N-Butyl Iodide.

In an experimental run, 600 g. (theory calls for 582 g.) *N*-butyl alcohol, 50 g. of yellow phosphorus, 60 g. red phosphorus and one kg. iodine were allowed to react. After the alcohol started to boil, 40 minutes were required to complete the reaction. The oil bath temperature should be kept approximately at 175°. After purification as described under propyl iodide, the product boiled at 126–128° and weighed 1430 g. (98% yield).

Isoamyl Iodide.

Technical isoamyl alcohol was used in this experiment, consequently pure isoamyl iodide was not obtained. From 700 g. of isoamyl alcohol (theory calls for 693 g.) 50 g. yellow phosphorus, 60 g. red phosphorus and one kg. iodine, complete reaction occurred in 40 minutes after the alcohol refluxed. The oil bath temperature was about 190°. The yield of product purified as described under propyl iodide amounted to 1480 g. (94% theory). It boiled at 138–148°.

URBANA, ILLINOIS.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY, NO. 318.]

THE SYNTHESIS OF CERTAIN SUBSTITUTED PYROGALLOL ETHERS, INCLUDING A NEW ACETOPHENETIDE DERIVED FROM THE ETHYL ETHER OF SYRINGIC ACID.[1]

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Received March 1, 1919.

Introductory.

Chassevant and Garnier[2] have maintained that triatomic phenols as a class are less toxic than monotomic phenols, and there is already in the literature ample evidence to the effect that alkylation of a phenolic hydroxyl tends to reduce its poisonous action.

With these generalizations in mind, the thought suggested itself that a dialkyloxy derivative of the ordinary phenacetin of commerce might be synthesized which would retain the valuable antipyretic and analgesic properties of the latter and at the same time show reduced toxicity. It was with this end in view that the investigation described in the following pages was undertaken, and it constitutes a first step in the study of a problem which we hope to follow further as opportunity offers.

[1] The investigation described in this paper formed part of the work carried out by Mr. Ehrlich in fulfilment of the requirements for the degree of Doctor of Philosophy under the Faculty of Pure Science, Columbia University. It was completed in the spring of 1917, but its publication has been delayed by the war duties of the senior author.—M. T. B.

[2] *Compt. rend. soc. biol.*, 55, 1584 (1903), and *Arch. Pharmacodyn.*, 14, 93 (1905).

Having had considerable experience in the preparation of syringic acid, it was chosen as the initial material for this research, being converted first into its ethyl ether, then into the chloride and amide of the latter, the amide yielding 3,5-dimethoxy-phenetidine when subjected to the Hoffman reaction. Acetylation of this amine gave the compound sought, namely 3,5-dimethoxy-acetophenetide in the form of its monohydrate.

A preliminary pharmacological study of this new compound by Professor Charles C. Lieb of the College of Physicians and Surgeons, Columbia University, shows that it possesses decided antipyretic action. Whether its toxicity is much less than that of phenacetin itself is as yet undetermined, experiments hitherto having shown only that it is not more toxic. This part of the work will be described more fully later.

In the course of the investigation, the following new compounds in addition to the above were prepared and examined: methyl and ethyl esters of syringic acid ethyl ether; 2-bromo-3,5-dimethoxy-4-ethoxy-acetanilide; 3,5-dimethoxy-4-ethoxyphenylurea; 3,5-dimethoxy-4-ethoxy-*s*-diphenylurea; 3,5-dimethoxy-4-ethoxyphenol; 3,5-dimethoxy-4-ethoxy-iodobenzene and 3,5-dimethoxy-4-ethoxybenzene-azo-β-naphthol. Of these, the most interesting are the dimethoxy-ethoxyphenol, which is a homolog of the so-called "antiarol" found in nature; and the urea derivative, which is a dimethoxydulcin.

The various steps in the synthetic work may be represented concisely as follows:

$(CH_3O)_2(3,5)(HO)(4)C_6H_2COOH \longrightarrow (CH_3O)_2(3,5)(C_2H_5O)(4)C_6H_2.$-
$COOH \longrightarrow -CO.Cl \longrightarrow -CO.NH_2 \longrightarrow -NH_2 \longrightarrow -NHCOCH_3,$
$-NHCONH_2$, $-NH.CO.NHC_6H_5$, $-N:N.C_{10}H_6.OH$, $-OH$, and I.

The nitrogen determinations recorded in this paper were carried out by the Kjeldahl method.

Experimental.

