Anal. Calcd. for $(CH_3)_4NSCN$: SCN, 43.90. Found: 43.45, 43.50, 43.62 (by precipitation as silver thiocyanate).

Tetramethylammonium sulfate. To 2.754 g. (0.03022 mole) of tetramethylammonium hydroxide in 125 ml. of water was added 1.997 g. (0.01511 mole) of ammonium sulfate. The solution was boiled and brought to dryness as in preparation (I), whereupon the residue was heated in an oven for 12 hr. at 120° and 6 hr. at 130°. Yield: 92% (3.4 g.).

Anal. Calcd. for $[(CH_3)_4N]_2SO_4$: SO_4, 39.30. Found: 39.44, 39.47 (by precipitation as barium sulfate).

Tetramethylammonium bromide. To 2.661 g. (0.02925 mole) of tetramethylammonium hydroxide in 125 ml. of water was added 2.865 g. (0.02925 mole) of ammonium bromide. The resulting solution was treated as in preparation (II). Yield: 100% (4.5 g.).

Anal. Calcd. for $(CH_3)_4NBr$: Br, 51.88. Found: 51.19, 51.27, 51.28 (by precipitation as silver bromide).

Tetramethylammonium iodide. To 2.9651 g. (0.03253 mole) of tetramethylammonium hydroxide in 125 ml. of water was added 4.7157 g. (0.03252 mole) of ammonium iodide which had been previously washed with carbon tetrachloride to remove all traces of free iodine formed as a result of decomposition during prolonged storage. The resulting solution was treated as in preparation (II); yield: 100% (6.5 g.).

Anal. Calcd. for $(CH_3)_4NI$: I, 63.12. Found: 62.42, 62.54, 62.64 (by precipitation as silver iodide).

Tetramethylammonium chromate. To 3.518 g. (0.03860 mole) of tetramethylammonium hydroxide in 125 ml. of water was added 1.5 ml. of aqueous 28% ammonia and 2.433 g. (0.00965 mole) of ammonium dichromate. The additional ammonia was needed to bring about conversion of the dichromate ion to the chromate ion. The resulting solution was treated as in preparation (II).

Anal. Calcd. for $[(CH_3)_4N]_2CrO_4$: CrO_4, 43.89. Found: 43.14, 43.20, 43.41 (by precipitation as barium chromate).

Tetramethylammonium oxalate. To 3.170 g. (0.03478 mole) of tetramethylammonium hydroxide in 125 ml. of water was added 2.471 g. (0.01739 mole) of ammonium oxalate monohydrate. The resulting solution was treated as in preparation (II).

Anal. Calcd. for $[(CH_3)_4N]_2C_2O_4$: C_2O_4, 26.85. Found: 26.40, 26.45, 26.46 (by precipitation as calcium oxalate monohydrate).

Tetramethylammonium thiosulfate. To 2.265 g. (0.02484 mole) of tetramethylammonium hydroxide in 125 ml. of water was added 1.841 g. (0.01242 mole) of ammonium thiosulfate. The solution was boiled down twice to 25 ml. with replacement of water, evaporated, and dried for 12 hr. at 105°, and for 4 hr. at 130°; yield 97% (3.1 g.).

Anal. Calcd. for $[(CH_3)_4N]_2S_2O_3$: S_2O_3, 43.03. Found: 41.97, 42.10, 42.13 (by conversion to sulfate and precipitation as barium sulfate).

Tetraethylammonium iodide. To 2.221 g. (0.01508 mole) of tetraethylammonium hydroxide in 125 ml. of water was added 2.186 g. (0.01508 mole) of ammonium iodide. The solution was boiled down twice to 10 ml. with replacement of water, evaporated, and dried for 20 hr. at 85°; yield 100% (3.9 g.).

Anal. Calcd. for $(C_2H_5)_4NI$: I, 49.35. Found: 48.84, 48.87, 48.92.

Tetraethylammonium thiocyanate. To 2.468 g. (0.01676 mole) of tetraethylammonium hydroxide in 125 ml. of water was added 1.276 g. (0.01676 mole) of ammonium thiocyanate. The resulting solution was treated as in preparation (VII); yield 94% (3.0 g.).

Anal. Calcd. for $(C_2H_5)_4NSCN$· SCN, 30.84. Found: 29.83, 29.84, 29.87.

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Synthesis of Compounds for Chemotherapy of Tuberculosis. VII. Pyridine *N*-Oxides with Sulfur-Containing Groups[1]

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In view of the high activity of thioisonicotinamide in the chemotherapy of experimental tuberculosis in mice,[2] a number of pyridine derivatives containing a —CSNH— moeity were prepared.

Reduction of the pyridine ring eliminated activity; *N*-oxidation reduced activity, and separation from the ring of the —CSNH— group (thioureas and pseudothioureas) eliminated activity as did also the conversion of the group into a ring system (thiazole and thiazolone).

