The **piperonylidene derivative** of the keto-acid was prepared by heating 0.2 g. of the keto-ester and 0.30 g. of freshly distilled piperonal in 10 cc. of ethanol with a solution of 0.5 g. of potassium hydroxide in 2 cc. of water. In fifteen minutes the bright yellow solution was cooled, diluted with water and acidified with hydrochloric acid. The brown, solid piperonylidene derivative of the keto-acid was collected and repeatedly recrystallized from aqueous ethanol. The product which proved difficult to purify was a canary-yellow and melted at 149° with previous softening and decomposition. It dissolved in concentrated sulfuric acid to give a blue solution which soon turned a deep purple. Analysis would indicate that it contained a molecule of ethyl alcohol of crystallization.

*Anal.* Calcd. for $C_{25}H_{26}O_6$: C, 71.06; H, 6.21. Found: C, 71.27; H, 5.85.

**2-Methylphenanthrene.**—A solution of methylmagnesium iodide (from 1.28 g. of methyl iodide) in 30 cc. of ether was added dropwise, with stirring, to a solution of 2.1 g. of the above keto-ester in 100 cc. of dry ether. After the Grignard reagent had been added the reaction mixture was refluxed for half an hour and allowed to stand overnight. The reaction product was decomposed with cold 10% sulfuric acid and the ether layer separated, washed with water and dried over anhydrous sodium sulfate. The residual oil, after removal of the solvent was dehydrated by distillation; b. p. 170–180° (4 mm.); yield, 1.5 g.

The dehydration product (1.5 g.) was dehydrogenated with 2.0 g. of selenium at 320–330° for twenty hours. The dehydrogenation product was recovered in dry ether, the solvent removed and the product distilled in a small von Braun flask. The distillate (0.7 g.) soon solidified and for purification was converted to the picrate; m. p. 116–117°. Several crystallizations from alcohol raised the melting point to 118–119°. This product when mixed with picric acid melted at 95–100°.

The pale orange crystals were decomposed with ammonia and the hydrocarbon extracted with ether, washed with water and dried over sodium sulfate. Upon removal of the solvent and crystallization from aqueous methanol the 2-methylphenanthrene was obtained in glistening plates; m. p. 53–54°. 2- and 3-methylphenanthrene[22] melt, respectively, at 55–56° and 62–63°; their picrates at 118–119° and 137–138°.

## Summary

In attempts to prove the location of the ethanamine chain in the morphine alkaloids, efforts were made to prepare methyl 1-bromo-3,4-dimethoxy-6-keto-5,6,7,8,9,10,13,14-octahydrophenanthrene-13-carboxylate for comparison with possible degradation products of the alkaloids.

The addition of 2-ethoxybutadiene to methyl 5-bromo-7,8-dimethoxy-3,4-dihydro-1-naphthoate gave a 13.8% yield of one, of two possible adducts, which by hydrolysis of the enol ethyl ether was converted to the corresponding ketone. Subsequent work has indicated this to be methyl 1-bromo-3,4-dimethoxy-7-keto-octahydrophenanthrene-13-carboxylate. The analogous ketone fromme thyl 3,4-dihydro-1-naphthoate provided evidence for this conclusion. The tertiary alcohol, resulting from the action of methylmagnesium iodide, when dehydrated and dehydrogenated gave 2-methylphenanthrene.

(22) Haworth, *J. Chem. Soc.*, 1125 (1932).

SASKATOON, SASKATCHEWAN RECEIVED JANUARY 21, 1947

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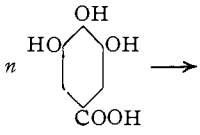
[CONTRIBUTION FROM THE EASTERN AND NORTHERN REGIONAL RESEARCH LABORATORIES[1]]

# Direct Esterification of Gallic Acid with Higher Alcohols

BY WALDO C. AULT,[2] JAMES K. WEIL,[2] GEORGE C. NUTTING[2] AND J. C. COWAN[2a]

The esters of gallic acid with alcohols containing more than six carbon atoms have not been prepared by the usual direct esterification process. Recently, however, Morris and Riemenschneider[3] prepared esters of all the alcohols containing an even number of carbon atoms from 6 to 18, inclusive, by an indirect method that involved protection of the hydroxyl groups of gallic acid by benzylation and treatment of the resulting tribenzyl ether with thionyl chloride to form the corresponding galloyl chloride, which was then esterified with the appropriate alcohol. The resulting ester was debenzylated by hydrogenation.

