possible, as was shown in the second 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).



I



II



III

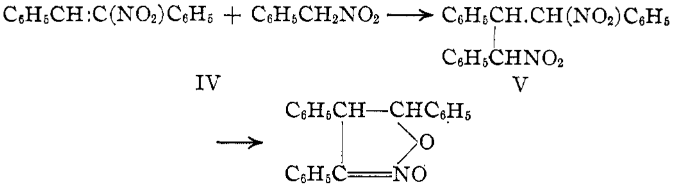
This oxide was made by condensing phenyl-nitromethane with nitrostilbene under certain rather narrowly prescribed conditions. It is present in small quantities in the by-products obtained when nitrostilbene is made by the method of Knoevenagel and Walter,[3] doubtless as the result of addition of phenyl-nitromethane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

---

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

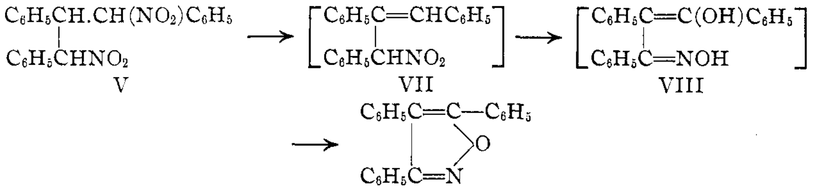
[2] Kohler, *ibid.*, **46,** 1733 (1924).

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



IV V

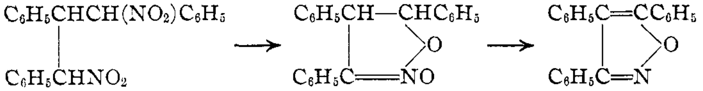
Heim,[4] who carried out this condensation on a moderately large scale and studied these by-products, isolated the dinitro compound (V), a small quantity of a substance that appeared to be an unsaturated nitro compound and the isoxazole (IX). Since he had no knowledge of the oxide (III), he accounted for the formation of the isoxazole by assuming elimination of nitrous acid from the dinitro compound, intramolecular oxidation of the resulting unsaturated nitro compound to a ketolic oxime and finally elimination of water.



V VII VIII IX

This mechanism was quoted with approval by Meisenheimer and Weibezahn[5] who determined the conditions most favorable for the formation of the isoxazole and established its structure by oxidation with ozone.

Our experiments show that when the dinitro compound is treated with one equivalent of base, the product is the isoxazoline oxide, and that excess of base strips this cleanly to the isoxazole. The sequence of substances, therefore, doubtless is



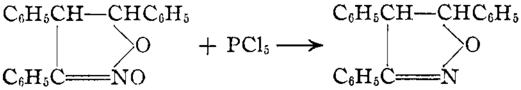
It is possible that the stripping of the isoxazoline oxide involves the formation of the ketolic oxime (VIII). As was shown in the preceding paper a substance constituted like this is an intermediate product between the oxide (II) and the corresponding isoxazole. In the case under consideration no evidence of such an open-chained compound could be secured. The process, which takes place rapidly only in the presence of concentrated alcoholic solutions of alkalies, can be brought about by the prolonged action of dil. hydroxylamine solutions but even under these conditions in which at least some of the dioxime corresponding to the ketolic oxime might be expected to be formed, the sole product is the isoxazole.

---

[4] Heim, *Ber.*, **44**, 2016 (1911).

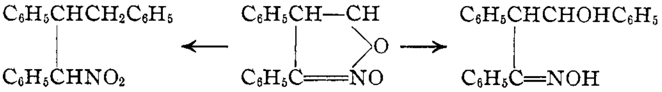
[5] Meisenheimer and Weibezahn, *Ber.*, **54**, 3195 (1921).

It is clear from the facts cited that while there is a great difference in the ease, and perhaps also the mechanism of the action of bases on the new oxide and on those described previously, the final result is the same in both. In reactions other than those with bases, the two types of oxides give quite different products. Thus phosphorus pentachloride, instead of removing water as it does in the case of the ketonic compounds, removes oxygen from the phenyl compound and transforms it into an isoxazoline derivative.



