In this connection it may be of interest to note that the well known reaction

$$HCOOH = CO_2 + H_2$$

catalyzed by copper, according to an experiment of mine also proceeds with formation of an excess of carbon dioxide, presumably on account of reduction of formic acid.[1]

Summary.

Experiments are reported showing that the reactions $CH_3OH + H_2O = CO_2 + 3H_2$ and $CH_2O + H_2O = CO_2 + 2H_2$ proceed when suitable vapor mixtures are led through finely divided reduced copper at temperatures about 230° to 250°.

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[CONTRIBUTION FROM THE ABBOTT LABORATORIES.]

PREPARATION AND HYDROLYSIS OF BENZYL ESTERS.

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In his classical researches on the therapeutic properties of combined opium alkaloids, and particularly of the alkaloids of the papaverine group, Macht[1] found that the antispasmodic effect of these compounds is due to the benzyl nucleus. This discovery was followed by his investigation of two simple organic esters of benzyl alcohol, namely, benzyl acetate and benzyl benzoate. It was found that the former is undesirable due to gastric disturbances which it induces, whereas benzyl benzoate is quite effective in relaxing unstriped muscle, and is better tolerated than benzyl acetate.

Up to the present time benzyl benzoate is the only benzyl ester which has come into extended use, although benzyl stearate and benzyl succinate have recently been introduced. The chief obstacle in studying new benzyl esters is the difficulty of determining the relative merits of the various esters by any methods that are rapid and fairly accurate. The general insolubility of the esters in water makes pharmacological tests difficult. Hence, in determining the comparative values of new benzyl esters, actual clinical use has always been necessary in spite of the length of time and of the uncertainties incident to such examinations.

A rapid chemical method of gaining a preliminary idea of the value of these esters would be extremely desirable. In devising such a test, it would be necessary to know whether the effect of benzyl esters is due to the entire benzyl ester molecule or to benzyl alcohol formed by hydrolysis of the ester in the body. The fact that benzyl benzoate and benzyl

[1] Cf. Sabatier, "Die Katalyse in der organischen Chemie," Leipzig, **1914**, p. 151.

[1] Macht, *J. Pharmacol.*, **9**, 287 (1917); **11**, 389–446 (1918).

acetate are excreted as hippuric acid and that benzyl alcohol itself has a relaxing effect on unstriped muscle[2] seems to indicate that the effect is due, to some extent at least, to the hydrolysis of the esters. If it develops that the action is due to the benzyl alcohol split off in the body by hydrolysis, it is very probable that the therapeutic effects would be proportional to the rates of hydrolysis of the esters. On the other hand, if the effect is due to the intact benzyl ester molecule, the esters that are more slowly hydrolyzed in the body would probably have the more pronounced action.[3]

We have, therefore, determined the rates of hydrolysis of a number of benzyl esters in dil. alcoholic potassium hydroxide solution. A comparison of these data with the corresponding pharmacological and clinical tests should go far towards indicating the basis on which the therapeutic action of these compounds rests.

The benzyl esters investigated were the benzoate, acetate, cinnamate, salicylate, *p*-aminobenzoate, stearate, fumarate, succinate and acetylsalicylate.

Preparation of the Esters.

Good grades of commercial benzyl benzoate (boiling at 222 to 225°, at 40 mm.) and benzyl acetate (boiling at 210 to 213°, at 745 mm.) were used. Benzyl stearate (melting at 40 to 42°) was furnished by Eli Lilly and Company and benzyl succinate (melting at 41 to 43.5°) by Frederick Stearns and Company.

Benzyl fumarate was prepared from fumaric acid and benzyl alcohol by the method of Bischoff and Hedenström[4] and purified by recrystallizing twice from alcohol. A product was obtained boiling at 210 to 211° at 5 mm. and melting at 58.5 to 59.5°.

Benzyl salicylate[5] was prepared by heating sodium salicylate with a slight excess of benzyl chloride and a small amount of diethylamine in an oil-bath at 130 to 140° for 17 hours. Upon cooling, the mixture was washed with water, the excess of benzyl chloride was removed by steam distillation and the remaining oil was distilled in a vacuum. Practically the entire amount came over between 165° and 192° at 7 mm. Upon redistilling, a yield of 85% of a product boiling at 170 to 175° at 7 mm. was obtained. In this reaction a temperature higher than 140° causes the formation of high-boiling side products while the absence of diethylamine as a catalyst greatly decreases the yield.

