TABLE VI

TIE-LINE DATA

% BuOH in org. phase	% H_2O in org. phase	% BuOH in aq. phase
1	0.0	0.85
2	.0	1.55
3	.0	2.00
4	.1	2.35
5	.2	2.55
10	.4	3.20
20	1.2	3.75
30	2.3	4.15
40	3.5	4.55
50	5.4	5.00
60	7.8	5.40
70	11.4	5.85
75	14.9	6.35
79.4	20.6	7.10

Table I gives the refractive indices for anhydrous toluene–butanol mixtures; comparison with the data of Table II shows that the decrease in refractive index due to the water is nearly linear in the weight fraction f of butanol in the organic components. In the last column of Table III, $\Delta v = v - \Sigma v_i p_i/100$ is the difference between the actual specific volume and the volumes calculated from the composition and the specific volumes of the components, assuming additivity. An expansion occurs when butanol is added to toluene; as the butanol and water contents increase, this is followed by a contraction.

In Table V, the solubility of water in toluene–butanol mixtures is given; a plot of % H_2O–% BuOH is sharply concave up on the butanol-rich end, but a plot of mole fraction x of water against percentage of butanol in the organic components is only slightly curved, and is more accurate for interpolation. The data extrapolate to the value given by Hill and Malisoff[2] for the solubility of water in pure *n*-butanol.

The tie line data are given in Table VI; a smooth curve was drawn through the experimental points (Fig. 4), and interpolated values for round concentrations up to saturation are given. It will be noted that the distribution of butanol between water and toluene depends on concentration; it is such that extraction of butanol from water by toluene is not very efficient.

Summary

Equilibrium concentrations at 30° for the two-phase system of water, butanol and toluene have been determined. A new method of determining liquid solubilities is described. Densities and indices of refraction for the system are given.

SCHENECTADY, N. Y. RECEIVED OCTOBER 13, 1942

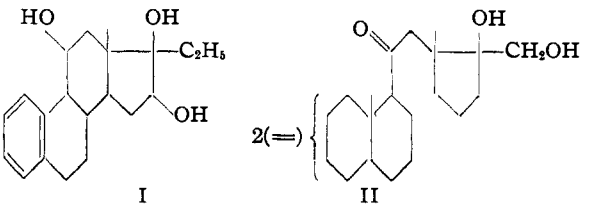
[CONTRIBUTION FROM THE DEPARTMENTO DE QUIMICA DA FACULDADE DE FILOSOFIA, CIÊNCIAS E LETRAS DA UNIVERSIDADE DE SÃO PAULO, BRAZIL]

Cafesterol. II[1]

BY HEINRICH HAUPTMANN AND JANDYRA FRANÇA[2]

Slotta and Neisser[3] isolated cafesterol from the unsaponifiable fraction of coffee oil and proposed formula I for its structure. The results of our experiments of the past few years[1] led us to suggest formula II, in which there are two olefinic double bonds (and no benzenoid ring), a non-reactive keto group, and a —C(OH)CH_2OH group.

It must be admitted that the steroid skeleton and the position of the groups are hypothetical. Moreover, the question remains open as to whether there is present a non-reactive keto group or an oxide ring.



Recently, Wettstein, Fritzsche, Hunziker and Miescher[4] proved that the two double bonds in cafesterol are conjugated by the preparation of an addition product with maleic anhydride. By an independent method they also established the presence of a —C(OH)CH_2OH group, and located it next to a methylene group in a five-mem-

(1) Paper I, *Z. physiol. Chem.*, **259**, 245 (1939).

(2) The results of this paper are in large part taken from a thesis submitted to the *Faculdade de Filosofia, Ciências e Letras de Universidade de São Paulo*, Brazil, by Jandyra França on April 15, 1941, in partial fulfillment of the requirements for the degree of Doctor of Science. The examination and discussion of the thesis were delayed due to administrative reasons, until March 23, 1942. As the law allows only unpublished theses, we were forced to postpone the publication of this paper.

(3) Slotta and Neisser, *Ber.*, **71**, 1991, 2342 (1938).

(4) Wettstein, Fritzsche, Hunziker and Miescher, *Helv. Chim. Acta*, **24**, 332 (1941). We received this issue on June 23, 1942.

bered ring. They prepared the saturated hydrocarbon $C_{19}H_{30}$, which is isomeric but not identical with etiocholane and named it norcafestane on the basis of cafestane, the unknown hydrocarbon corresponding to cafesterol. Cafesterol, then, is the ox-cafestadiendiol (not ox-cafestadienol, as termed in the Swiss publication), the "ox" indicating the oxygen present as a keto or ether group.