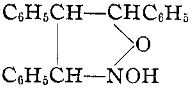
XI

The behavior of the two classes of oxides towards reducing agents is also quite different. Most reducing agents first strip the ketonic oxides and then reduce the resulting isoxazoles; others produce a complicated mixture of reduction and condensation products which it has not yet been possible to handle. In contrast with this, triphenyl-isoxazoline oxide is reduced easily, there is no stripping, and instead of losing oxygen it combines with two atoms of hydrogen. The product is a stable compound which can be benzoylated and acetylated in the usual manner, and which forms a copper derivative when shaken with copper acetate. Few of the many substances that might be formed in the reduction of the oxide would have this rather uncommon combination of properties. Thus if addition of hydrogen resulted in the opening of the ring, the product would have to be either a saturated nitro compound (XII) or an oxime (XIII).

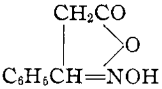


XII XIII

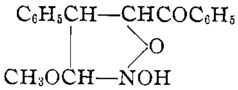
As neither of these substances would form a copper compound when shaken with copper acetate, the reduction of the oxide must consist in the addition of two hydrogen atoms to the system C=NO. It is possible to write a number of formulas for a substance formed by such a process, but these in all probability merely symbolize variants between which it is at present impossible to distinguish by experiment.



XIV



XV



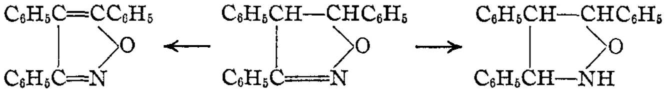
XVI

We prefer to represent the substance by Formula XIV for the following reasons. Posner,[6] by indirect methods, obtained the hydroxy-isoxazolidone (XV) and found that it was sufficiently acidic to form a copper derivative.

[6] Posner, *Ber.*, **39**, 3515 (1906); **39**, 3705 (1906).

He then methylated the NOH group and found that the ethers were indifferent; the acidity must, therefore, be due to the NOH group in the isoxazolidone. Also, in the first paper of this series it was shown that the most probable formula for a substance obtained by adding methyl alcohol to an isoxazoline oxide is that of an hydroxy-isoxazolidine (XVI). This substance likewise forms a copper derivative when shaken with copper acetate. An hydroxy-isoxazolidine such as is represented by XIV would, therefore, be expected to form a copper derivative; it would also be sufficiently stable to permit acylation without loss of water.

The reduction product is insensitive to alkalies and to dilute acids. It is readily attacked by concd. sulfuric acid which transforms it into at least three other substances. The composition of one of these indicates that it is due to loss of water from the hydroxy-isoxazolidine. Since this substance is oxidized to triphenyl-isoxazole by chromic acid it is doubtless a triphenyl-isoxazoline, stereo-isomeric with the product of the reaction between phosphorus pentachloride and the oxide (XI). Another product, formed in small amount only, is triphenyl-isoxazole (X) which contains two hydrogen atoms less than the isoxazoline, while the third product contains two hydrogen atoms more than this substance. As this third product contains active hydrogen and forms a nitroso compound it must be triphenyl-isoxazolidine (XVII).



X XI XVII

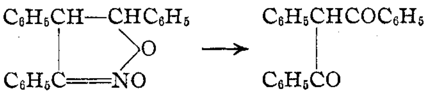
We are as yet unable to account for the formation of the isoxazolidine (XVII). Since reciprocal oxidation-reduction reactions are common in nitrogen compounds it would be natural to assume that the isoxazole and the isoxazolidine are the products of such a process. The quantitative relations, however, are not in keeping with such an assumption. Thus in one experiment 0.65 g. of hydroxy-isoxazolidine gave 0.50 g. of almost pure isoxazolidine and only 0.05 g. of the higher-melting isoxazole and isoxazoline.

