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.

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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

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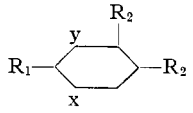
(1) Friedman, Braitberg, Tolstoouhov and Tisza, THIS JOURNAL, **69**, 1204 (1947); **69**, 1795 (1947).

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

TABLE I



Substituents											
R_1	R_2	R_3	X	Y	Empirical formula	M. p., °C.	B. p., °C.	Mm.	Nitrogen, % Calcd.	Found	Tbc[d] stasis, mg. %
C_4H_9O	H	NH_2	N	C	$C_9H_{14}N_2O$		147–148	12	For di-HCl%		1/32
									30.5	30.5	
C_4H_9O[a]	H	NH_2	C	C	$C_{10}H_{15}NO$		148–149	13			1/16
C_4H_9O	H	NO_2	N	N	$C_8H_{11}N_3O_3$	49.5–50			21.3	21.6	1/4
C_4H_9O	H	NH_2	N	N	$C_8H_{13}N_3O$	72–72.5			25.2	25.5	1/8
C_4H_9O	H	$NHCH_2SO_2Na$	N	N	$C_9H_{14}N_3O_4SNa$				14.8	15.0	1/2
$C_6H_{13}O$[b]	H	NH_2	N	N	$C_{10}H_{17}N_3O$	81–82			21.5	21.5	1/16
NH_2[c]	CH_3O	H	N	N	$C_5H_7N_3O$	119–121					64
NH_2	C_4H_9O	H	N	N	$C_8H_{13}N_3O$	57–57.5	123–125	3.5	25.2	25.5	32

[a] Gutekunst and Gray, THIS JOURNAL, **44,** 1741 (1922). [b] Prepared as the butoxyamine above. The intermediate nitro compound was directly reduced without isolation. [c] Adams and Whitmore, THIS JOURNAL, **67,** 735 (1945). [d] Tested against avirulent strain 607 (see ref. 2).

lower acute toxicity than 2-butoxy-5-aminopyridine[2] it also possessed a lower tuberculostatic activity. Further data will be required before the pyrimidine compounds can be evaluated in relation to their pyridine analogs.

Experimental

2-Butoxy-5-nitro-pyrimidine.—Sodium (0.61 g.) was dissolved in *n*-butanol (40 cc.). To the cooled solution 4.1 g. of 2-chloro-5-nitropyrimidine[3] was added with stirring at a temperature of 5–10°. After the mixture stood overnight at room temperature it was heated to 80–90° for three and one-half hours. The butanol was removed by distillation *in vacuo*, 100 cc. of water added and the mixture extracted with ether. On evaporation of the ether 4.1 g. (83%) of yellow crystals remained. Recrystallization from methanol–water gave lustrous plates of m. p. 49.5–50°.

2-Butoxy-5-amino-pyrimidine.—A mixture of 3.2 g. of 2-butoxy-5-nitropyrimidine, 7 g. of iron powder, 0.5 cc. of acetic acid, 25 cc. of methanol and 15 cc. of water was stirred and refluxed four hours. To this was added 0.9 cc. of 40% sodium hydroxide solution and 25 cc. of methanol. Filter aid was added and the suspension filtered through a bed of Super-cel. After washing with methanol the solvents were removed *in vacuo*. The residue was made alkaline and extracted with ether. On evaporation there remained 2.4 g. (89%) of residue of m. p. 71–72°. Recrystallization from a mixture of benzene–petroleum ether gave a product of m. p. 72–72.5°.

(3) Roblin, Winnek and English, THIS JOURNAL, **64,** 567 (1942).

2-Butoxy-5-pyrimidylaminomethyl Sodium Bisulfite.—To a solution of 1.39 g. of sodium bisulfite, 10 cc. of water and 1 cc. of 37% formaldehyde solution was added 1.97 g. of 2-butoxy-5-aminopyrimidine. Digestion on the steam-bath for one hour produced complete solution. Crystals, formed on cooling the solution, were removed, recrystallized from 50% methanol and dried at 100°. Yield was 3.34 g. (74%) of pearly-white plates. The anhydrous product chars on heating without melting.

2-Butoxy-4-aminopyrimidine.—Two grams of sodium was dissolved in 80 cc. of butanol, 6.9 g. of 2-amino-4-chloropyrimidine added and the mixture stirred and heated at reflux for five and one-half hours. The alcohol was removed by distillation *in vacuo* and the residue extracted with ether after the addition of a little water. The ether was evaporated and the product distilled at 3.5 mm. The fraction boiling at 123–125° was retained (6.3 g.). The distillate solidified on cooling and was crystallized from petroleum ether to yield 5.4 g., m. p. 57–57.5°.

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Summary

The preparation of some alkoxy-aminopyrimidines is described. Some of these possessed tuberculostatic activity similar to that of the benzene and pyridine isosteres.

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