In our further study we have prepared cafesterol from an industrially extracted coffee oil. Often the purification was difficult, particularly when we employed an oil extracted with trichloroethylene. We solved this difficulty by the observation that cafesterol forms with methanol a well-crystallized, difficultly soluble addition complex $C_{20}H_{28}O_3 \cdot CH_3OH$. By alternative recrystallizations from methanol and petroleum ether we obtained a cafesterol with the constant m. p. of 156–158°, $[\alpha]_D$ −114°. Passed through an aluminum oxide column it showed under ultraviolet light only one zone with a homogeneous violet fluorescence, which indicated to us that our product was pure. Wettstein and co-workers obtained cafesterol with the m. p. 160–162° and $[\alpha]_D$ −107°. Their supposition that preparations with the m. p. 155–157° and $[\alpha]_D$ −137° still contain 20–25% of impurity does not seem justified. In order to make such an estimate, based on the observed optical rotation, it would be necessary to know the optical rotation of the impurity. We observed that even large variations in the optical rotation on different samples were accompanied by only slight changes in the melting point as shown in the table.

M. p., °C.	α_D in chloroform
156–158	−114°
156–158	−134°
154–158	−171°
154–158	−181°

Moreover, Wettstein and co-workers obtained a 70% yield of a maleic anhydride addition compound from a cafesterol acetate of m. p. 155–160°. This meant that the compound contained 30% of impurities at most. Hence, samples of m. p. 163–165° and $[\alpha]_D$ −134° and particualrly our purer samples of m. p. 164–166° and $[\alpha]_D$ −112° must have contained much less.

We tried to confirm our formula by the preparation of partially hydrogenated derivatives. With palladized barium sulfate catalyst[5] in glacial acetic acid solution we got the same ox-cafestandiol monoacetate, $C_{22}H_{34}O_4$, m. p. 151–252°, $[\alpha]_D$ − 26.8°, obtained by Wettstein and co-workers with palladized charcoal in alcohol.[4] Refluxed with methanolic potassium hydroxide it gave ox-cafestandiol, $C_{20}H_{32}O_2$, m. p. 162°, $[\alpha]_D$ −8.6°. Because it is related to norcafestanone-A, we propose to call it ox-cafestandiol-A to distinguish it from the second tetrahydro product, the acetate of which is formed by hydrogenation of cafesterol acetate with Raney nickel[6] in alcohol. This ox-cafestandiol monoacetate, $C_{22}H_{34}O_4$, melts at 156° and its mixed melting point with ox-cafestandiol-A acetate is much lower. It does not give a dark color with tetranitromethane or consume oxygen when treated with monoperphthalic acid, from which we deduce that the two conjugated double bonds become saturated during hydrogenation. Like all other hydrogenated products of cafesterol, it is not changed by dilute acids at room temperature. With methanolic potassium bicarbonate it is easily saponified to the corresponding ox-cafestandiol, $C_{20}H_{32}O_2$, m. p. 188°. This still contains solvent which seems to be removed only with partial decomposition, so that we did not obtain a completely pure product. By treatment with acetic anhydride in pyridine it is retransformed into ox-cafestandiol monoacetate, m. p. 156°. This indicated that we actually had had the free diol. Both of the ox-cafestandiols are

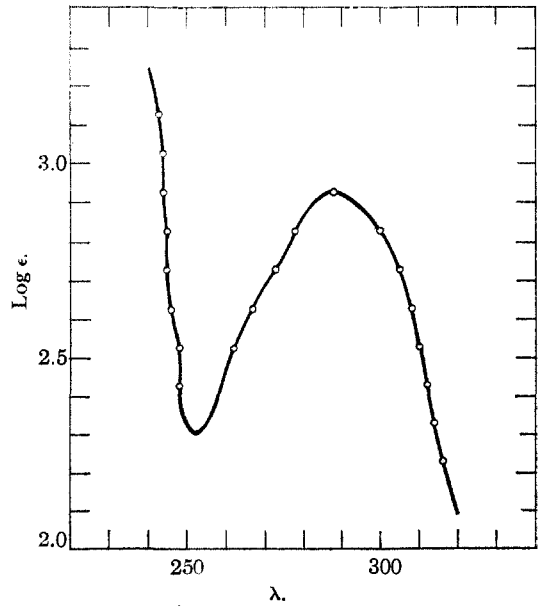


Fig. 1.—Ox-cafestatrien-ol-acetate 1 *M* in alcohol, $\lambda_{max.}$ 288 mμ.

