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NEW BENZYL ESTERS POSSESSING AN ANTI-SPASMODIC ACTION.

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The anti-spasmodic action of the combined opium alkaloids has been shown by Macht[1] to be due to the presence of the benzyl nucleus in the alkaloids of the papaverine group. Simpler compounds containing the benzyl nucleus have the same action. Thus benzyl alcohol, some of its esters, and benzaldehyde have been shown to possess anti-spasmodic properties. Veratryl and piperonyl alcohols, piperonal, vanillin, and veratryl aldehyde, and *o*- and *p*-hydroxy-benzaldehyde possess this action to a higher degree than do benzyl alcohol and benzaldehyde.[2] This inhibitory action, present in benzyl alcohol and benzaldehyde is lost in benzoic acid. Apparently the benzyl group acts upon the muscle cell itself and not upon the ends of the nerve fiber in the muscle.

Considerable attention has been directed to the therapeutic value of some of the known esters of benzyl alcohol. As no information was available, however, concerning the benzyl esters of the higher fatty acids, of the amino-sulfonic acids, of the aliphatic and aromatic amino acids or of the sulfo-benzoic acids, the benzyl esters of a number of these acids were prepared, and their physical properties and their therapeutic activity determined.[3]

Benzyl laurate, myristate, palmitate, stearate, and oleate were first prepared. The benzyl esters of the saturated higher fatty acids are tasteless, odorless liquids or low melting solids. The esters of both the saturated and unsaturated higher fatty acids are insoluble in water but are readily soluble in chloroform, ether, and benzene; and somewhat less soluble in alcohol, olive oil and petroleum oil. The slight but distinct local anesthetic effect noticeable in the lower esters, as well as their irritating action on the mucous membrane was absent in the higher esters, due presumably to their low solubility. Because of the insolubility of these esters the usual physiological tests on animals or on excised tissues were not entirely satisfactory as a means of estimating their relative activity on smooth muscle structure. Clinical tests were, therefore, resorted to, which demonstrated the anti-spasmodic action of these esters in asthma, dysmenorrhea, high blood pressure, pylorospasm and spastic constipation.

While these esters are very resistant to hydrolysis by steam, they are readily hydrolyzed by the action of lipase. In one case the benzyl ester

[1] Macht, *J. Pharmacol.*, **9**, 287 (1917); **11**, 263 (1918).

[2] Unpublished work from the Department of Experimental Medicine.

[3] In preparing these esters the desirability of securing a solid ester free from a disagreeable taste or irritating effect upon the mucous membrane was always considered.

of commercial stearic acid was hydrolyzed to the same extent as was the olive oil which was used as a control. When the aliphatic acids are replaced by the aromatic acids a very marked reduction of the rate of hydrolysis occurs. Fig. 1 gives the results in graphic form.