The syringic acid (3,5-dimethoxy-4-hydroxybenzoic acid) used as the initial material for the investigation was prepared from trimethylgallic acid (3,4,5-trimethoxybenzoic acid) by the following modification of the method outlined by Bogert and Isham:[1]

60 g. pure and finely powdered trimethylgallic acid was added slowly with vigorous stirring to 300 g. fuming (20%) sulfuric acid, allowing complete solution to take place between successive additions. The solution was maintained at 33° to 40° until all trimethylgallic acid had been added and then was stirred for 30 minutes at 40°, and left overnight in the ice box. The solution then set to a crystalline mass which was poured slowly and with vigorous stirring into 300–325 cc. water. The precipitate which formed at first redissolved before the temperature of the solution reached its maximum of 120°. Two minutes after the

[1] THIS JOURNAL, 36, 519 (1914).

addition was completed, the syringic acid crystallized out rapidly. After standing at room temperature overnight, the crude acid was filtered out on a hardened paper, washed with water, and crystallized twice from 1300 cc. water, the solution having been decolorized with boneblack. Yield, 42 g., or 75% theory; colorless needles; m. p. 204–5° (corr.).

If the above procedure is reversed by pouring the water *into* the fuming sulfuric mixture, the yield of syringic acid is reduced to 20–30% of the theory. If the acid mixture is poured upon ice, a clear solution results from which a very impure syringic acid slowly separates on long standing.

Boiling a solution of trimethylgallic acid in dil. sulfuric acid of about the same strength (50%) as that resulting from the addition of the fuming sulfuric mixture to water as outlined above, yielded no syringic acid whatever, the trimethylgallic acid being recovered unchanged. Attempts to isolate a sulfonic acid as an intermediate step in this reaction were unsuccessful.

In the preparation of methyl syringate, the following modification of the method of Bogert and Isham[1] was found advantageous:

60 g. powdered syringic acid was suspended in 420 cc. pure methyl alcohol and dry hydrogen chloride passed in until a clear solution saturated with gas was obtained. After standing for three hours, this solution was evaporated nearly to dryness on a boiling water bath in order to eliminate most of the hydrochloric acid, the residue being then dissolved in 200 cc. warm methyl alcohol and poured with stirring into a liter of water containing about 12 g. of sodium hydrogen carbonate, whereby the hydrate of the ester was precipitated. After stirring the mixture for 30 minutes to complete the neutralization of all hydrochloric acid, and the solution now being faintly alkaline to litmus, the ester was filtered out, washed with water, recrystallized twice from 2300 cc. water and dried on porous tiles. By heating this hydrate for three hours at 110° the pure anhydrous ester was obtained in a yield of 50 g. or 78% of the theory, m. p. 107–8° (corr.).

This anhydrous ester is readily soluble in methyl or ethyl alcohol, in chloroform or glacial acetic acid; moderately soluble in ether, benzene or boiling ligroin, but is difficultly soluble in cold ligroin (b. p. 110°). Syringic acid itself is difficultly soluble in boiling ligroin. An alcoholic solution of methyl syringate treated with a trace of ferric chloride gives a deep blue solution which turns steel gray on dilution with water. If a little aqueous silver nitrate solution is added to water previously saturated with methyl syringate, blue colloidal silver is slowly formed and soon coagulates to a suspension of black metallic silver. Solutions of syringic acid do not show this behavior.

Methyl sodium syringate dissolves readily in cold alcohol, whereas

[1] *Loc. cit.*

the corresponding potassium salt is but slightly soluble. To what extent this difference in solubility may prove of value in the separation of the two alkali metals has not yet been determined.

It was observed that a pale green mold usually appeared in the mother liquors from syringic acid or its ester on exposure to the laboratory air for a few weeks. The nature of this mold was not investigated.

Syringic Acid Ethyl Ether (3,5-Dimethoxy-4-ethoxybenzoic Acid) was readily prepared pure and in excellent yield by the action of diethyl sulfate and sodium hydroxide upon syringic acid or its methyl ester. When the methyl ester was used as the initial material, the process was carried out as follows:

