Thioisonipecotamide. 4-Cyanopiperidine (35 g.) was treated in 300 ml. of 30% ammonia in methanol with hydrogen sulfide gas until saturation. After standing for 48 hr. at 25°, the solution was concentrated to a solid which was recrystallized from water as a very light cream colored compound; yield, 30 g., m.p. 173–174°.

Anal. Calcd. for $C_6H_{12}N_2S$: N, 19.4. Found: N, 19.2.

Attempts to convert isonipecotamide to thioisonipecotamide using phosphorus pentasulfide in pyridine failed with or without potassium sulfide as a catalyst. In all cases, the ring was dehydrogenated and only thioisonicotinamide was obtained in 25–40% yields.

5-Methyl-2-(4-pyridyl)-4(5H)-thiazolone hydrobromide. Thioisonicotinamide (50 g.) and 56 g. of α-bromopropionic acid were heated together in toluene at the boiling point for 6 hr. The excess toluene was decanted and the solid residue dissolved in ethanol and decolorized using activated charcoal. On cooling, a yellow product crystallized which was recrystallized from ethanol; yield, 25 g., m.p. >250°.

Anal. Calcd. for $C_9H_8N_2OS \cdot HBr$: C, 39.8; H, 3.3; N, 10.3. Found: C, 40.5; H, 3.5; N, 10.4.

4-Methyl-2-(4-pyridyl)thiazole hydrochloride. Thioisonicotinamide (50 g.) was heated at the boiling point in 250 ml. of chloroacetone. The excess chloroacetone was removed *in vacuo* and the residue triturated with ether. The yellow residue was then crystallized from methanol; recrystallization after charcoal decoloration gave a buff yellow material; yield, 11.5 g., m.p. 219–220(dec.).

Anal. Calcd. for $C_9H_8N_2S \cdot HCl$: N, 13.1. Found. N, 12.9.

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Some 3,4,5-Trialkoxybenzoic Acids and Esters

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In a previous report,[1] we described the methods of synthesis and properties of the β-diethylaminoethyl esters of the isomeric trimethoxybenzoic acids. It appeared to be of interest to extend this study by varying the nature of the ether groupings in a representative member of the series. Accordingly, we have prepared the esters of the 3,4,5-trialkoxybenzoic acids which are listed in Table I. The 3,4,5-trialkoxy acids were chosen because of the availability of gallic acid, and because of the relationship of the 3,4,5-trimethoxybenzoate radical to the reserpine molecule.

The 3,4,5-triethoxy-, tri-*n*-propoxy-, and tribenzyloxybenzoic acids were obtained from gallic acid by conventional alkylation procedures. They were converted then to the β-diethylaminoethyl esters by the Horenstein and Pählicke, method.[2]

Difficulties were encountered in attempts to alkylate gallic acid with *n*-butyl and *n*-amyl bromides in the presence of alkali. However, it was possible to convert the trisodium salt of methyl gallate to the corresponding ethers. Hydrolysis of methyl 3,4,5-tri-*n*-butoxybenzoate produced an oil which afforded a small amount of crystalline 3,4,5-tri-*n*-butoxybenzoic acid. Treatment of methyl 3,4,5-tri-*n*-amyloxybenzoate in a similar fashion led to oils which could not be induced to crystallize.

Pharmacological tests[3] have shown that the β-diethylaminoethyl esters of the trimethoxybenzoic acids are relatively impotent in producing local anesthetic action in guinea pigs, whether tested by intradermal administration or topical application to the eye. The corresponding esters of the 3,4,5-triethoxy- and tri-*n*-propoxybenzoic acids apparently do not possess local anesthetic properties. The tribenzyloxy ester is not sufficiently soluble in water to be tested under comparable conditions.

EXPERIMENTAL[4]

Materials. 3,4,5-Triethoxybenzoic acid (m.p. 108–110°; lit.[5] m.p. 110°) was obtained by the ethylation of gallic acid with ethyl sulfate. *3,4,5-Tribenzyloxybenzoic acid* (m.p. 190–191°; lit.[6] m.p. 187°) resulted from the action of benzyl chloride on gallic acid. Treatment of a methyl alcohol of the latter with *n*-propyl bromide and alkali gave 3,4,5-*n*-propoxybenzoic acid; m.p. 89–91° after recrystallization from aqueous alcohol. Esterification of gallic acid by means of methanol, which had been saturated with hydrogen chloride, produced the corresponding ester (m.p. 194–195°; lit.[6] m.p. 198°).

β-Diethylaminoethyl 3,4,5-trialkoxybenzoate hydrochlorides. The three amino ester hydrochlorides listed in Table I were prepared according to previously described directions,[1] and were purified by recrystallization from a mixture of absolute ethanol and absolute ether.