[2] Macht, *J. Pharmacol.*, **11**, 263 (1918).

[3] Pharmacological tests on these esters have been carried out in the Department of Pharmacology, of the Abbott Laboratories and published. Nielsen and Higgins, *J. Lab. Clin. Med.*, **6**, No. 7, April (1921); **6**, No. 12, Sept. (1912).

[4] Bischoff and Hedenström, *Ber.*, **35**, 4089 (1902).

[5] Aktien Gesellschaft, *Friedlaender.*, **6**, 1108; (Ger. pat. 119, 463); Gomberg and Buchler, THIS JOURNAL, **42**, 2065 (1920).

Benzyl cinnamate[6] was prepared in a manner similar to that for benzyl and after purification by repeated fractional distillation in a vacuum salicylate product was obtained which boiled at 228 to 230° at 22 mm. and crystallized as a white solid melting at 33 to 34°.

Benzyl acetylsalicylate was prepared by heating a mixture of 50 g. of benzyl salicylate, 30 g. of acetic anhydride and 10 g. of finely pulverized anhydrous sodium acetate on a boiling-water bath for 2 hours. The mixture was then cooled, taken up in benzene, washed with dil. sodium hydroxide solution and water; and after drying with calcium chloride the benzene was distilled, leaving a very viscous liquid. This was placed out of doors overnight at a temperature of about 20° whereupon it solidified. The material was purified by dissolving in hot ligroin from which, upon cooling, triturating and inoculating, 40 g. of a white solid was obtained melting at 25 to 25.5°. A portion of this was recrystallized several times from petroleum ether containing a little carbon tetrachloride and a product was obtained melting at 25.5 to 26°. The product is extremely soluble in benzene, xylene, carbon tetrachloride, acetone and ethyl acetate but is only slightly soluble in cold petroleum ether and ligroin. It boils at 197 to 200° at 7 mm.

Subs., 0.1347: CO_2, 0.3505; H_2O, 0.0644. Calc. for $C_{16}H_{14}O_4$: C, 71.08; H, 5.22. Found: C, 70.96; H, 5.35.

Benzyl-*p*-aminobenzoate was prepared from benzyl *p*-nitrobenzoate. The nitro ester was prepared by heating 50 g. of sodium *p*-nitrobenzoate, 50 g. of benzyl chloride and 2 cc. of diethylamine in an oil-bath at 130° for 24 hours. Upon cooling, the mixture was taken up in water and benzene. The residue obtained from the benzene layer was freed from benzyl chloride by steam distillation and further purified by two crystallizations from 95% alcohol. An 85% yield of a product melting at 82 to 83° was thus obtained.

The nitro ester was reduced with iron and hydrochloric acid. After two crystallizations from carbon tetrachloride, the solid material had only a faintly yellow tinge and melted at 88.5° to 89.5°. From 42 g. of nitro ester, 25.5 g. of purified benzyl *p*-aminobenzoate was obtained.

Calc. for $C_{14}H_{13}O_2N$: N, 6.17. Found (Kjeldahl): 5.89.

The hydrochloride was prepared by treating an ether solution of the purified base with alcoholic hydrochloric acid. This gave a beautiful white solid melting at 188 to 189° with the formation of some gas.

Shonle and Row[7] give the melting point of the hydrochloride as 184° and state "the free base is a yellow viscous liquid having no definite melting point and becoming wax-like on standing."

[6] Grimaux, *Z. Chem.*, **5**, 157 (1869); Kalle and Co., *Friedlaender*, **6**, 1234, Ger. pat. 127,649; Gomberg and Buchler, *loc. cit.*

[7] Shonle and Row, THIS JOURNAL, **43**, 364 (1921).

Hydrolysis.

The velocity of saponification of the esters was determined by a method similar to that used by Bischoff and Hedenström.[8] A definite amount of ester was dissolved in 20 cc. of acetone, and 50 cc. of 0.0633 *N* potassium hydroxide solution in 97% alcohol was added, the temperature being kept at 20°. At regular intervals 5-cc. portions were pipetted from the mixture and the excess of potassium hydroxide was titrated with 0.02 *N* hydrochloric acid, using phenolphthalein as indicator. The ratio of the number of moles of ester to the number of moles of potassium hydroxide varied according to the nature of the ester. With esters of dibasic acids, such as fumaric and succinic, two moles of potassium hydroxide were used to one mole of ester while the ratio with esters of monobasic acids (benzoic, acetic, etc.) was 1:1.