43.2 g. of the anhydrous ester was dissolved in 400 cc. (calc. 200 cc.) of hot 10% aqueous sodium hydroxide solution and boiled for two hours in an open vessel, renewing the evaporated water from time to time until the ester was completely hydrolyzed and the solution freed from methyl alcohol. After cooling to room temperature, 112 cc. (calc. 56 cc.) of commercial diethyl sulfate was added and the temperature gradually raised while stirring vigorously to 50–60°, kept there for two hours, and then raised slowly to the boiling point under a reflux condenser, 160 cc. 10% sodium hydroxide solution added and the boiling continued for two hours to hydrolyze all of the ester. After cooling the solution, 104 cc. conc. hydrochloric acid was added gradually with stirring, and the mixture left in the ice box overnight, the precipitate syringic acid ethyl ether filtered out, dried on porous tiles, and crystallized two or three times from ligroin (b. p. 110°), washed with ligroin, then with low boiling petroleum ether, dried for three hours at 50°, and then at 80° for the same period, the ether forming lustrous, white, sword-shaped needles; m. p. 123–4° (corr.); yield, 42 g. or 91% theory. The substance is difficultly soluble in cold water but readily soluble in boiling; difficultly soluble in cold ligroin, readily soluble in hot; moderately soluble in cold benzene, readily in hot; easily soluble in cold alcohol, glacial acetic acid, or ether.

Subs., 0.2345: CO_2, 0.4989; H_2O, 0.1279.
Calc. for $C_{11}H_{14}O_5$: C, 58.4; H, 6.2. Found: C, 58.2; H, 6.1.

The compound responded negatively to phthalic anhydride, Liebermann and Baeyer tests for a free hydroxyl group, thus indicating that the hydroxyl of the syringic acid had been etherified. Syringic acid (in 70% yield) was obtained when this ethyl ether was treated with fuming (20%) sulfuric acid under the same conditions as trimethylgallic acid. Heated to 300°, the acid lost no carbon dioxide but remained apparently unchanged.

Syringic acid, ethyl ether was also prepared by heating methyl potassium syringate with ethyl iodide in a sealed tube at 110° and hydrolyzing the product, but the yield was very poor.

The interaction of the acid with aqueous solutions of various metallic ions led to the formation of the following salts:

Silver Salt, AgA.—White, curdy, amorphous precipitate difficultly soluble in cold water.

Mercury Salt, HgA_2.—White precipitate, consisting of rosets of minute needles; difficultly soluble in cold water.

Lead Salt, PbA_2.—White, amorphous precipitate, difficultly soluble in cold water.

Bismuth Salt, BiA_3.—White needles, difficultly soluble in cold water.

Antimony Salt, SbA_3.—Like the bismuth salt.

Copper Salt, CuA_2.—Green, amorphous precipitate, difficultly soluble in cold water.

Tin Salt, SnA_2.—White needles, difficultly soluble in cold water.

Aluminum Salt. AlA_3.—White, gelatinous precipitate, difficultly soluble in cold water.

Chromium Salt, CrA_3.—Green, minute needles, appreciably soluble in cold water.

The Methyl Ester prepared from 4.0 g. of the acid by the action of dry hydrogen chloride and 50 cc. methyl alcohol crystallized from 40% ethyl alcohol in colorless, rhombic plates, or from dil. (10%) acetic acid in long, beautiful needles; m. p., 64.5–65° (corr.); yield, 3.6 g., or 85% of the theory.

Subs., 0.2330: CO_2, 0.5111; H_2O, 0.1399.

Calc. for $C_{12}H_{16}O_5$: C, 60.0; H, 6.7. Found: C, 59.8; H, 6.7.

The product is difficultly soluble in cold water and only slightly soluble at boiling point. It dissolves rapidly in methyl or ethyl alcohol, ligroin, ether, chloroform, carbon tetrachloride, acetone, glacial acetic acid or benzene.

The Ethyl Ester prepared in similar manner and purified by distillation under reduced pressure formed hexagonal crystals; m. p., 46–47° (corr.); b. p., 195–196° at 30 mm.; yield, 50% of the theory. Solubility about the same as those given for the methyl ester. It does not crystallize well either from dilute alcohol or dilute acetic acid.

Acid Amide, $C_{10}H_{13}O_3CONH_2$.—30 g. dry syringic acid ethyl ether was treated with an equal amount (theory 27.6 g.) phosphorus pentachloride in a distilling flask with side tube temporarily closed and with calcium chloride guard tube. After immersion in hot water for a few seconds, the reaction proceeded spontaneously with copious evolution of hydrogen chloride and formation of a deep purple solution. Upon the cessation of evolution of hydrogen chloride the flask was immersed in a boiling water bath for 20 minutes to complete the reaction. This effected the complete solution of all phosphorus pentachloride, and the liquid changed from purple to a clear yellow. The phosphorus oxychloride was distilled off under a reduced pressure (about 20 mm.), the temperature of the outside bath being gradually raised to 100°. When cold, the residual crude acid chloride was dissolved in 500 cc. anhydrous ether, the flask buried in an ice bath and the solution saturated with dry ammonia. After standing for 15 minutes, the bulky, white precipitate was filtered

out, washed twice with ether, dried, finely powdered, agitated mechanically for two hours with 300 cc. water to dissolve out all ammonia salts, filtered, washed again with water and dried on porous tiles. Yield, 24 g. or 80% of the theory.

