It is obtained from water in crystalline aggregates; m. p., 165–166° (uncorr.), giving an intense violet coloration with ferric chloride.

Anal. Calcd. for $C_{10}H_{10}O_4$: C, 61.84; H, 5.20. Found: C, 61.75; H, 5.76.

Mol. wt. (Rast[17]) Subs., 0.0210 g. in 0.2759 g. of camphor: Δt, 14°. Calcd. for $C_{10}H_{10}O_4$: mol. wt., 194. Found: 222.5.

My thanks are due to Mr. E. Tilly who carried out the determinations of the phenol coefficients according to the method of the Hygienic Laboratory.

Summary

In order to obtain more data on the influence of introduction of aryl and alkyl groups into the nucleus of polyphenols on the germicidal action, a number of new compounds were prepared and their phenol coefficients determined. Methods are given for the preparation of *m*-dihydroxydiphenylpropane, *m*-trihydroxydiphenylpropane, diethyl-, dipropyl-, dibutyl-, dihexyl- and dodecylresorcinol and triethylphloroglucinol and the corresponding mono-, di- and triketo compounds from which they are derived. The antiseptic actions of these compounds and their dependence upon the introduced side chains are discussed and a chemical explanation is attempted. Halogen alkyl compounds could not be obtained since the halogen is either split off when the reduction of the keto compound is attempted or a coumaranone derivative forms when the keto-imide is to be transformed into the ketone.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF SASKATCHEWAN]

STUDIES IN URETHANS. II. ISOMERIC URETHAN DERIVATIVES OF PHENYLACETIC ACID, AND SOME RELATED COMPOUNDS

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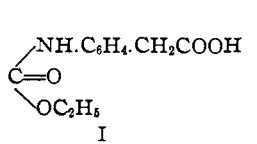
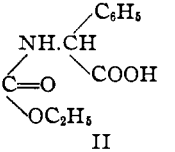
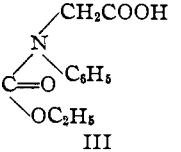
This study was undertaken in order to compare the physiological action of the three isomeric urethans, *p*-carbethoxy-aminophenylacetic acid (I), *dl*-α-carbethoxy-aminophenylacetic acid (II), and N-carbethoxy-phenylglycine (III).



I



II



III

Urethans in general are depressing to the central nervous system, and some of those containing aromatic radicals are antipyretic (for ex-

[17] Rast, *Ber.*, **55**, 1051 (1922).

ample, phenylurethan, *p*-ethoxy-phenylurethan). Another effect that may be related to some extent to the antipyresis is a diminution in tone and rhythmic movement of involuntary muscle in a variety of tissues.[1]

The last effect might well be expected in Substances I and II since they contain substituted benzyl groups in addition to the urethan group. While the carboxyl group might tend to offset the expected properties, it affords the opportunity of converting the compounds into alkali salts or esters at will, and of producing corresponding changes in the solubility relations of the compounds.

Preliminary experiments with some of the compounds prepared have been carried out on rabbits. No well-defined systemic effects have been obtained. The compounds seem to be non-toxic and generally inert. Detailed studies now in progress, especially on the action on smooth muscle tissues, will be reported elsewhere.

Experimental Part

***p*-Carbethoxy-aminophenylacetic Acid,** $C_2H_5O.OC.NH.C_6H_4.CH_2.COOH$.—This was prepared by dissolving 5 g. of *p*-aminophenylacetic acid in a slight excess of sodium hydroxide solution and adding the calculated amount of ethyl chlorocarbonate during vigorous shaking and cooling. A heavy, pale yellow precipitate was formed, the reaction being complete in 15 to 20 minutes. The product was dissolved in dil. sodium hydroxide solution and reprecipitated with hydrochloric acid. Colorless crystals were obtained; m. p., 125°; yield, 93%. The acid is only slightly soluble in water.