Recent indications of the potential value of the higher fatty alcohol esters of gallic acid as antioxidants[4] made a more direct synthesis of these compounds desirable. This need led to speculation as to why the higher fatty alcohol esters of gallic acid should be so difficult or impossible to prepare by techniques that give excellent yields of the short-chain alcohol esters. Although gallic acid is soluble in the lower alcohols and almost insoluble in the higher ones, in view of the excess proportions of the latter which were tried, it does not seem probable that solubility is the determining factor. One of the most interesting theories presumes that the carboxyl group of the gallic acid is coördinated in such a manner that the higher alcohols cannot readily react with it. For example, a chelate ring may be formed from two molecules of gallic acid as




(1) Laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

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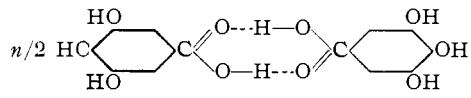
(3) Morris and Riemenschneider, THIS JOURNAL, **68**, 500 (1946).

(4) "Antioxidant Properties of the Fatty Alcohol Esters of Gallic Acid," by Morris, Kraekel, Myers and Riemenschneider. Paper presented at the fall Meeting of American Oil Chemists' Society, 1946.



Such a chelate form seems most probable because of the superior strength of the hydrogen bond between carboxyl groups, and because there is thus no free carboxyl group left on the associated molecule. Linear association between the carboxyl and hydroxyl groups seems much less likely, and in view of the work of Kailan and Brabbée[5] it seems probable that the *para*-OH group is not involved. These investigators found that in the esterification of gallic acid in ethylene glycol or glycerol, the effect of methylation of a *p*-OH group on the rate of esterification is small. It would be necessary to assume that the lower alcohols are capable of "cleaving" such coördination bonds as shown above, since they react readily even at 0°.

Several ways to promote the cleavage of such bonds seemed worthy of trial. They include the use of relatively high temperatures and the use of solvents having high dielectric constants as diluents. Proper choice of diluting solvent or solvent mixtures permits convenient maintenance of relatively high constant temperatures and their use at the reflux point also facilitates continuous removal of the water formed during the reaction. The use of such a diluting solvent seems to be particularly promising, because alcohols which readily esterify gallic acid have dielectric constants above 10. At approximately the point at which the dielectric constant of the alcohols is rapidly approaching a constant minimum value, as shown in Fig. 1, the esterification reaction becomes very slow. Another possible advantage to be gained by the use of the proper diluting solvent is increased solubility of gallic acid in the reaction mixture.

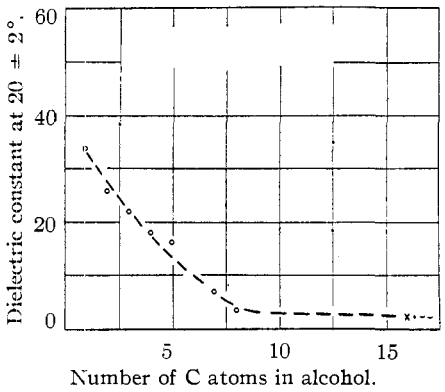



Fig. 1.—Dielectric constant of *n*-aliphatic alcohols. Data for the $C_1$ to $C_8$ alcohols were taken from "International Critical Tables," 1st ed., Vol. VI, pp. 83–94; for the $C_{16}$ alcohol from Baker and Smyth, THIS JOURNAL, **60**, 1229 (1938).

(5) Kailan and Brabbée, *Monatsh.*, **50**, 149–180 (1928); *C. A.*, **23**, 1126 (1929).