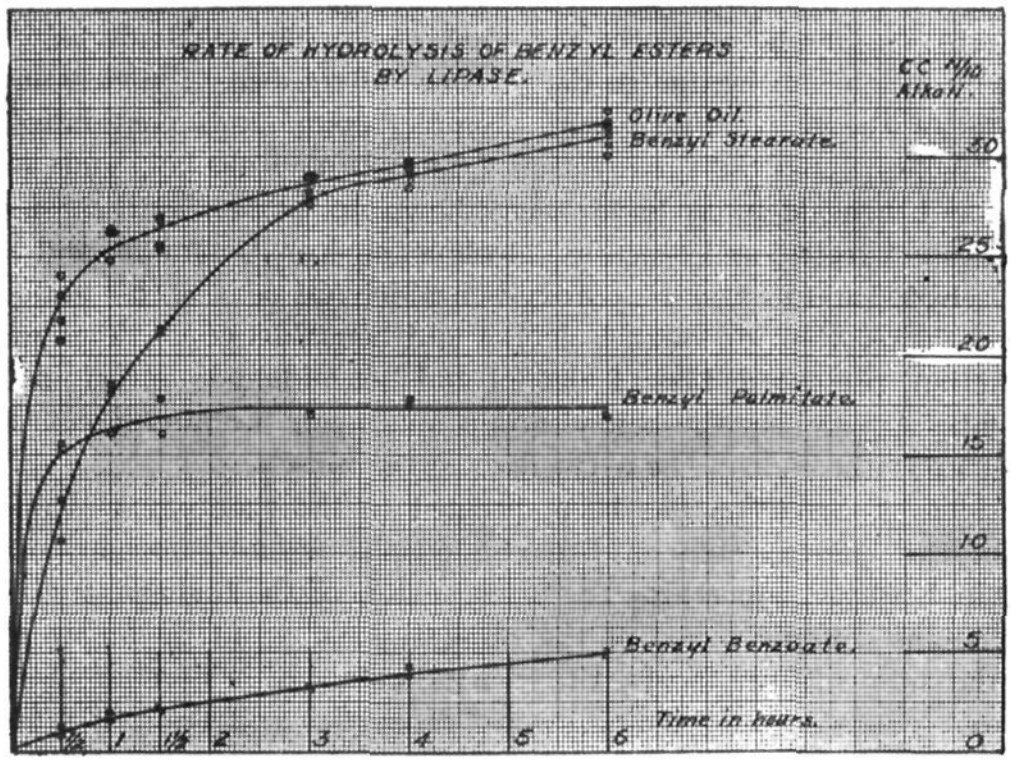

Fig. 1.

Of the esters of the aromatic amino benzoic acids, benzyl *p*- and *m*-amino-benzoates were prepared. Because of the insolubility of their hydrochlorides and because of their irritating effect on mucous membrane, they were not tested for anti-spasmodic action. Both esters possess local anesthetic properties.

Benzyl lactate was prepared but because of its irritating effect was not tested clinically.

The benzyl esters of the individual fatty acids such as stearic or palmitic have nothing to recommend their therapeutic use over that of the benzyl esters of mixtures of fatty acids derived from naturally occurring sources; consequently various fats and oils were saponified and the benzyl esters of the resulting mixtures of fatty acids were prepared. Since it was found that mixtures of fatty acids containing any considerable amount of unsaturated fatty acids formed colored esters which possess an unpleasant taste, attention was given to the preparation of the benzyl esters of those acid mixtures which were saturated, and especially to the preparation of the benzyl esters of commercial stearic acid. These mixed esters were found to be identical in therapeutic action with those of the individual esters.

Experimental.

The benzyl alcohol used was prepared partly from benzaldehyde by the Cannizzaro reaction and partly by boiling benzyl chloride with a solution of sodium carbonate.

Preparation of the Acid Chlorides and of the Benzyl Esters.—The chlorides of the fatty acids used in the preparation of the benzyl esters were formed by treating the acids either with phosphorus pentachloride or thionyl chloride. About 10% excess of the theoretical amount of phosphorus pentachloride was added to the acid and the reaction allowed to proceed at room temperature. When the reaction was completed, the phosphorus trichloride formed was removed by vacuum distillation and the resulting acid chloride purified by distilling at a pressure of 10 mm. to 20 mm. In no case was it possible to secure more than 50% of the theoretical yield by this method, while the usual yield was about 30%.

An unsuccessful attempt was made to replace phosphorus pentachloride with phosphorus trichloride. Although a reaction occurred, all attempts to separate any acid chloride by vacuum distillation failed.

Thionyl chloride was found to be the best chlorinating agent. Five times the theoretical amount of thionyl chloride was added to the acid and the reaction allowed to proceed at room temperature. Upon its completion the reaction flask was placed on the water-bath and the excess of thionyl chloride was distilled off. The acid chloride secured in this manner was sufficiently pure to be used without further treatment.

The esters were prepared by allowing benzyl alcohol to react with an ethereal solution of the acid chloride prepared by one of the 2 above methods. They were subsequently purified either by crystallization from alcohol or by vacuum distillation.