(5) Rosenmund, *Ber.*, **51**, 585 (1919).

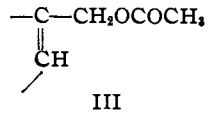
(6) Raney, U. S. Patent 1,915,473 (1930); THIS JOURNAL, **54**, 4116 (1932); Rüggli and Preiswerk, *Helv. Chim. Acta*, **22**, 478 (1939).

inactive in androgenic as well as in cortinic tests.[7]

We failed to obtain an addition product with maleic anhydride at 135° (eight hours).[8] Wettstein and co-workers[4] obtained their product under very mild conditions. We were also unable to obtain any information about the carbon skeleton of cafesterol by dehydrogenation with selenium. Cafesterol and its derivatives gave no crystalline products with the conditions under which cholesterol readily gave 3'-methyl-1,2-cyclopentenophenanthrene.

In view of the results of Wettstein and co-workers, we omit our oxidations with periodic acid, mentioning only that we too proved the formation of formaldehyde by oxidizing cafestantriol, $C_{20}H_{34}O_3$, m. p. 227°, with periodic acid in methanol. We obtained this compound by saponification of cafestantriol monoacetate, m. p. 103–105°, with potassium bicarbonate in aqueous methanol.

One of the hydroxyl groups of cafesterol, probably the tertiary, is rather easily split off by boiling cafesterol or its acetate with acetic anhydride or, better, with a mixture of this reagent and pyridine. The crystalline reaction product melts at 114° and its analysis corresponds to that of an ox-cafestatrienol acetate. Its formula (III, only part of the five-membered ring is shown) was confirmed by the following observations. During the saponification one mole of sodium hydroxide was consumed, which indicated the presence of a monoacetate. By adding four moles of hydrogen in the presence of platinum oxide catalyst[9] to ox-cafestatrienol acetate and then saponifying the perhydro acetates, we obtained a mixture of isomeric cafestandiols which were indifferent to periodic acid. The new double bond present in ox-cafestatrienol acetate does not appear to be conjugated with the others since the maximum of the absorption band is in the range of 290 mμ as is that of cafesterol and is not shifted to the region of longer wave length. Neither ox-cafestatrienol acetate in 10-mg. doses nor cafesterol in 4-mg. doses had an estrogenic activity[10] and they are both inactive in androgenic and cortinic tests in 2-mg. doses.[7]



III

We are inclined to consider the inert oxygen atom to be present in the form of an oxide ring. Slotta and Neisser were unable to get an oxime or a semicarbazone from cafesterol, and we obtained similar results even under the most drastic conditions. Wettstein and co-workers considered the possibility of an oxide ring in view of the failure of the Clemmensen reduction of the dicarboxylic acid $C_{19}H_{28}O_5$. We have found that cafesterol is not reduced by a boiling solution of aluminum isopropoxide in isopropyl alcohol. Even after four hours no acetone could be detected in the distillate with 2,4-dinitrophenylhydrazine reagent and cafesterol was isolated unaltered from the mixture. Under the same condition, camphor, which is difficult to reduce,[11] gave an acetone test in ten minutes. The reduction of ox-cafestadienone to ox-norcafestadienol with aluminum isopropoxide in isopropyl alcohol by Wettstein and co-workers[4] in which the inert oxygen atom did not react agrees with the preceding result. Still another result which contests the existence of a keto group is the absorption spectrum of ox-cafestandiol monoacetate, m. p. 156°, which does not show any band at a higher wave length than 250 mμ. Ruzicka[12] demonstrated by several examples that even extremely unreactive keto groups can be recognized by showing a band with a flat maximum at 290 mμ in its absorption spectrum. We chose ox-cafestandiol monoacetate rather than cafesterol because the absorption of cafesterol in the region of 290 mμ may possibly result from the double bonds.