Anal. Calcd. for $C_{11}H_{13}NO_4$: N, 6.28. Found: 6.34.

Sodium Salt.—The acid was dissolved in an excess of sodium hydroxide, the solution made exactly neutral, and evaporated to dryness on the hot-plate at 60–65°. The solid residue was extracted with alcohol and the solution filtered. From the concentrated alcoholic solution, colorless crystals separated. They sintered at 168–170°; yield, 60–65%.

The ester was obtained in a 92% yield by heating an absolute alcoholic solution of the acid with dry hydrogen chloride, and allowing the mixture to stand in the ice box overnight. A heavy white precipitate was obtained, which after recrystallization from alcohol melted at 80°.

Anal. Calcd. for $C_{13}H_{17}NO_4$: C, 62.15; H, 6.77; N, 5.58. Found: C, 61.91; H, 6.57; N, 5.57.

During the course of this experimental work both the ester and the carbethoxy-amino acid were hydrolyzed in alkaline solution. After the reaction mixture had been heated for half an hour or so, and the liquid neutralized with acid, a small amount of white, gelatinous precipitate was obtained, which was filtered off. The filtrate was evaporated to dryness and the residue extracted with alcohol. The alcoholic solution yielded glassy, brownish crystals of the sodium salt of *p*-aminophenylacetic acid, containing alcohol of crystallization. The crystals melted at 69° and after being kept in a desiccator over sulfuric acid effloresced to a brown powder; m. p., 130–135°.

If the hydrolysis was prolonged, it was found that larger and larger amounts of the white gelatinous material were obtained and smaller quantities of the sodium salt of the amino acid.

[1] Franklin, *J. Pharmacol.*, **26**, 227 (1925).

Ethylation of *p*-Carbethoxy-aminophenylacetic Ethyl Ester

Attempts were made to ethylate the alpha carbon atom of the ester by the usual method with sodium and ethyl iodide in absolute alcoholic solution, but without success. The ester was always recovered unchanged.

Ethylation of the nitrogen of the carbethoxy-amino group was moderately successful by the use of diethyl sulfate.

Ammonium Salt of *p*-Carbethoxy-ethylaminophenylacetic Acid, $C_2H_5OOC.N(C_2H_5).C_6H_4.CH_2.COONH_4$.—To 4 g. of the ester dissolved in 50 cc. of absolute alcohol was slowly added 8 cc. of diethyl sulfate. The mixture was shaken and warmed to 60° during the operation, after which it was refluxed for one hour. Twenty-five cc. of concd. ammonium hydroxide was added to destroy unchanged diethyl sulfate, and the mixture allowed to stand overnight in the ice chest. A precipitate of unchanged ester was filtered off, and the filtrate concentrated and strongly cooled. Crystals were obtained that melted at 99–100°. They were very soluble in water and evolved ammonia on being warmed with alkali.

Anal. Calcd. for $C_{13}H_{20}N_2O_4$: N, 10.46. Found: 10.54.

***dl*-α-Carbethoxy-aminophenylacetic Acid,** $C_6H_5.CH(NHCOOC_2H_5)COOH$.—The amino group of the α-aminophenylacetic acid appeared at first to be very unresponsive to the action of ethyl chlorocarbonate. When the two compounds were refluxed together there was no sign of reaction. This may have been due to the insolubility of the acid in the ester. The reaction was found to proceed slowly but fairly completely in an aqueous medium.

Four g. of the acid was dissolved in 13 cc. of 10% sodium hydroxide solution and 150 cc. of water was added. The calculated amount of ethyl chlorocarbonate was added in small portions during thorough shaking. After several hours a pale yellow oil separated and was extracted with ether. After removal of the ether by evaporation, the oil was cooled in a freezing mixture but failed to solidify. It was found in a subsequent preparation that the oil solidified when allowed to stand in contact with the aqueous reaction medium for 48 hours in the ice chest. The solid was recrystallized from alcohol and gave small, colorless crystals; m. p., 121–122°; yield, 80%.