Prepared in this way, the amide was sufficiently pure for use in further syntheses. For analysis, it was recrystallized from water to constant melting point, whereby white, glistening leaves were obtained; m. p., 154–5° (corr.).

Subs., 0.3346: 0.1 *N* H_2SO_4 neutralized, 14.90 cc.
Calc. for $C_{11}H_{15}O_4N$: N, 6.23. Found: 6.24.

It is readily soluble in methyl or ethyl alcohol, acetone, chloroform, ethyl acetate, or boiling water, less readily in carbon tetrachloride, ether, carbon disulfide, or benzene, and difficultly soluble in boiling ligroin. In cold 10% aqueous sodium hydroxide solution it dissolves but slowly: on heating solution occurs with simultaneous hydrolysis and evolution of ammonia.

3,5-Dimethoxy-*p*-phenetidine (**3,5-Dimethoxy-4-ethoxyaniline**) was obtained from the above amide by the action of aqueous sodium hydroxide solution and sodium hypochlorite.

23.7 g. pulverized amide was suspended in 150 cc. (theory 147 cc. with respect to hypochlorite content) of a solution containing 5.31 g. sodium hypochlorite (previously determined by titration against a standard arsenite solution) and 3.1 g. sodium hydroxide per 100 cc. After adding 39 cc. 10% sodium hydroxide to bring the total amount of the latter present up to 8.7 g. (theory 8.4 g), the mixture was stirred vigorously for two hours, the amide dissolving with slow evolution of heat and with the formation of a red solution. This solution was filtered from a trace of insoluble material and the filtrate heated at 90–96° for 30 minutes. An oil precipitated which solidified in nodules on cooling and, after standing in the ice box overnight, the crude amine was filtered out and without washing was pressed as dry as possible. After crushing up the lumps, the crude material was washed with a little water, pressed on a porous tile, and dried in a vacuum desiccator over conc. sulfuric acid for 12 hours. The yield of crude, pale brown substance was 18 g., or 85% of the theory.

Even when kept in a dry atmosphere, the amine oxidized slowly to a blue, amorphous material, hence it was necessary to convert it to the hydrochloride for analysis and further syntheses.

This conversion to the hydrochloride was accomplished by dissolving in absolute ether, filtering out any insoluble matter, cooling the filtrate in ice water, and saturating with hydrogen chloride. The amine hydrochloride precipitated in colorless, microscopic needles which were filtered out on a hardened paper, washed with ether, dried at 50° and kept in a vacuum desiccator. From 10 g. of crude amine a similar amount of pure

hydrochloride was obtained, which is equal to 83% of the theory on the basis of the crude amine. The substance turned blue at 190° (corr.) and charred at 200° (corr.) without melting. Long, white needles were obtained by recrystallization from conc. hydrochloric acid. The compound remained unaltered in dry air.

Subs., 0.7357: 0.1 *N* H_2SO_4 neutralized, 29.85 cc.
Calc. for $C_{10}H_{15}O_3N.HCl$: N, 6.0. Found: 5.7.

When an excess of silver nitrate solution was added to an aqueous or alcoholic solution of this hydrochloride, a precipitate of silver chloride formed first, followed by the deposition of a silver mirror.

When a trace of ferric chloride was added to a dil. hydrochloric acid solution of the substance, no coloration resulted, but if dil. sodium hydroxide solution was then added drop by drop, a rich crimson color developed.

On treating a cooled concentrated aqueous solution of the compound with slight excess of dil. sodium or ammonium hydroxide, the amine was first liberated as a pale blue precipitate which turned deep blue almost immediately. When, however, the calculated amount of sodium carbonate solution was used, the oxidation did not proceed so rapidly, and this method was therefore made use of to isolate the free amine in a state of purity.