In the meantime we have received two more publications about cafesterol. A. Wettstein and K. Miescher [*Helv. Chim. Acta*, **25**, 718 (1942)] prove the existence of an oxide ring in cafesterol, which corresponds to our results. Purnendu Nath Chakravorty and Mildred M. Wesner [THIS JOURNAL, **64**, 2235 (1942)] add new evidence for the non-existence of a benzenoid ring in cafesterol, already proved by us in 1939 (*Z. physiol. Chem.*, **259**, 245 (1939), *C. A.* **33**, 7813 (1939)) to which A. Wettstein and collaborators refer in detail. The former's interesting observation that the addition product of cafesterol with maleic anhydride is decomposed by heating, explains why we were not able to obtain it. Their tetrahydro product, m. p. 153–155°, as can be deduced from the method of preparation and the m. p. of the acetate, is nothing but a not quite pure ox-cafestandiol, m. p. 162°. (October 20, 1942.)

(7) Hauptmann, Sawaya and Bruck-Lacerda, *Boletin da Faculdade de Filosofia, Ciências e Letras, Quimica I*, 181 (1942).

(8) Windaus and Lüttringhaus, *Ber.*, **64**, 850 (1931).

(9) Voorhees and Adams, THIS JOURNAL, **44**, 1397 (1922); Adams and Shriner, *ibid.*, **45**, 2171 (1923).

(10) Wettstein and co-workers likewise report that cafesterol, even in 30-mg. doses, is inactive in the estrogenic test.

(11) Lund, *Ber.*, **70**, 1520 (1927).

(12) Ruzicka and Cohen, *Helv. Chim. Acta*, **20**, 804 (1937); Ruzicka and Schellenberg, *ibid.*, **20**, 1270 (1937).

Acknowledgments.—We are greatly indebted to the "Departamento Nacional do Cafe" (President, Dr. Jayme F. Guedes) for a research grant which has made this investigation possible. We are very grateful to Dr. Francisco Maffei, who measured the absorption spectrum in the Instituto de Pesquisas Technologicas da Universidade de São Paulo. Acknowledgment is also made to Miss L. Bruck-Lacerda for technical aid in several experiments.

Experimental Part

Preparation of the Cafesterol–Methanol Compound.—Fifty mg. of cafesterol, m. p. 156–158°, was dissolved in 5 ml. of methanol. By cooling, large plates of the methanolic compound were deposited. They were filtered and dried between filter paper. They lost their methanol at 120°, forming needles, m. p. 156–158°; loss of weight at 100° and 0.002 mm.; calcd. for $C_{29}H_{48}O_3 \cdot CH_3OH$: 8.96. Found: 8.96.

Hydrogenation of Cafesterol Acetate with Raney Nickel.—One gram of cafesterol acetate (m. p. 164–166°) was dissolved in 50 ml. of alcohol and hydrogenated in the presence of Raney nickel. At 25° and 696 mm. 190 ml. of hydrogen was absorbed (calcd. 186.5 ml.). The product was filtered from the catalyst and poured into water. The white substance which precipitated melted after some recrystallizations from acetone–water at 156°; yield, 0.6 g. (60%); mixed m. p. with ox-cafestandiol acetate A 122–145°, $[\alpha]^{28}D$ −37.5° (0.02% in alcohol). *Anal.* Calcd. for $C_{32}H_{54}O_4$: C, 72.86; H, 9.45. Found: C, 74.72; H, 9.15. Equivalent weight by saponification, calcd.: 362. Found: 368.2.

Saponification of Ox-cafestan-diol Acetate.—269.6 mg. of ox-cafestandiol acetate was dissolved in 20 ml. of methanol and a solution of 1 g. of potassium bicarbonate in 20 ml. of water was added. After boiling for three hours the greater part of the methanol was evaporated and more water was added. The precipitated product melted after recrystallization from acetone–water at 188°; yield 222 mg. (92%). It still contained solvent; loss of weight at 100°, 0.01 mm. (5.74%). *Anal.* Calcd. for $C_{29}H_{52}O_3$: C, 74.94; H, 10.07. Found after drying at 60° and 0.01 mm.: C, 69.87; H, 9.86; after drying at 100° and 0.01 mm.: C, 76.58; H, 10.69.

Cafestan-triol.—216 mg. of cafestan-triol monoacetate was refluxed with 20 ml. of 0.1 *N* potassium hydroxide for one hour. The solution was concentrated, poured into water and filtered. The residue was crystallized repeatedly from acetic ester to give 20 mg. of white needles, m. p. 227°, $[\alpha]^{32}D$ −33.7° (0.02% in alcohol). *Anal.* Calcd. for $C_{29}H_{54}O_3$: C, 74.42; H, 10.63; Found: C, 74.05, 74.23; H, 10.53, 10.93.