Benzyl laurate.—The lauric acid used was prepared from the fatty acids of coconut oil and had a melting point of 43.3°.[1] Benzyl laurate boils at 209–211° (12 mm.), melts at 8.5°, has d_{25}^{25} 0.9457, and n^{24} 1.4812.

Benzyl myristate.—The myristic acid was prepared by saponifying the colored fat secured by exhaustively extracting ground nutmegs with ether and alcohol.[2] After recrystallizing 3 times from alcohol, the acid melted at 54–55° and had a molecular weight of 229. Four pounds of nutmegs gave 132 g. of the pure acid. Benzyl myristate boils at 229–231° (11 mm.), melts at 20.5°; has d_{25}^{25} 0.9321; and n^{24} 1.4803.

Benzyl palmitate.—The palmitic acid was prepared by saponifying bayberry wax and recrystallizing the acid 4 or 5 times from alcohol.[2] The yield was about half the initial weight of the wax. It has a melting point of 62–63° and a molecular weight of 259. Benzyl palmitate melts at 36.0°; has d_{25}^{38} 0.9136; and n^{50} 1.4689.

Benzyl stearate.—The stearic acid was prepared by saponifying cocoa butter and recrystallizing the acids secured from alcohol until a constant melting point was secured.[3] Ninety-five g. of stearic acid with a melting point of 68–69° and a molecular weight of 283 was secured from one kg. of cocoa butter. Benzyl stearate melts at 45.8°; has d_{25}^{50} 0.9075; and n^{50} 1.4663.

Benzyl oleate.—The oleic acid was prepared from tallow by the usual lead salt method. The acid secured had an iodine value of 91.5 and a molecular weight of 284. Benzyl oleate boils at 237° (7 mm.), and is liquid at 0°. It has d_{25}^{25} 0.9330, and n^{25} 1.4875.

Benzyl lactate.—This ester was prepared by heating benzyl alcohol with lactic

[1] Secured from the Department of Chemistry, University of Illinois.

[2] Prepared according to directions kindly furnished by Dr. G. D. Beal, University of Illinois.

[3] Hehner and Mitchell, THIS JOURNAL, **19**, 32 (1897).

acid which had previously been freed from water by heating to 180°. Dry hydrogen chloride was used as a catalyzer. It was found necessary to keep the temperature between 220° and 230° for 10 to 12 hours in order to secure esterification. Upon fractionation, benzyl lactate was secured, in the fraction boiling at 128–130° (5–6 mm.). The ester has n^{25} 1.5252.

Benzyl amino Benzoates.—The benzyl ester of *p*-amino-benzoic acid was prepared by allowing theoretical amounts of *p*-nitro-benzoyl chloride to react with benzyl alcohol in dry ether. The theoretical yield of the nitro-ester melting at 84.7° was secured. The amino ester was secured by reducing the latter either by tin in alcoholic hydrochloric acid or by powdered iron and hydrochloric acid. The hydrochloride of this ester is a white crystalline solid melting at 184° with the formation of a slight amount of gas. On analysis 13.41% of chlorine was found, the calculated amount being 13.47%. The free base is a yellow viscous liquid having no definite melting point and becoming wax-like on standing. Neither the ester, the ester hydrochloride, nor lactate was appreciably soluble in water.

Benzyl-*m*-amino-benzoate was prepared in the same manner. The benzyl-*m*-nitro-benzoate is a light yellow liquid which boils at 308° (760 mm.), The amino ester is a dark liquid forming a crystalline hydrochloride which has no definite melting point.

Other Benzyl Esters.—The benzyl ester of *o*-sulfo-benzoic acid could not be prepared either from the acid chloride or from the alcohol and the acid. In both cases a syrup-like material was secured which could not be resolved into a definite substance.

Glycocoll, heated at 120° to 140° with an excess of benzyl alcohol in the presence of a stream of dry hydrogen chloride for 8 hours, was not esterified.