A concentrated solution of the hydrochloride was cooled in a freezing mixture and the theoretical amount of sodium carbonate dissolved in a little water added with stirring. A pale brown precipitate separated, consisting of small needles, which was filtered out, washed thoroughly with water, pressed on a porous tile, and dried in a vacuum desiccator overnight. Prepared in this way, it melted at 92–3° (corr.), but on standing, this melting point gradually sank due to increasing formation of the blue impurity. Heating with any solvent in the presence of air accelerated this change. From carbon tetrachloride or ligroin the substance crystallized in the form of needles grouped in rosets, from water, in needles and prisms. Boiled with 10% sodium hydroxide solution, no ammonia was evolved, indicating the absence of amide nitrogen. The presence of primary amine nitrogen was demonstrated by positive isonitrile and mustard oil tests.

An aqueous solution of the amine assumed a deep emerald hue when treated with a little ferric chloride solution. The addition of an excess of aqueous silver nitrate to an aqueous solution of the amine resulted in a deposit of spangles of metallic silver. A comparison of the behavior of the amine and of its hydrochloride in these two tests is interesting.

A crystal of the solid amine dropped into a little conc. nitric acid produced a deep crimson solution which changed to a clear yellow. With conc. sulfuric acid the amine gave a colorless solution. Diazotized and coupled with alkaline solution of α-naphthol, a deep crimson dye was

produced; with β-naphthol, a bright vermilion dye. The latter is described beyond.

3,5-Dimethoxy-*p*-acetophenetide (3,5-Dimethoxy-4-ethoxyacetanilide).—This new derivative of phenacetin was obtained in the form of its interesting hydrate by the acetylation of the crude amine dissolved in dil. acetic acid. On account of the peculiar behavior of this hydrate, as described in another article, its preparation is briefly stated here:

22 g. crude amine was dissolved in 23 cc. (theory 21.5 cc.) of 3% acetic acid by gently warming on a water bath. After cooling to room temperature, 23 cc. (theory 11.5 cc.) of acetic anhydride was added and the mixture vigorously stirred. Heat was evolved and a dark green solution resulted. After shaking for two hours, 46 cc. water was added, and the solution heated with stirring for 20 minutes at 90–100° to hydrolyze any excess of acetic anhydride. On cooling in a freezing mixture and scratching the inner surface of the vessel, or seeding with a crystal of the material, an abundant microcrystalline precipitate rapidly separated. After standing in the ice box for a few hours, the precipitate was filtered out, washed with 3% acetic acid, then with water, and dried in the air on a porous tile, giving the pure hydrate; m. p., 90° (corr.); yield, 21 g. or 78% of the theory. For analysis and solubility measurements, the substance was recrystallized from water in the presence of bone-black which removed a slight trace of coloring matter and gave well-formed white prisms, but failed to raise the melting point.

The water of crystallization was determined by placing the hydrate previously dried in the air in a vacuum desiccator over sulfuric acid. Constant weight was obtained after two days, and the samples then had the melting point of the pure anhydrous substance (129°).

Subs., 0.2070, 0.2126: H_2O lost, 0.0143, 0.0148.
Calc. for $C_{12}H_{17}O_4N.H_2O$: H_2O, 7.02. Found: 6.92 and 6.97.

The solubility in water of the liquid and solid hydrate is discussed in another article. The compound is not volatile with steam.

A solution of the substance in hot 10% sodium hydroxide solution boiled for three hours showed no appreciable hydrolysis to the amine, but this hydrolysis was accomplished by boiling with dil. sulfuric acid.

When the hydrate was heated for two hours at 80° and then for three hours at 100°, it gave a quantitative yield of the pure anhydrous 3,5-dimethoxy-*p*-acetophenetide, m. p. 129° (corr.). Recrystallized from a mixture of benzene and ligroin, long, white needles were obtained of the same melting point.

Subs., 0.1367: CO_2, 0.2997; H_2O, 0.0875.
Calc. for $C_{12}H_{17}O_4N$: C, 60.3; H, 7.1. Found: C, 59.9; H, 7.2.
Subs., 0.7348: 0.1 *N* H_2SO_4 neutralized, 29.40 cc.
Calc. for $C_{12}H_{17}O_4N$: N, 5.8. Found: 5.6.

The substance is more or less soluble in most of the ordinary solvents with the exception of cold ligroin. Attempts at nitration resulted unsuccessfully.