Since triphenyl-isoxazoline oxide contains neither active hydrogen nor any active group other than the unsaturated system —C=NO, it provided an opportunity of studying the behavior of this system towards organic magnesium compounds. Wieland,[7] had previously brought together diphenyl-furoxane and phenylmagnesium bromide and obtained an addition product from which the furoxane was regenerated by acids. Our oxide behaves differently; it reacts readily both with phenyl- and alkyl-magnesium bromides. The reaction with phenylmagnesium bromide gave oils which have not been investigated. That with ethylmagnesium bromide is accompanied by evolution of gas, and when the resulting magnesium

[7] Wieland and Semper, *Ann.*, **358**, 36 (1908).

compound is acidified the main product is the same hydroxy-isoxazolidine that is formed when the oxide is reduced with zinc and acetic acid. A preliminary study of the reaction between the oxide and methylmagnesium iodide shows that this goes in a different manner. For while, here too, large volumes of gas are evolved, neither the hydroxy-isoxazolidine nor any of the other known reduction products of the oxide could be detected among the solid products. We prefer to postpone discussion of the mechanism of the Grignard reaction until the structure of these products has been established.

A number of unsuccessful attempts were made to remove the two hydrogen atoms in the oxide. The substance is not attacked either by permanganate or nitrous acid. Bromine in glacial acetic acid acts on it slowly but in part strips it to the isoxazole and in part converts it into a nitrogen-free compound. It is readily oxidized by chromic acid in acetic acid, but in this reaction also the nitrogen is lost, the product being phenyl-dibenzoyl-methane,



Experimental Part

Triphenyl-isoxazoline Oxide (III)

Triphenyl-isoxazoline oxide is formed in the preparation of nitrostilbene from benzaldehyde and phenyl-nitromethane and in the reaction between bases and diphenyl-dinitro-propane. Our method of preparation is based on the observation that in the preparation of nitrostilbene by the method of Knoevenagel and Walter the amount of oxide obtained as a by-product increases very rapidly with increase in the quantity of condensing agent employed. An attempt to prepare the oxide from benzaldehyde and phenyl-nitromethane in one step, by using more of the latter and employing sodium methylate or sodium hydroxide as condensing agent, failed because the first step—condensation of the aldehyde with the nitro compound—cannot be brought about with this agent. It is best, therefore, to operate in two steps, using methylamine as condensing agent for making nitrostilbene and sodium methylate for condensing this with more phenyl-nitromethane. The procedure is as follows.

A solution of sodium methylate containing 0.9 g. of sodium is added in the course of five minutes to a solution of 9 g. of nitrostilbene and 6 g. of phenyl-nitromethane in 100 cc. of anhydrous methyl alcohol. The solution is vigorously shaken and kept at the boiling point throughout the operation. The clear yellow mixture is heated for a few minutes after all of the methylate has been added, then chilled first under the tap, finally in a freezing mixture, and filtered immediately. The solid is composed of nitrite and the oxide which, after washing with water and alcohol, melts only a few degrees below the pure substance. The yield is 7 to 8 g. The principal by-product is triphenyl-isoxazole.

It is difficult to separate a mixture of this substance and the oxide, but when the chilled reaction mixture is filtered at once, all of the isoxazole remains in the filtrate. The amount of isoxazole is greater in the presence of water, and as sodium methylate rapidly transforms the oxide into the isoxazole, excess of base must be avoided.

3,4,5-Triphenyl-isoxazoline Oxide (III).—The crude product was recrystallized from acetone. It separated in slender, white needles melting at 162°. It is sparingly soluble in alcohol, moderately soluble in ether and cold acetone, readily in boiling acetone.

Anal. Calc. for $C_{21}H_{17}O_2N$: C, 80.0; H, 5.4. Found: C, 80.4; H, 5.6.

"Stripping" to Triphenyl-isoxazole.—When the oxide is boiled for a few minutes with strong aqueous-alcoholic sodium hydroxide it is converted completely into the isoxazole. This was recognized by its melting point and an analysis, and completely identified by comparison with a sample prepared according to the directions of Meisenheimer.[8] Dilute solutions of bases have scarcely any effect on the oxide at the ordinary temperature. Thus, when an ethereal solution containing 2 g. of the substance was shaken with 200 cc. of a 3% solution of sodium hydroxide in equal volumes of water and alcohol for two weeks all but 8% was recovered unchanged. This mixture would convert the same amount of the corresponding benzoyl derivative completely into isoxazole and other substances in ten hours. The sole product in the case of the triphenyl compound was the isoxazole, and prolonged shaking with an hydroxylamine solution of the same concentration produced the same result.