The Rate of Hydrolysis of Benzyl Esters by Lipase.—A 5% acacia emulsion was made of the ester and the aqueous extract of fresh pancreas in such a manner that each 20 g. of the emulsion contained 2.25 g. of the ester, the extract of one g. of pancreas, and 0.15 g. of sodium tauroglycocholate. This emulsion was incubated in 20-g. duplicate samples for the desired periods of time. During the incubation, the samples were frequently agitated since the emulsion showed a slight tendency to break up. At the end of the incubation period, the samples were removed and immersed in boiling water for 10 minutes. They were then cooled and 60 cc. of a neutral mixture of 5 parts of alcohol and one part of ether was added. They were titrated with 0.1 *N* sodium hydroxide, using phenolphthalein as an indicator. The end-point was taken as that point at which the pink color persisted for 30 seconds.

A control was run with olive oil in place of the ester and a blank was made up in the same manner but containing neither the oil nor the ester. In this way correction was made for the hydrolysis of the fat contained in the pancreatic extract. The results are reported in terms of 0.1 *N* alkali required.

TABLE I.—RATE OF HYDROLYSIS OF BENZYL ESTERS BY LIPASE.

(Results in cc. of 0.1 *N* alkali).

Time: hours.	½.	1.	1½.	3.	4.	6.
Olive oil	23.0	26.5	26.7	28.9	29.5	31.6
5–5–20	24.0	26.4	26.8	28.8	29.8	31.7
Olive oil	20.6	24.9	26.2	28.7	29.4	32.3
5–6–20	21.8	26.4	25.5	27.6	28.4	27.6
Benzyl stearate	10.6	18.2	21.0	28.2	29.2	31.0
5–5–20	12.9	18.5	..	27.7	29.0	30.6
Benzyl palmitate	15.5	16.1	16.0	16.9	17.5	16.8
5–6–20	15.0	16.0	17.8	17.2	17.7	16.8
Benzyl benzoate	1.2	1.9	2.1	3.1	3.9	4.8
5–6–20	0.9	2.0	2.1	3.1	4.1	4.8

Reaction of Benzyl Chloride with the Sodium Salts of the Higher Fatty Acids.—The usual laboratory methods of esterification are not feasible for the production of large amounts of the benzyl esters of the higher fatty acids. It was found, however, that such benzyl esters could be readily prepared by allowing benzyl chloride to react with the anhydrous alkali salt of the fatty acid dissolved in an excess of that acid.

The acid was first heated to 150–170° and half neutralized with anhydrous or mono-hydrated sodium carbonate. At this temperature the soap formed was completely dissolved. Benzyl chloride was then added in an amount ufficient to react completely with the sodium salt and the temperature kept at 170° to 180° for several hours when the reaction was completed. Half of the remaining acid was then neutralized and an amount of benzyl chloride sufficient to react with it added. By repeating this process the acid can be converted into the benzyl ester without the addition of any solvent or catalyzer. The temperature should not be allowed to go above 200° and the mixture must be stirred to prevent foaming and charring.

When the esterification is completed the sodium chloride is removed by washing with water, the ester is crystallized from alcohol, and any trace of benzyl chloride left is removed by steam distillation.

Commercial stearic acid having a melting point of 55–56° and an iodine value of 2 to 3 was esterified by this method. The resulting benzyl stearate which melts at 30–34° can be resolved into fractions melting from 12° to 39° by fractional crystallization from alcohol.[1]

Summary.

1. Methoxy and hydroxy derivatives of benzyl alcohol and benzaldehyde possess marked anti-spasmodic action.

2. The benzyl esters of the higher fatty acids are tasteless, odorless, liquids or low-melting solids possessing anti-spasmodic action. They are more readily hydrolyzed by lipase than are the benzyl esters of aromatic acids.

3. Benzyl chloride readily reacts with the alkali salts of the higher fatty acids when they are dissolved in the hot acid, forming the benzyl ester of these acids.

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[1] In the course of this investigation the following new compounds were prepared and identified, benzyl laurate, benzyl myristate, benzyl palmitate, benzyl stearate, benzyl oleate, benzyl lactate, benzyl-*p*-amino-benzoate, benzyl-*m*-nitro-benzoate, and benzyl-*m*-amino-benzoate.