2 - Bromo - 3,5 - dimethoxy - 4 - ethoxyacetanilide, $Br(2)(CH_3O)_2(3,5)(C_2H_5O)(4)C_6H.NHCOCH_3$.—Two g. of the anhydrous dimethoxyacetophenetide was dissolved in 50 cc. of absolute chloroform, and a standardized solution (5 g. per 100 cc.) of bromine in the same solvent was then added slowly from a buret until a slight excess was evident by the persistence of the bromine color. The bromine solution added was decolorized instantly at first and an evolution of hydrogen bromide occurred. Excess of bromine was indicated after 27 cc. of the bromine solution had been added. The theory would require 26.8 cc. of the same solution for one mole bromine, *i. e.*, for the formation of a monobromo derivative. The solution was agitated with water containing sufficient sulfur dioxide to decolorize it. The chloroform layer was then washed with water, filtered through a dry paper, dried overnight with fused calcium chloride, the solution decanted and the solvent removed by careful evaporation. The colorless residual oil soon solidified, after which it was recrystallized from water, dried for three hours at 50° and analyzed with the following results:

Subs., 0.2506: AgBr, 0.1480.
Calc. for $C_{12}H_{16}O_4NBr$: Br, 25.2. Found: 25.2.

The product is soluble more or less freely in the ordinary solvents with the exception of cold water in which it dissolves with difficulty. It can therefore be recrystallized from the latter. That the bromine was attached to carbon and not to nitrogen in the final product was shown by the facts that it did not liberate iodine from an aqueous solution of potassium iodide when acidified with a little hydrochloric acid, nor did it liberate oxygen from hydrogen peroxide. While it might be urged that the method of preparation involving the concentration of the chloroform solution and recrystallization of the product from water would have caused a migration of the bromine from nitrogen to carbon, no effort was made to determine whether there was such an initial attachment of the bromine to the nitrogen or not.

Homoantiarol (1,3,4,5-Tetrahydroxybenzene - 3,5 - dimethyl - 4 - ethyl Ether).—Kiliani[1] isolated from *Antiaris Toxicaria* the substance known as antiarol, which Graebe and Suter later[2] showed to be 1,2,3,5-tetrahydroxybenzene-1,2,3-trimethylether. After many abortive attempts, we succeeded in preparing from the above dimethoxy-phenetidine a homolog of this antiarol which we have therefore designated as *homoantiarol*. The method which led finally to its synthesis was the following:

[1] *Arch. Pharm.*, **234**, 444 (1896).
[2] *Ann.*, **340**, 225 (1905).

One g. of the powdered amine hydrochloride was dissolved in 235 cc. water, 33 cc. conc. hydrochloric acid added, the solution cooled to 5° and diazotized by adding slowly with stirring two cc. (slightly more than theory) of a solution containing 16.7 g. sodium nitrite per 100 cc. After standing 4 minutes, the yellow solution gave a positive starch-iodide test for free nitrous acid. The solution then was poured as rapidly as possible with constant stirring into 200 cc. water heated to 90°. The resultant clear yellow solution was placed immediately on a boiling water bath and stirred vigorously until no red coloration was produced on adding a drop to an alkaline β-naphthol solution (15 minutes). In this way, no tar was formed and the solution remained clear yellow. After cooling the solution under running water, it was extracted with three 100 cc. portions of chloroform, the chloroform extracts filtered, dried overnight with anhydrous sodium sulfate, the chloroform filtered off, and all but a few cubic centimeters removed by distillation on a boiling water bath, the remainder being driven off by heating in an oven at 50°. The total yield of this crude material from 5 separate runs was 2.8 g. As thus obtained, it was a crystalline material contaminated by a small amount of resin. By recrystallization from ligroin in the presence of boneblack, it was secured in long, hair-like, pale yellow needles; m. p., 119° (corr.). Even at 100°, it slowly volatilized. Yield, 0.5 g., or 12% of the theory.

Large excess of hydrochloric acid and low concentration of diazonium chloride were used in the above method to avoid coupling and tar formation.

Subs., 0.2202: CO_2, 0.4893; H_2O, 0.1350.

Calc. for $C_{10}H_{14}O_4$: C, 60.7; H, 7.1. Found: C, 60.6; H, 6.9.

The compound is difficultly soluble in cold ligroin but more or less readily soluble in the other ordinary solvents. The presence of a free hydroxyl group was demonstrated by the following reactions: (1) an aqueous solution became green on addition of a trace of ferric chloride; (2) the substance dissolved readily in aqueous sodium hydroxide solution; (3) an aqueous solution of the compound became turbid on addition of bromine water; (4) dilute aqueous potassium permanganate solution was decolorized by the addition of an aqueous solution of the compound; (5) hydrogen was evolved when metallic sodium was allowed to act on a dry benzene solution of the compound; (6) it dissolved to a colorless solution in conc. sulfuric acid which changed to a pale red when a trace of solid titanium dioxide was added.