The oxide is not stripped by acetic acid or even by prolonged heating with acetic anhydride, but it loses water slowly when heated by itself. Thus when 2 g. of the oxide was heated in a vacuum, above the melting point, it gave a distillate containing water and benzonitrile which was identified by its odor and by hydrolysis to benzoic acid. The residue, after recrystallization, yielded 1.2 g. of isoxazole.

Oxidation.—Nitrous acid in glacial acetic acid and permanganate in acetone are without appreciable effect on the oxide. By prolonged heating with bromine in glacial acetic acid there was obtained, besides isoxazole, unchanged isoxazoline, an oil and a small amount of nitrogen-free product melting at 125°. Chromic acid gave more definite results. A suspension of 5 g. of the substance in acetic acid was treated with a solution of chromic acid in the same solvent until reduction, judging by the permanent red color of the solution, was ended. The solution was then poured into much water and the amorphous precipitate collected. By crystallization from alcohol or ether, and in part by mechanical separation a small amount of a new product was freed from oxide and isoxazole. This new product crystallized first in colorless plates, later in needles melting at 146–147°. It was identified as phenyl-dibenzoyl-methane by comparison with a sample made according to Meisenheimer.[9]

Reduction.—Triphenyl-isoxazoline oxide was reduced in small lots with zinc and acetic acid by the same procedure that was used with isoxazoline oxide di-ester. After removing the excess of zinc the product was precipitated in crystalline form by cautiously diluting the acetic acid solution. Ether extraction of the still further diluted solution gave small additional amounts. The yield was 50%. The product was purified by recrystallization from benzene.

Anal. Calc. for $C_{21}H_{19}O_2N$: C, 79.5; H, 6.0. Found: C, 79.8; H, 6.3.

2-Hydroxy-3,4,5-triphenyl-isoxazoline (XIV) is very sparingly soluble in benzene,

---

[8] Meisenheimer, *Ber.*, **54,** 3206 (1921). The substance described by Knoevenagel and Weissgerber, *Ber.*, **26,** 443 (1893), as the oxime of benzal-desoxy-benzoin was found to be triphenyl-isoxazole, as was also the substance described by Meyer and Oelkers, *Ber.*, **21,** 1300 (1888). The true oxime of desoxy-benzoin was made by Kohler and Drake, This Journal, **45,** 1286 (1923).

[9] Ref. 5, p. 3205.

moderately soluble in alcohol. It crystallizes in needles and melts at 188°. When its ethereal solution is shaken with copper acetate it at once assumes a yellow or greenish-brown color and soon becomes cloudy with a precipitate of the copper derivative. The precipitate is so finely divided and so sensitive that it cannot be collected on a filter. When the suspension is acidified it regenerates the oxide; but when it is allowed to stand it gradually changes to black copper oxide, and triphenyl-isoxazole crystallizes from the ethereal layer.

ACETYL DERIVATIVE OF THE REDUCTION PRODUCT.—The hydroxy-isoxazolidine dissolves in cold acetyl chloride and in cold acetic anhydride and in each case forms an acetyl derivative which gradually crystallizes from the solution. When crystallized from dil. acetic acid or from alcohol it always contains an extra molecule of water. Attempts to free it from this by recrystallization from water-free solvents were unsuccessful, but inasmuch as the corresponding benzoate crystallizes without water, this is doubtless water of crystallization. A part of it can be removed by heating the substance very cautiously to near the melting point under diminished pressure. The acetate crystallizes in small plates and melts with decomposition at 100–110°, the melting point depending upon the rate of heating. Both acids and bases hydrolyze it to the corresponding hydroxide.

Anal. Calc. for $C_{23}H_{21}O_3N.H_2O$: C, 73.2; H, 6.1. Found: C, 73.3; H, 6.0.

THE BENZOATE.—The benzoate was easily obtained by the usual Schotten-Baumann procedure. It crystallizes from methyl alcohol in colorless plates melting at 130°.