Oxidation of Cafestan-triol with Periodic Acid.—133.5 mg. of cafestan-triol was dissolved in methanol and 5 ml. of a mixture of 325 mg. of sodium periodate, 15 mg. of 2 *N* sulfuric acid and 15 ml. of water was added. After standing at room temperature for twenty-two hours, the solution was neutralized with sodium carbonate and distilled, and the vapors were received in a methanolic solution of dimedon; 18.1 mg. of crystals was obtained; m. p. 189–190°.

Ox-cafestatrien-ol Acetate.—One gram of cafesterol was dissolved in 6 ml. of pyridine (dried over barium oxide) and after addition of 6 ml. of acetic anhydride was boiled during twelve hours under reflux and protection of a calcium chloride tube. The dark liquid was then poured into ice-water, where it solidified quickly. After filtering it was recrystallized once from methanol and then distilled twice *in vacuo* at 0.002 mm. The substance that distills up to 200° was then recrystallized from methanol until constant m. p. 114°; yield 0.52 g. (52%) of white needles; $[\alpha]^{26}D$ −78.5° (0.02% in chloroform). *Anal.* Calcd. for $C_{32}H_{48}O_3$: C, 77.60; H, 8.23. Found: C, 77.68; H, 8.25. Equivalent weight by saponification, calcd., 340. Found: 348. Treated with monoperphthalic acid in ether, 99.2 mg. of ox-cafestatrienol acetate added 9.88 mg. of oxygen. Calcd. for 1 double bond: 4.67.

Experiences with Ox-cafestatrien-ol Acetate.—1.012 g. of ox-cafestatrien-ol acetate hydrogenated with platinum-IV-oxide in glacial acetic acid at 20° and 697 mm. added 300 ml. of hydrogen (calcd. for 4 double bonds, 308 ml.). After filtering from the catalyst, the solution was poured into water and extracted with chloroform. After drying with sodium sulfate and evaporating, 0.835 g. (81.5%) of a colorless oil remained, which did not crystallize even when treated with different solvents.

206 mg. of this oil in 25 ml. of alcohol was treated with 25 ml. of 0.1 *N* potassium hydroxide for eight hours. After evaporating a part of the alcohol, the rest was poured into water and extracted with acetic ester. After washing with water and drying with sodium sulfate by evaporating a colorless oil resulted, 142 mg., which did not crystallize even when treated with different solvents.

71.1 mg. of this oil dissolved in 5 ml. of dioxane was treated with 5 ml. of a mixture of 342.1 mg. of sodium periodate, 15 ml. of 2 *N* sulfuric acid and 10 ml. of water in a 25-ml. flask. After three days the volume of the flask was completed with dioxane. A blank was prepared in the same manner without the substance. Five ml. of each solution was poured into 20 ml. of a 30% solution of potassium iodide and titrated with 0.1 *N* sodium thiosulfate (correction factor, $f = 0.4979$). The blank required 8.00 ml.; the solution 8.08 ml.

Hydrogenation of Ox-cafestatrien-ol Acetate with Raney Nickel.—600 mg. of ox-cafestatrien-ol acetate was dissolved in 50 ml. of alcohol and hydrogenated in the presence of Raney nickel. At 27° and 703.6 mm., 90 ml. was absorbed (calcd. for 2 double bonds, 93.2 ml.). The product was filtered and poured into water, extracted with ether and dried. After evaporating there remained 560 mg. of a colorless oil which gave a brown coloring with tetranitromethane. It was not obtained crystalline by distillation *in vacuo* or by recrystallization from petroleum ether, methanol, ether, acetic ester and mixture of these solvents.

Treatment of Cafesterol with Aluminum Isopropylate.—A hydrogen introduction tube and a dropping funnel were fixed on the straight tube of a 150-ml. Claisen flask and a descending condenser and a thermometer on the curved tube. After careful drying we put 20 ml. of a solution of aluminum isopropylate in isopropyl alcohol in the Claisen

flask. A weak flow of hydrogen was let pass through the apparatus and the solution was heated gently, so that only small quantities of isopropyl alcohol distilled. When benzophenone was added, the precipitation of acetone 2,4-dinitrophenylhydrazone began after five minutes; in the case of camphor, after ten minutes. When cafesterol was added, even after four hours we did not observe precipitation. Then we interrupted the experiment and by decomposition of the aluminum isopropylate with 10% sodium hydroxide and extraction with ether, we isolated cafesterol, m. p. 154–155°, after recrystallization from petroleum ether.