Benzyl salicylate was treated in a slightly different manner, because of the acidic hydroxyl group which holds one mole of potassium hydroxide as long as an excess of alkali is present. Therefore, potassium hydroxide approximately twice as concentrated as that used in the other tests was employed for the salicylate and that for the benzyl acetylsalicylate was about three times as concentrated. A run was made with acetylsalicylic acid in order to determine the rate of hydrolysis of the acetyl group alone, so that the velocity of saponification of the benzyl group in benzyl acetylsalicylate could be estimated.

An attempt was made to determine the rate of saponification of benzyl *p*-aminobenzoate but this proved to be impossible by the method used because the amino group in the free acid is strongly basic, while the amino group in the ester is practically neutral. Hence, the same amount of hydrochloric acid was required to neutralize the mixture, regardless of the extent to which the hydrolysis had proceeded. That hydrolysis had actually occurred was evidenced by the fact that during the first few hours a precipitate was obtained when the alcohol-acetone reaction mixture was diluted with water, whereas after 24 hours, no precipitate formed under these conditions.

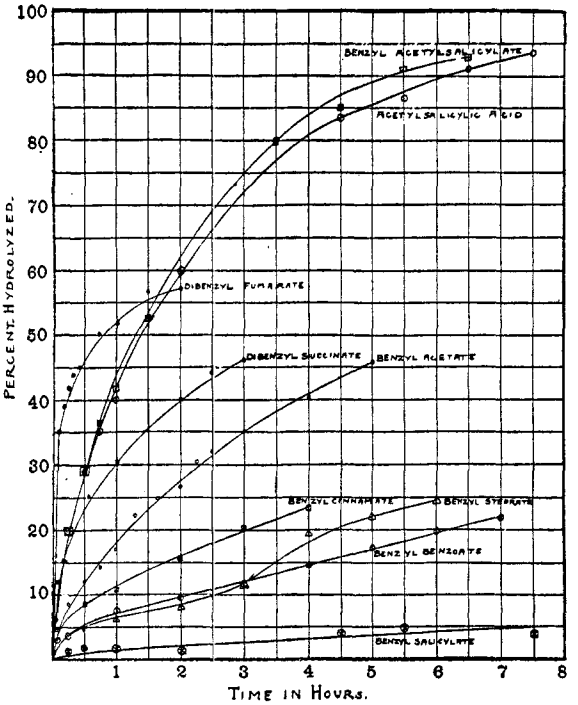
Duplicate runs were made in nearly all cases, which indicate that the results are accurate within about 3%. The results are shown by the accompanying curves.

The irregularity of the curve for benzyl stearate is perhaps due to the fact that a precipitate of potassium stearate separated from the reaction mixture after the hydrolysis had proceeded for about 3 hours. This would tend to decrease the concentration of the reaction products and allow the hydrolysis to proceed more rapidly. A check run showed close agreement at all points. No precipitate formed from any of the other esters.

The result for benzyl acetylsalicylate is calculated so that if both the

[8] Bischoff and Hedenström, *Ber.*, **35**, 3433 (1902).

acetyl and benzyl groups were completely hydrolyzed, the result would be 200%. The difference between these values and those for acetylsalicylic acid alone should give the velocity of hydrolysis of the benzyl group,



assuming that the rate of hydrolysis of the acetyl group is the same for both compounds. This seems to be true, for the difference is approximately equal to the rate of hydrolysis of the benzyl group in benzyl salicylate.

Summary.

1. The comparative rates of hydrolysis of benzyl benzoate, acetate, cinnamate, salicylate, stearate, fumarate, succinate and acetylsalicylate were determined in order to obtain a basis for the correlation of chemical properties and physiological action.

2. The rates of hydrolysis of these benzyl esters increase in the following order: salicylate, benzoate, stearate, cinnamate, acetate, succinate and fumarate.

3. The results indicate that the rate of hydrolysis of the benzyl group in benzyl acetylsalicylate is of the same order as in benzyl salicylate.

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