Methyl 3,4,5-tri-n-butoxybenzoate and corresponding acid. To a solution of 6.9 g. (0.3 g. atom) of sodium in 400 ml. of absolute ethanol was added 18.4 g. (0.1 mole) of methyl gallate and the resulting slurry was heated to reflux. A solution of 54.8 g. (0.4 mole) of *n*-butyl bromide in 50 ml. of alcohol was added dropwise over a period of 1 hr. and the reaction mixture was stirred and heated for an additional 17 hr. Most of the solvent was removed by distillation, 200 ml. of water was added to the residue, and the mixture was extracted with ether. The ether solution was washed several times with dilute sodium hydroxide solution, dried, and concentrated. There was obtained 13 g. (37%) of water which distilled at 190–195°/1 mm.; n_D^{20} 1.4947.

A sample of the ester was hydrolyzed in 10% aqueous alcoholic potassium hydroxide solution. The reaction mixture was acidified, kept cool for several days, and filtered. The resulting solid was recrystallized from aqueous alcohol to give 3,4,5-tri-*n*-butoxybenzoic acid which melted at 68.5–70°.

Methyl 3,4,5-tri-n-amyloxybenzoate. A slurry of the trisodium salt of methyl gallate, prepared from 55.2 g. (0.3

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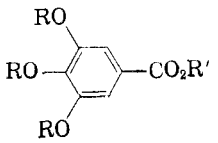
TABLE I

3,4,5-TRIALKOXYBENZOIC ACIDS AND ESTERS,



Compound		M.P. or B.P., °C.	Analyses, %			
			Carbon		Hydrogen	
R	R'		Calcd.	Found	Calcd.	Found
C_2H_5	$C_6H_{15}ClN$[a]	128–130	58.52	58.59	8.27	8.22
$C_6H_5CH_2$	$C_6H_{15}ClN$[a]	153–155	70.87	70.51	6.65	6.92
n-C_3H_7	H	89–91	64.84	65.06	8.16	8.12
n-C_3H_7	$C_6H_{15}ClN$[a]	125–126	61.16	60.82	8.87	8.98
n-C_4H_9	H	68.5–70	67.43	67.45	8.94	9.01
n-C_4H_9	CH_3	190–195/1 mm.	68.15	68.37	9.15	9.42
n-C_5H_{11}	CH_3	203–205/1 mm.	70.01	69.71	9.71	9.58

[a] $C_6H_{15}ClN = CH_2CH_2N(C_2H_5)_2 \cdot HCl$.

mole) of the ester and 0.9 mole of sodium ethoxide, in 1 l. of absolute ethanol was stirred and heated to reflux. A solution of 181.2 g. (1.2 moles) of *n*-amyl bromide in 100 ml. of alcohol was added dropwise, and the reaction mixture was heated for 10 hr. It was worked up in a fashion similar to that described in the preceding experiment. Distillation of the residue which remained after concentration of the ether solution yielded 48.5 g. (41%) of the ester; b.p. 203–205°/1 mm., n_D^{20} 1.4971.

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Isolation of Maltose from Honeydew on Alsike (*Trifolium hybridum*) Seeds[1]

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Recently Northrup King and Company, Minneapolis, drew our attention to the presence of a sticky substance on alsike (*Trifolium hybridum*) seeds harvested in Idaho. The material, a type of honey dew arising from infestation of the plants by aphids, *Therioathis maculata* (Buckton), was obtained by washing the seeds with water, filtering, and concentrating the brownish yellow filtrate *in vacuo* to a sirup. This sirup reduced Fehling solution and gave a positive Molisch test. Paper chromatographic analysis, using three different solvents; 1-butanol:ethanol:water, (4:1:5);[2] 1-propanol:water azeotrope;[3] ethylacetate : pyridine:water (2.5:1.0:3.5)[4] and *p*-anisidine phosphate spray,[5] revealed the presence of glucose, fructose, maltose, maltotriose, and other more slowly moving components.[6] Inasmuch as the material arose from aphids it was expected that one of the components might be melezitose[7] but none was present. The maltose component was separated by sheet paper chromatography using Whatman No. 3 paper and the above pyridine-ethyl acetate-water solvent in the usual way and extracted from the appropriate segments of the paper with water. Removal of the solvent *in vacuo* produced a colorless sirup which crystallized when dissolved in the minimum quantity of water and treated with ethanol to incipient turbidity. The crystalline product proved to be maltose, melting point and mixed melting point 118–123°, $[\alpha]_D^{22}$ + 126° in water (*c*, 0.5). The maltose was further characterized by reduction with sodium borohydride[8] to maltitol which was tranformed by means of sodium acetate and acetic anhydride into the crystalline nonacetate,[9,10] melting point and mixed melting point 82–83°.

Paper chromatography has shown in other experiments that the honey dew exuded by the leaves of a young peach tree (*Amygdalus sp.*) contained glucose, fructose, and sucrose; that from the leaves of a House Balsam (*Impatiens sultani*) contained

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