Anal. Calc. for $C_{28}H_{23}O_3N$: C, 79.8; H, 5.5 Found: C, 79.6; H, 5.4.

Action of Concentrated Sulfuric Acid on the Hydroxide.—When brought in contact with concd. sulfuric acid the hydroxy-isoxazolidine in part dissolves, and in part is transformed into a gummy mass which also dissolves when rubbed vigorously with a glass rod. In order to get a good yield of solid products it is necessary to work with very small quantities (0.5 g.) and to effect complete solution as quickly as possible. The greenish-yellow solution is immediately poured onto ice and sodium carbonate and the milky suspension extracted with ether. Evaporation of the ether and partial solution in alcohol of the resulting solid give a fairly complete separation into a sparingly soluble, high-melting solid and an alcoholic solution of a lower-melting substance.

3,4,5-Triphenyl-isoxazoline (XI).—The sparingly soluble solid formed by the action of concd. sulfuric acid on the hydroxide was recrystallized from benzene. Most of it was thus obtained in microscopic needles melting at 208°.

Anal. Calc. for $C_{21}H_{17}ON$: C, 84.3; H, 5.7. Found: C, 84.3; H, 5.6.

Triphenyl-isoxazoline is very sparingly soluble in alcohol and moderately soluble in boiling benzene. It does not react with ethylmagnesium bromide as any possible open-chained isomer would be expected to do. Chromic acid in glacial acetic acid oxidizes it to triphenyl-isoxazole at the ordinary temperature.

The benzene filtrates from the isoxazoline were evaporated to dryness; they left a small quantity of another solid which was purified by recrystallization from alcohol and identified as triphenyl-isoxazole melting at 211°. The melting point of a mixture of these two substances was about 190°.

The alcoholic filtrates which contained the other products that were formed by the action of sulfuric acid on the isoxazoline oxide were allowed to evaporate slowly. They deposited, along with the fine needles of triphenyl-isoxazole and isoxazolidine, a different substance that crystallizes in plates. These plates were separated by hand and recrystallized from aqueous alcohol.

Anal. Calc. for $C_{21}H_{19}ON$: C, 83.7; H, 6.3. Found: C, 83.3; H, 6.3.

3,4,5-Triphenyl-isoxazolidine (XVII).—The substance which crystallizes in plates constitutes the principal product of concd. sulfuric acid on the oxide. It is readily soluble in all common solvents and melts at 96°. A test with ethylmagnesium bromide showed that it contained active hydrogen, and nitrous acid in glacial acetic acid formed an amorphous orange-colored product which gave the usual Liebermann test for nitroso compounds.

Reaction between Phosphorus Pentachloride and the Oxide.—A mixture of 6 g. of triphenyl-isoxazoline oxide and 4 g. of phosphorus pentachloride was introduced into a flask provided with an outlet tube that ended over a solution of potassium iodide. The flask was heated slowly in a metal bath. When the temperature of the bath reached 90°, a reaction started locally and spread rapidly through the entire mass. It was accompanied by a brisk evolution of gas, and the temperature rose sufficiently to distil a few drops of liquid—probably phosphorus oxychloride. The evolved gas liberated iodine in quantity from the iodide solution. A few moments sufficed to complete the reaction and the flask then contained a residue of dark red oil.

The flask was cooled and the residue was shaken with ether and sodium carbonate solution. The oil disappeared, most of it dissolving in the ether while a part of it changed to a solid that remained suspended in the ethereal layer. The solid proved to be triphenyl-isoxazole, due to stripping of the oxide; its weight was about 2 g. The ethereal layer from which the isoxazole had been removed by filtration was washed with water, dried and allowed to evaporate. It left a red oil that solidified almost completely upon addition of a little alcohol. The alcoholic filtrate from the solid contained only a small amount of a substance that was left as a red lake when the alcohol was evaporated.

3,4,5-Triphenyl-isoxazoline (XI).—The solid product was recrystallized from alcohol. It separated in colorless needles; m. p., 136–137°.

Anal. Calc. for $C_{21}H_{17}ON$: C, 84.3; H, 5.7. Found: C, 83.8; H, 5.6.