Obviously no diluting solvent should be used which is capable of forming a stable compound with either of the reacting groups. Moreover, since gallic acid decomposes at about 235°, it is desirable to use a solvent or mixture of solvents which boil somewhat below that point. Although a number of diluting solvents were tried, the most complete data were obtained for the synthesis of *n*-dodecyl (lauryl) gallate, in which nitrobenzene, *o*-dichlorobenzene, anisole or phenetole, or mixtures of the first with one of the other three, were used. Table I shows the yields obtained by direct esterification procedures in which naphthalene-β-sulfonic acid is used as a catalyst.

TABLE I

EFFECT ON YIELD OF AMOUNT OF NITROBENZENE USED IN PREPARATION OF DODECYL GALLATE[a]

| Moles nitrobenzene per mole of gallic acid | *o*-Dichlorobenzene solvent, 7.4 g. lauryl alc., 15 hr. % yield | Anisole solvent, 7.4 g. lauryl alc., 15 hr. % yield[b] | Phenetole solvent, 5.5 g. lauryl alc., 10 hr. % yield[b] |
|---|---|---|---|
| 0 | 0[c] | 2 | 10 |
| 0.5 | 11 | 30 | 9 |
| 1 | 31 | 74 | 65 |
| 1.5 | 22 | 19 | 13 |
| 2 | 17 | 8 | 28 |
| 3 | 8 | 38 | 18 |
| 13 | 29 | | |

[a] All preparations used 40 ml. of solvent with 3.4 g. of gallic acid, and 0.2 g. of naphthalene-β-sulfonic acid as a catalyst. [b] Nearly all the yield values shown below are averages of two or more determinations. [c] With prolonged refluxing an appreciable yield was obtained.

Since all reactions were run at the boiling point of the particular mixture under investigation, it seems obvious that the effect is not due to temperature conditions, because the addition of 1 mole of nitrobenzene per mole of gallic acid would not increase the boiling point of the relatively large volume of solvent mixture significantly over that of the mixture containing 0.5 mole of nitrobenzene per mole of gallic acid. On the other hand, if the dielectric constant of the solvent were the sole controlling factor, the yields should increase with increasing amounts of nitrobenzene. It is of interest that the best yields were obtained under any given set of conditions when molar equivalents of nitrobenzene and gallic acid were present at the start of the reaction.

Perhaps these solvents function by virtue of their ability to form hydrogen bonds. It is possible that the special value of nitrobenzene in promoting these esterifications may be due to the fact that the two oxygen atoms to which bonding may occur are adjacent in space. Simultaneous bonding of a gallic acid molecule and an alcohol molecule would bring these two reactants into close proximity.

The information gained in these experiments has been used in the preparation of gallic acid esters of all the normal alcohols having an even

number of carbon atoms from 8 to 18, inclusive, except decyl. Yields and melting points are shown in Table II. The melting points of these

TABLE II

ESTERS OF GALLIC ACID

| Alcohol used | Yield, % Crude | Yield, % Pure | M. p., °C. |
|---|---|---|---|
| *n*-Octyl | | 58 | 93.7–94.9 |
| *n*-Dodecyl | 81 | 75 | 96.3–96.8 |
| *n*-Tetradecyl | 80 | 72 | 97.5–98.0 |
| *n*-Hexadecyl | 27 | | ..... |
| *n*-Octadecyl | 86 | 29 | 103.5 |
| *n*-Octadecenyl (oleyl) | 25 | >10 | 85.5 |
| γ-Phenyl *n*-propyl | | 26 | 143–144.5 |

products have been checked with those of the corresponding esters obtained by Morris and Riemenschneider.[3] The new method of synthesis has also been used in the preparation of oleyl gallate, which was obtained in small yield as a crystalline material, m. p. 85.5–86.5° (uncor.). The synthesis of this compound is not feasible by the procedure of Morris, *et al.*,[3] the corresponding saturated compound being formed during removal of the benzyl groups during hydrogenation.

## Experimental

**Materials.**—The gallic acid used in these experiments was a technical grade which had been purified by recrystallization from water after being decolorized with carbon. It was ground to a powder and heated at 125° for four hours to remove water of crystallization.