The previously known *N*-oxides of picolinamide,[3,9] thiopicolinamide,[4] nicotinamide,[3] and isonicotinamide,[3] as well as 4-pyridylthiourea,[5] also showed no activity in the same test in which nicotinamide is active.[6] All other compounds prepared were either inactive or less active than thioisonicotinamide.[2]

EXPERIMENTAL[7]

Isonicotinonitrile-1-oxide. Isonicotinamide-1-oxide (147 g.) was heated at reflux for 0.5 hr. with 1500 g. of phosphorus oxychloride. The solution was concentrated to a small volume under vacuum and poured onto cracked ice. The solution was made alkaline with concentrated ammonia and the separated nitrile filtered off. The solution was extracted five times with chloroform using a total of 800 ml. for the extractions. The previously separated solid was extracted at the boiling point with the chloroform extractants and filtered. On cooling, almost pure nitrile separated which could be recrystallized from chloroform or methanol; yield, 85 g., m.p. 229–230°.

Anal. Calcd. for $C_6H_4N_2O$: N, 23.3. Found. N: 22.9.

This compound has been previously reported,[8] with a melting point of 220–221° by preparation from 4-aminopyridine-1-oxide using the Sandmeyer reaction.

Thioisonicotinamide-1-oxide. Isonicotinonitrile-1-oxide (30 g.) was dissolved in 300 ml. of a methanol solution containing 30% ammonia by weight. The solution was saturated with hydrogen sulfide gas and on standing 2 days the thioamide separated. The recovered yellow-orange product was recrystallized from hot water; yield, 12 g., m.p. 205–206°.

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Anal. Calcd. for $C_6H_6N_2OS$: C, 46.7; H, 3.9. Found: C, 47.0; H, 4.0.

Thionicotinamide-1-oxide. Nicotinonitrile-1-oxide was prepared in a 55% yield by treating the nicotinamide-1-oxide with phosphorus oxychloride for 0.5 hr. at reflux. Nicotinonitrile-1-oxide (28 g.) was dissolved in 300 ml. of a methanol solution containing 20% ammonia gas by weight. This solution was saturated with hydrogen sulfide gas and a small quantity of the thioamide separated in 18 hr. The solution was concentrated to a solid and the residue crystallized as a colorless compound from hot water; yield, 14 g., m.p. 161–164°.

Anal. Calcd. for $C_6H_6N_2OS$: S, 20.8. Found: S, 20.9.

Thioisonicotinamide hydrochloride. Thioisonicotinamide (10 g.) was dissolved in 200 ml. of ethanol and 20 ml. of 9*N* hydrogen chloride in ethanol was added. The orange colored hydrochloride separated and was reerystallized from hot ethanol; yield, 9 g., m.p. 231–232°.

Anal. Calcd. for $C_6H_6N_2S\cdot HCl$: N, 16.1. Found: N, 16.1.

The hydrochloride exhibited the same order of activity as the free base in tuberculosis of mice.

Picolinamide-1-oxide. Picolinamide (70 g.) was heated at 80° for 6 hr. in a solution of 100 g. of pearcetic acid (40%) and 300 ml. of acetic acid. The solution was diluted with 500 ml. of water and concentrated to a solid in vacuum. The colorless solid was recrystallized from methanol; yield, 51 g., m.p. 165–166°.

Anal. Calcd. for $C_6H_6N_2O_2$: C, 52.1; H, 4.4; N, 20.3. Found: C, 52.6; H, 4.5; N, 19.8.

The investigation of the picolino-type *N*-oxide gave several anomalies. The reaction of phosphorus pentasulfide and potassium sulfide in pyridine on picolinamide 1-oxide deoxygenated the *N*-oxide and gave only thiopicolinamide.

The reaction of hydrogen peroxide in glacial acetic acid on picolinamide[9] has been reported to give the ammonium salt of picolinic acid 1-oxide. We have verified this reaction although we separated free picolinic acid 1-oxide instead of the salt.

Picolinonitrile-1-oxide. A diatomaceous earth (Hyflo, 70 g.) was dried at 110° and mixed with 150 g. of phosphorus pentoxide by shaking in a closed vessel. The dehydrating mixture was added to 500 ml. of sodium dried toluene and 25 g. of dry picolinamide 1-oxide. The mixture was agitated with an efficient stirrer and held at reflux temperature for 4 hr. The gummy mixture was filtered on a dry Hyflo bed. The residue was treated with water and concentrated ammonium hydroxide, and then extracted with chloroform. The chloroform extract was added to the toluene filtrate. The solution of toluene and chloroform was concentrated to a small volume (50 ml.); 20 ml. of chloroform and 20 ml. of ether were then added. On chilling, crystals separated which were recrystallized from ether; yield, 5 g., m.p. 122–123° for which Leonard and Wajngurt[4] report 117–118° by a different method of preparation.

Anal. Calcd. for $C_6H_4N_2O$: C, 60.1; H, 3.4. Found: C, 60.6; H, 3.5.

The reaction of boiling phosphorus oxychloride on picolinamide-*N*-oxide rapidly deoxygenated the compound to yield 2-picolinonitrile. In contrast, over 6 hr. of boiling phosphorus oxychloride was required to deoxygenate isonicotinamide-1-oxide to give isonicotinonitrile.