Summary

The partial hydrogenation of cafesterol acetate with Raney nickel confirms the existence of only two carbon–carbon double bonds. The oxidation of cafestan-triol with periodate yields formaldehyde. One hydroxy group of cafesterol can be split off, whereby a new double bond is formed. The inert oxygen atom seems to be present as an oxide ring rather than as a keto group.

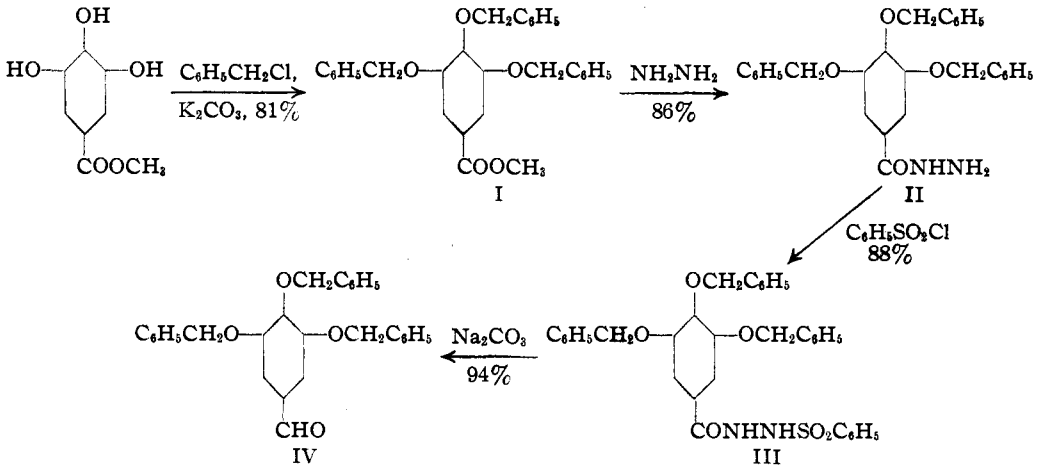
SAO PAULO, BRAZIL RECEIVED AUGUST 17, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

Gallaldehyde Tribenzyl Ether

BY R. O. CLINTON AND T. A. GEISSMAN

Studies in the flavanone series being carried out in this Laboratory have necessitated the synthesis of certain flavanones containing the 3′,4′,5′-trihydroxyphenyl group. Since this group could not be introduced by the use of gallaldehyde[1] in the usual Claisen–Schmidt condensation, due not only to the difficulty of obtaining the aldehyde in sizable quantities, but to its great instability in basic solution, it became necessary to prepare the analogous aldehyde in which the hydroxy groups were protected by labile benzyl ether groups. This was accomplished through use of the McFadyen–Stevens synthesis,[2] as shown in the accompanying diagram.



Heretofore, the usual procedure for the benzylation of phenols has involved the use of acetone as solvent,[3] thus imposing a low maximum temperature upon the reaction, and necessitating long reaction periods. As a rule the yields obtainable by this method are low. It has been found in the present work that the substitution of acetophenone for acetone as solvent, with an increase in temperature, enables the reaction to be completed in a few hours, and with a greatly increased yield.

Both methyl and benzyl tris-benzylgallate were readily saponified to the corresponding acid.[4] The latter compound could be debenzylated to give gallic acid by heating with acids; however, removal of but one benzyl group, namely, that in the 4-position (in analogy with the loss of the 4-methyl group in trimethylgallic acid[5]), could not be accomplished.

(1) Rosenmund and Zetzsche, *Ber.*, **51**, 594 (1918); Rosenmund and Pfannkuch, *ibid.*, **55**, 2357 (1922).
(2) McFadyen and Stevens, *J. Chem. Soc.*, 584 (1936).
(3) Baker and co-workers, *ibid.*, 77 (1929); 1924 (1939).
(4) Schöpf and Winterhalder, *Ann.*, **544**, 62 (1940).
(5) Graebe and Martz, *Ber.*, **36**, 216 (1903); *Ann.*, **340**, 220 (1905).