In general, the alcohols were pure. When alcohols of high purity was not available commercially, the grades available were carefully purified either by fractional distillation through a column having about 10 plates or by crystallization from petroleum ether, or both. Oleyl alcohol (purity, 98%) was prepared from the commercial product.[6]

The solvents used were purchased. Their purity was not determined.

**Esterification Procedures.**—A typical experiment is described. Fifty-one grams of gallic acid (anhydrous) (0.3 mole) and 112 g. of *n*-dodecyl alcohol (0.6 mole) were refluxed slowly in 535 ml. of anisole (5.8 moles) and 31 ml. of nitrobenzene (0.3 mole) in the presence of 2.5 g. of naphthalene-β-sulfonic acid for twenty hours. Refluxing was conducted under a device similar to the Barrett distilling receiver which permitted easy separation of any water carried out by the refluxing solvent. Under the conditions generally used, the gallic acid was not completely dissolved. The solvent mixture was then removed by steam distillation, which was continued until a considerable portion of the unreacted alcohol had also been removed. Removal of the catalyst prior to this step was unnecessary. The product was dissolved in 1 liter of benzene, washed with water to remove excess gallic acid and catalyst and precipitated by the addition of petroleum ether, yielding 73.6 g. of crude ester. An additional crystallization from benzene–petroleum ether mixture yielded 67.8 g. (66.8% of the theoretical yield) of pure product, m. p. 96–97°.

Oleyl gallate was prepared in an essentially identical manner, except that crystallization at about −20° was advantageous during its recovery and purification. Its identity was established by hydrogenation with a palladium catalyst to the corresponding octadecyl gallate, which was checked against a known sample, prepared by Morris and Riemenschneider, by the mixed melting point method.

(6) Swern, Knight and Findley, *Oil & Soap*, **21**, 133 (1944).

## Summary

Direct esterification of gallic acid with the normal aliphatic alcohols having an even number of carbon atoms from 8 to 18, inclusive, except decyl, has been accomplished. This procedure requires relatively high-boiling, polar, inert solvents such as *o*-dichlorobenzene, anisole, phenetole or nitrobenzene, by which the water formed is removed azeotropically. Naphthalene-β-sulfonic acid is an effective catalyst. Highest yields are obtained by using solvent mixtures in which the nitrobenzene is present in a 1:1 molar ratio with respect to the gallic acid and one of the other three solvents makes up the bulk of the solvent mixture. This procedure has been used in the preparation of oleyl gallate, which has not been previously prepared.

PHILADELPHIA 18, PA. RECEIVED MARCH 28, 1947

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF PYRIDIUM CORP.]

# Tuberculostatic Compounds. III. Alkoxy-aminopyrimidines

BY LEO D. BRAITBERG, MICHAEL ROBIN, HARRIS L. FRIEDMAN* AND EDMOND T. TISZA

In the previous papers of this series[1] various derivatives of 2-hydroxy-5-aminopyridine, which possessed *in vitro* tuberculostatic activity, were described. A representative group of alkoxy-aminopyrimidines has now been prepared. All of the pyrimidines are listed in Table I, and, with the exception of 4-methoxy-2-aminopyrimidine, they are all new compounds. They were made by reaction similar to those used for the pyridine analogs.[1] It can be seen that the 2-alkoxy-5-aminopyrimidines are tuberculostatic, but they are slightly less so than the corresponding benzene and pyridine isosteres which are included in the table for comparative purposes. We attribute the lowered activity of 4-butoxy-2-aminopyrimidine to the non-aromatic character of the $-NH_2$ group rather than to the meta arrangement of groups because, in the benzene series, *m*-butoxyaniline was quite active[2] (1/4 mg. per cent.). While 2-butoxy-5-aminopyrimidine possessed a somewhat

(*) Present address: Galat Chemical Development Co., Yonkers, N. Y.

(1) Friedman, Braitberg, Tolstoouhov and Tisza, THIS JOURNAL, **69**, 1204 (1947); **69**, 1795 (1947).

(2) Feinstone, Friedman, Rothlauf, Kelly and Williams, *J. Pharmacol.*, **89**, 153 (1947).