The substance is isomeric with the isoxazoline obtained by the action of sulfuric acid on the oxide. It also has the same chemical properties as the higher-melting isomer; a test with ethylmagnesium bromide showed the absence of active hydrogen and chromic acid in acetic acid oxidized it to triphenyl-isoxazole. The oxide was dissolved in concd. sulfuric acid in order to ascertain whether it could be transformed into its higher-melting isomer, or could undergo self oxidation and reduction to isoxazole and isoxazolidine. The only effect was to lower, slightly, the melting point of the recovered isoxazoline.

Action of Ethylmagnesium Bromide on the Oxide.—When a suspension of the oxide in ether is added to a solution of ethylmagnesium bromide containing a large excess of the reagent, the solution turns slightly yellow, becomes warm and gas is evolved. Most of the powdered oxide becomes coated with a gummy magnesium compound which interferes with the reaction and which cannot be removed by boiling the solution. It is better, therefore, to dissolve the oxide in benzene and effect the reaction in a benzene-ether solution. This remains clear throughout the operation and it is easy to complete the reaction.

When the reaction was carried out in the presence of a large excess (6 molecules) of the magnesium compound, the principal product was the same hydroxy-isoxazolidine that is formed by reducing the oxide with zinc and acetic acid. The yield of pure hydroxyl compound, isolated and purified in the usual manner, was about 50%. When the reaction was carried out in reverse fashion, a solution containing but one molecule of magnesium compound being added to a benzene solution of the oxide, the product was exactly the same, but 75% of oxide was recovered. No intermediate products could be detected.

Summary

1. The paper gives a method for preparing an isoxazoline oxide which differs from those described in earlier papers in that it contains no active

hydrogen and no active group other than the system C═NO which is characteristic of isoxazoline oxides.

2. Triphenyl-isoxazoline oxide while less readily "stripped" than the oxides, which contain an acyl group, can be dehydrated with basic or acidic dehydrating agents and to some extent by heat alone. There is no evidence that the process involves an intermediate opening of the ring.

3. Phosphorus pentachloride removes the oxido oxygen; in this respect alone the oxide behaves like diphenyl-furoxan.

4. The oxide, when reduced with mild reducing agents, combines with two atoms of hydrogen and forms a substance which is sufficiently acidic to give a copper compound when it is shaken with copper acetate.

CAMBRIDGE 38, MASSACHUSETTS

[CONTRIBUTION FROM THE BIOCHEMICAL LABORATORY, NEW YORK AGRICULTURAL EXPERIMENT STATION]

SITOSTEROL

BY R. J. ANDERSON AND FRED P. NABENHAUER

RECEIVED JUNE 9, 1924 PUBLISHED SEPTEMBER 5, 1924

Introduction

There is much confusion in the literature dealing with plant sterols regarding such physical properties as melting points and optical rotation, but the substance known as sitosterol is probably more fully characterized than any other plant sterol. The original description of sitosterol by Burian[1] was amplified by Ritter,[2] and the properties described by these authors have in general been confirmed by other investigators.

Sitosterol is stated to melt at 137.5° and to have a specific rotation in chloroform solution of about —34°. The acetyl derivative melts at 127°. A phytosterol possessing the above-mentioned properties is rather easily obtained from fats extracted from the germ of wheat, rye or corn. It would seem, therefore, that the sterol deposited in the germ is practically homogeneous.

It has been found in this Laboratory that the endosperm of corn[3] and of wheat[4] contains a mixture of sterols consisting of sitosterol and dihydrositosterol. It would not seem impossible that a mixture of these two sterols might also be deposited in the germ although they would probably exist there in different proportions from that in the endosperm.

In the hope of removing any dihydro-sitosterol that might be present we have attempted to purify some sitosterol preparations by fractional

[1] Burian, *Monatsh.*, **18,** 551 (1897).

[2] Ritter, *Z. physiol. Chem.*, **34,** 461 (1901).

[3] Anderson, THIS JOURNAL, **46,** 1450 (1924).

[4] Anderson and Nabenhauer, *ibid.*, **46,** 1717 (1924).