Anal. Calcd. for $C_{11}H_{13}NO_4$: N, 6.28. Found: 6.35.

SODIUM SALT.—This was prepared by dissolving the acid in a slight excess of sodium hydroxide, making the solution exactly neutral and evaporating to dryness. The residue was extracted with alcohol and the extract concentrated. As the salt failed to crystallize, the solution was cooled in a freezing mixture and 15–20 volumes of ether was added. After 12 hours in the ice box, a white precipitate of the salt was obtained. Precipitation continued for five or six days. The product consisted of fine, colorless crystals that sintered at 210° and decomposed with effervescence at 220–225°.

Anal. Calcd. for $C_{11}H_{12}NO_4Na$: N, 5.72. Found: 5.61.

N-Carbethoxy-N-phenylglycine, $C_2H_5OOC.N.(C_6H_5).CH_2.COOH$.—This was prepared according to the method of Leuchs and Manasse[2] in somewhat similar manner to the α-carbethoxy-amino acid described above.

[2] Leuchs and Manasse, *Ber.*, **40**, 3235 (1907).

SODIUM SALT.—This was prepared in the same manner as the salt of α-carbethoxy-aminophenylacetic acid. It gave small crystals, easily soluble in water and in 90–95% alcohol and only slightly soluble in absolute alcohol; yield, 45%; m. p., 227°.

Anal. Calcd. for $C_{11}H_{12}NO_4Na$: N, 5.72. Found: 5.81.

p-Carbethoxy-aminobenzoic Acid, $C_2H_5OOC.NH.C_6H_4.COOH$.—This and its ethyl ester were prepared in order that their physiological actions might be compared with those of the corresponding phenylacetic acid compounds. *p*-Aminobenzoic ethyl ester has local anesthetic properties and it seemed likely that its carbethoxy derivative would have similar properties, while the corresponding phenylacetic compound should not, if Kamm's generalization[3] is true.

Three g. of *p*-aminobenzoic ethyl ester was refluxed with sodium hydroxide until saponification was complete. The solution was almost neutralized with hydrochloric acid, the calculated amount of ethyl chlorocarbonate was added and the mixture was shaken and cooled. A heavy, pink precipitate was formed. The product was dissolved in sodium hydroxide solution and reprecipitated with hydrochloric acid. The crystals were faintly pink, m. p., 201°; yield, 95%.

Anal. Calcd. for $C_{10}H_{11}NO_4$: N, 6.70. Found: 6.61.

***p*-Carbethoxy-aminobenzoic Ethyl Ester,** $C_2H_5OOC.NHC_6H_4.COOC_2H_5$.—A solution of 3 g. of *p*-aminobenzoic ethyl ester in 75 cc. of ether was shaken with 6 cc. of ethyl chlorocarbonate in the presence of 20 cc. of 10% sodium hydroxide solution. After two hours the ether layer was evaporated and the solid residue recrystallized from alcohol; m. p., 130°; yield, 84%.

Anal. Calcd. for $C_{12}H_{15}NO_4$: N, 5.91. Found: 5.97.

Summary

1. The preparation of isomeric urethan derivatives of phenylacetic acid and some related compounds is described.

2. The following new compounds were prepared: *p*-carbethoxy-aminophenylacetic acid, and its sodium salt and ethyl ester, *dl*-α-carbethoxy-aminophenylacetic acid and its sodium salt, the sodium salt of N-carbethoxy-phenylglycine, *p*-carbethoxy-aminobenzoic acid and its ethyl ester, the ammonium salt of *p*-carbethoxy-ethylaminophenylacetic acid.

3. No definite systemic effects have been observed in the preliminary pharmacological study of these compounds.

SASKATOON, CANADA

[3] Kamm, THIS JOURNAL, **42**, 1030 (1920).