The preparation of picolinonitrile-1-oxide has recently been reported by Leonard and Wajngurt[4] by the direct oxidation of picolinonitrile using aqueous hydrogen peroxide and acetic acid, and from which was also prepared thiopicolinamide-1-oxide (m.p. 145–146°) using hydrogen sulfide and methanolic ammonia.

4-Pyridylthiourea-1-oxide. 4-Aminopyridine-1-oxide hydrochloride (20 g.) was treated with 12.5 g. of ammonium thiocyanate in 250 ml. ethanol at reflux temperature for 6 hr. The hot suspension was filtered, concentrated to a solid, and extracted with acetone. A colorless product was obtained by recrystallization from acetone; yield, 20 g., m.p. 126–127°.

Anal. Calcd. for $C_6H_7N_3OS$: N, 24.9. Found: N, 24.5.

2-(3'-Pyridyl)-2-thiopseudourea-1'-oxide hydrobromide. 3-Bromopyridine-1-oxide hydrochloride (53.5 g.) in 100 ml. water, was neutralized with dilute sodium hydroxide and extracted with chloroform. Concentration of the chloroform gave the free 3-bromopyridine-1-oxide. This material was treated at reflux for 5 hr. in 300 ml. of ethanol with 19 g. of thiourea. On cooling, the colorless product crystallized and was recrystallized from ethanol; yield, 50 g., m.p. 145–147°, for which 142° has recently been reported.[4]

Anal. Calcd. for $C_6H_7N_3OS\cdot HBr$: N, 16.8. Found. N, 16.5.

This compound could not be decomposed to yield 3-pyridinethiol 1-oxide using sodium hydroxide solution.

N-Ethylnicotinamide-1-oxide. *N*-Ethylnicotinamide (60 g.) was treated with 120 g. of 40% peracetic acid in acetic acid at 10–15°. Concentration at 80° to an oil gave a crystalline material on standing at 25° for 48 hr. The colorless product was recrystallized from acetone; yield, 35 g., m.p. 123–124°.

Anal. Calcd. for $C_8H_{10}N_2O_2$: N, 16.9. Found: N, 16.9.

3,5-Dibromopyridine-1-oxide. 3,5-Dibromopyridine (42 g.), 80 g. 40% peracetic acid in acetic acid and 300 ml. of acetic acid was heated at 80° for 3 hr. and then at 50° for 12 hr. Concentration to a solid and recrystallization from ethanol gave 30 g. of a colorless product; m.p. 143–144°.

Anal. Calcd. for $C_5H_3Br_2NO$: N, 5.3. Found: N, 5.5.

2-(5'-Bromo-3'-pyridyl)-2-thiopseudourea-1'-oxide hydrobromide. 3,5-Dibromopyridine-1-oxide (20 g.) was treated at reflux for 5 hr. in 300 ml. of ethanol with 15 g. of thiourea. On cooling, the product crystallized and was recrystallized from ethanol; yield, 20 g., m.p. 162–163°.

Anal. Calcd. for $C_6H_6BrN_3OS\cdot HBr$: N, 12.8. Found: N, 13.0.

N,N'-methylenebis(thioisonicotinamide) hydrate. Thioisonicotinamide (25 g.), in 1 l. of water, was treated with 30 ml. of 37% formaldehyde solution. The *p*H was adjusted and maintained at 7.5 using potassium hydroxide solution. After standing 6 hr. the *p*H was adjusted to 7 by formic acid. On cooling to 4°, a yellow product crystallized and was recrystallized from water; yield, 24 g., m.p. 146–147°.

Anal. Calcd. for $C_{13}H_{12}N_4S_2\cdot H_2O$: C, 51.0; H, 4.5; N, 18.3; H_2O, 5.9. Found: C, 51.4; H, 4.3; N, 18.1; H_2O, 5.8, 6.0.

This compound was less active than the parent compound in tuberculosis in mice.

The assignment of the linear structure was based on analyses and the fact that infrared analyses gave none of the characteristic absorption bands for the triazine structure which is found in the condensation product, hexahydro-1,3,5-triisonicotinamide-*s*-triazine, from the reaction of isonicotinyl hydrazine[10] with formaldehyde. However, it is interesting to note that picolinyl hydrazine[11] and formaldehyde also gave a linear condensation product, 1,1'-methylenebis(2-picolinylhydrazine)dihydrochloride instead of the triazine.

4-Cyanopiperidine. Isonipecotamide (100 g.) in 450 g. of phosphorus oxychloride was refluxed for 2 hr. and concentrated *in vacuo* to a small volume and poured onto ice. The solution was made alkaline with concentrated ammonia and extracted five times using 400 ml. of chloroform for each extraction. Concentration of the chloroform gave an oil, b.p. 100° at 7 mm., n_D^{23} 1.4741; yield, 37 g.

Anal. Calcd. for $C_6H_{10}N_2$: N, 25.4. Found: N, 24.8.

4-Cyanopiperidine has been prepared in a 12% yield from isonipecotamide using thionyl chloride.[12]

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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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