The phenyl ether of homoantiarol could not be prepared by extracting the diazotized amine hydrochloride from its aqueous solution by means of phenol and heating the resultant dark phenol layer according to the method of Hirsch.[1]

3,5-Dimethoxy-4-ethoxy-iodobenzene.—0.77 g. dimethoxy-phenetidine

[1] *Ber.*, **23**, 3707 (1890).

hydrochloride was dissolved in 50 cc. water, two cc. conc. hydrochloric added, the solution cooled to zero, and diazotized by adding slowly a 17% aqueous solution of sodium nitrite drop by drop with stirring, until a faint starch iodide test for free nitrous acid was obtained. After standing 10 minutes at 0°, a solution of one g. (theory 0.6 g.) potassium iodide in two cc. water (cooled to 0°) was added a drop at a time with constant stirring. A buff-colored precipitate separated. The mixture was then stirred for 20 minutes at 0° and gently heated from time to time on a warm water bath until the evolution of gas ceased, regulating the time intervals between successive heatings so that the decomposition of the diazonium iodide proceeded slowly, as indicated by the rate of evolution of nitrogen. A dark oil appeared under the aqueous layer. The mixture was cooled, made strongly alkaline with excess of aqueous sodium hydroxide solution while cooling, in order to remove most of the free iodine, extracted with ether, the ether extract filtered, dried with solid sodium hydroxide overnight, again filtered, and the solvent removed on a warm water bath. A pale yellow oil remained which, on cooling and scratching the sides of the vessel, solidified to a crystalline mass. Recrystallization from dil. alcohol containing a little sulfurous acid, and in the presence of boneblack, gave yellow needles, m. p. 53° (corr.); yield, 0.7 g., or 69% of the theory.

The substance has a powerful odor, resembling iodoform, and is easily soluble in most organic solvents and but difficultly soluble in cold water.

Subs., 0.1160: AgI, 0.0880.
Calc. for $C_{10}H_{13}O_3I$: I, 41.3. Found: 41.0.

3,5-Dimethoxy-4-ethoxyphenylurea (3,5-Dimethoxydulcin).—Two g. of the amine hydrochloride was dissolved in 20 cc. water and a solution of 0.8 g. (theory 0.7 g.) potassium cyanate in 5 cc. water was added slowly with stirring. A precipitate consisting of white needles soon separated with a slight evolution of heat. After standing in the icebox for an hour, it was filtered out, washed with water and dried on a porous tile, m. p. 182° (corr.); yield, 1.6 g., or 80% of the theory.

Prepared in this way, the compound was practically pure, the melting point remaining unchanged on recrystallization from water.

Subs., 0.5147: 0.1 *N* H_2SO_4 neutralized, 42.05 cc.
Calc. for $C_{11}H_{16}O_4N_2$: N, 11.7. Found: 11.5.

The substance is readily soluble in alcohol, acetone, glacial acetic acid or boiling water, slightly soluble in ether or warm chloroform; difficultly soluble in ligroin, carbon tetrachloride, carbon disulfide, ethyl acetate, benzene or cold water. It is worthy of note that while dulcin itself is remarkable for its sweet taste, this derivative is practically tasteless.

3,5-Dimethoxy-4-ethoxy-*s*-diphenylurea (3,5-Dimethoxy-4-ethoxycarbanilide).—0.3 g. freshly prepared dimethoxy-phenetidine was triturated

with 50 cc. absolute ether, the solution filtered from a small amount of insoluble blue amorphous material, and a solution of 1.5 g. (theory 0.2 g.) phenyl isocyanate in 20 cc. absolute ether added with constant stirring. A voluminous precipitate of microscopic needles soon appeared. After standing evernight, these were filtered out, washed with ether, dried on a porous tile and recrystallized from dil. alcohol. Long, hairlike, white needles, m. p. 185° (corr.), were thus obtained in a yield of 0.1 g., or 21% of the theory.

Subs., 0.0803: 0.025 *N* H_2SO_4 neutralized, 20.60 cc.
Calc. for $C_{17}H_{20}O_4N_2$: N, 8.9. Found: 9.0.

The compound is easily soluble in alcohol or glacial acetic acid, slightly soluble in ether or boiling water, and difficultly soluble in boiling ligroin or cold water. It may be of interest to note that while there is a difference of 91° between the melting points of phenylurea itself and carbanilide, the difference in melting points of the dimethoxyethoxy derivatives described above is but 3°. That the derivatives referred to are not identical, was further indicated by the melting point of a mixture of the two which showed a range of 157–170°.

3,5-Dimethoxy-4-ethoxybenzene-azo-β-naphthol (3,5-Dimethoxyphenetidine-azo-β-naphthol).—Two g. of the powdered amine hydrochloride was dissolved in 35 cc. water, 1.5 cc. conc. hydrochloric acid added, and the solution cooled to 0–5° in an ice bath, and 4 cc. (slight excess above theory) of a sodium nitrite solution containing 16.7 g. per 100 cc. slowly added with stirring. A few minutes later the clear, yellow solution was slowly poured into an aqueous solution of 1.4 g. (theory 1.2 g.) β-naphthol in 30 cc. (theory 15 cc.) of 10% sodium hydroxide solution stirring vigorously and maintaining the temperature at about 5°. The stirring was continued for one minute after all of the solution had been added, the voluminous vermilion precipitate was then filtered out, washed with water, dried, and recrystallized to constant melting point from ligroin. Dark red plates of a bronze metallic lustre resulted; m. p., 130° (corr.); yield, 2.0 g., or 67% of the theory.

Subs., 0.7103: 0.1 *N* H_2SO_4 neutralized, 39.10.
Calc. for $C_{20}H_{20}O_4N_2$: N, 7.9. Found: 7.7.

In the determination of nitrogen by the Kjeldahl method, it was necessary to dissolve the compound in conc. sulfuric acid and reduce with zinc dust in order to prevent loss of nitrogen before continuing the usual analytical procedure.

This azo dye readily forms a deep red solution in alcohol, benzene, glacial acetic acid, conc. hydrochloric or conc. sulfuric acid, or boiling ligroin. It is but slightly soluble in cold ligroin, boiling water or hot aqueous sodium hydroxide. Its slight solubility in the latter indicates that it probably possesses the usual hydrazone or quinone structure

characteristic of azo dyes formed by the coupling of diazonium salts with β-naphthol, the diazo group being alpha to the hydroxyl. Dropped on heated porcelain, the compound puffs suddenly in dense, red fumes and on combustion leaves no ash.

Ten g. skeins of silk, wool and cotton were dyed by developing the color directly in the fibre, by passing the wet skeins first through a bath containing 0.5 g. of the diazonium chloride and one cc. conc. hydrochloric acid in 300 cc. water, and then through a solution of 0.2 g. β-naphthol and one g. sodium hydroxide in 300 cc. water. The silk and cotton were dyed salmon pink, the wool a bright orange without exhausting the baths. The color proved fast to water, soap, dilute acid and light.

NEW YORK, N. Y.

[CONTRIBUTION FROM THE SHEFFIELD CHEMICAL LABORATORY OF YALE UNIVERSITY.]

RESEARCHES ON PYRIDINES. LXXXVIII. THE SYNTHESIS OF CYTOSINE ALDEHYDE.

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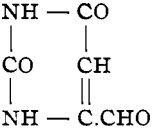
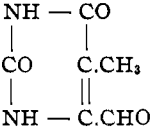
Received March 1, 1919.

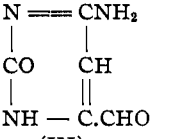
Comparatively little is known about pyrimidine aldehydes. Uracil-aldehyde (I), the first of the series of these interesting compounds to be described, was prepared by Johnson and Cretcher[1] and the only other representative known, namely, thymine-aldehyde (II), was prepared by the same investigators somewhat later.[2] In order to extend our knowledge of this class of compounds we decided to prepare cytosine-4-aldehyde (III), and the object of this paper is to give a description of a method of synthesis which gives promise of enabling us to prepare this combination in quantity. Our work, however, has not been brought to a satisfactory conclusion and this paper therefore deals only with the chemistry of the preliminary reactions involved in the process.



(I).



(II).



(III).

As the starting point of a cytosine aldehyde synthesis we selected the acetal of 2-ethylmercapto-6-oxy-4-aldehydopyrimidine (V), which was first described by Johnson and Cretcher,[3] and subjected this to the action of phosphorus halides ($POCl_3$ and PCl_5) in order to obtain the imide chloride or its chloro-ether as represented by Formulas VI and IV, respectively. To our surprise the product of the reaction proved to be the true

[1] THIS JOURNAL, **37**, 2144 (1915).

[2] *J. Biol. Chem.*, **26**, 99 (1916).

[3] *Loc. cit.*