(5) Best and Scott, *J. Met. Research*, 3, 177–9 (1923).

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THE RELAXING ACTION OF SOME AROMATIC ESTERS.

BY E. V. LYNN AND DOROTHY GASTON.

Theoretically the relaxation of spasmodic conditions of muscle or nerve may be described by the term antispasmodic but by custom this word is usually restricted to any substance which will relieve strong contractions of unstriated muscular tissue. This effect may be gained by depressing the cerebral, spinal or medullary centers which control, by action upon the peripheral nerve ends, ganglionic or post-ganglionic, or by direct effect upon the muscles. The first two methods are very effective and often utilized, but the accompanying secondary and side actions are generally undesirable or even dangerous. The opiates and atropine are good illustrations.

Of all the drugs which act directly upon the muscle structure, the nitrites are preëminent, but papaverine is the most important compound of the group from our standpoint. The antispasmodic action of papaverine was first reported[1] in 1902 and has since been extensively investigated. Macht, during a long series of experiments, noted that those opium alkaloids of the papaverine class which contained the benzyl group were relaxing, while the morphine alkaloids, which did not have this group, were not possessed of the property.[2] He, therefore, examined the action of several benzyl derivatives of a simpler nature and found that benzyl alcohol and a number of its esters are capable of relieving spasmodic contractions of excised muscular tissue of the blood vessels, intestines, ureter, uterus, etc. Benzyl benzoate was then introduced to the trade for therapeutic purposes and the succinate has since followed it. The acetate, acetylsalicylate and others have also been used occasionally. Administered by mouth they seem practically harmless in fairly large amounts, and the apparent lack of clinical success has, therefore, been rather surprising, for there seems no question at all about the paralyzing

[1] Pal, *Zeit. f. Physiol.*, p. 68 (1902).

[2] Macht, *J. Pharmacol.*, 8, 155, 261 (1916); 9, 197 (1916); 9, 287 (1917); 10, 96 (1917); 11, 419 (1918).

effect *in vitro*. Therapeutically the further development of the benzyl esters may appear futile, but the interest of the pharmacologist cannot but be spurred by this seeming contradiction.

One phase of the subject which does not seem to have been investigated is action of esters of alcohols closely related to benzyl alcohol and we deemed it worthy of some study. For this we selected phenyl propyl alcohol, $C_6H_5.CH_2.CH_2.CH_2OH$, which is closely related to cinnamyl alcohol and the cinnamates found naturally in storax and in Peru balsam. The two isomers of phenyl propyl alcohol, phenyl ethyl carbinol, $C_6H_5CHOH.C_2H_5$, and benzyl methyl carbinol, $C_6H_5.CH_2.CH(OH)CH_3$ were also prepared, and each of the three alcohols esterified to form the acetate and the benzoate. Mandelic acid has been found by others to possess antispasmodic action, also its ethyl ester, but no attempt appears to have been made to investigate the acyl or aryl derivatives; accordingly mandelyl acetate and benzoate were also prepared.

Phenyl n-Propyl Alcohol.—$C_6H_5.CH_2.CH_2.CH_2OH$. This compound, which was previously described by Conant and Kirner,[1] was prepared in the usual manner by the Grignard reaction from ethyl magnesium bromide, benzyl magnesium chloride and ethylene chlorhydrin. Dibenzyl was obtained in considerable quantities as a by-product but the yield of alcohol was yet nearly 60 per cent. It is a thick, colorless liquid with a slightly aromatic odor and boiling at about 235° C. at 760 mm., specific gravity 1.008 at 18° C. It is somewhat soluble in water and completely miscible with alcohol and ether.

The acetate is described by Rügheimer[2] as a thick fluid, boiling point 244–245°; the benzoate is spoken of as a thick brownish fluid and is not further described.

Phenyl Propyl Acetate.—The acetate was made by slowly adding acetyl chloride in equivalent quantity to the warm alcohol and continuing the heat for a few minutes, the product being poured into water and extracted with ether in the usual way. It is a liquid with a very pronounced odor strongly resembling that of bananas. It may also be prepared by the use of acetic anhydride in place of acetyl chloride and with a trace of sulphuric acid added.

Phenyl Propyl Benzoate.—The alcohol was warmed very gently with an equal quantity of benzoyl chloride for about one-half hour. Hydrogen chloride was evolved copiously in the first few minutes but disappeared after about fifteen. The product was poured into water and extracted with ether as before. Phenyl propyl benzoate is a thick liquid with a pleasant odor less noticeable than that of the acetate. Boiling point 262° C.

Benzyl Methyl Carbinol.—$C_6H_5.CH_2.CH(OH)CH_3$. This alcohol has been described as formed by the reduction of methyl benzyl ketone and Tiffeneau and Delange[3] mention that it may be prepared by the Grignard reaction. Accordingly, benzyl magnesium chloride was first prepared from 4 Gms. of magnesium turnings and 20.8 Gms. of pure benzyl chloride in the usual manner. When this reaction was apparently complete, the calculated amount of paraldehyde (12 cc.) in 50 cc.

[1] Conant and Kirner, *J. Am. Chem. Soc.*, 46, 232 (1924).
[2] Rügheimer, *Ann.*, 172, 122 (1874).
[3] Tiffeneau and Delange, *Compt. rend.*, 137, 573 (1903).

of anhydrous ether was allowed to flow in. After reaction had ceased, the flask was heated for thirty minutes and the contents then poured into acidified ice water to effect decomposition, the oily layer being extracted with ether and fractionated. The yield is considerably lowered by the formation of dibenzyl and of toluene, so that better results may be obtained using the method of Rassow and Burmeister[1] which, however, requires reagents not usually available. The alcohol is a liquid boiling at 214.5–215.5° C.

Benzyl Methyl Carbinol Acetate.—This was prepared by heating together the alcohol, acetic anhydride and a very small quantity of sulphuric acid, the product being poured into water and collected with ether as before. It is a liquid with a very pleasing aromatic odor, heavier than water, in which it is very slightly soluble, boiling point 225–226° C. It is miscible with alcohol and ether in all proportions.

Benzyl Methyl Carbinol Benzoate.—The alcohol was benzoylated by the Schotten Baumann reaction using very dilute sodium hydroxide solution. The ester separated after some time and was collected with ether. It is a somewhat thick liquid with a boiling point of 271–272° C. and a very pleasing odor resembling slightly that of the acetate.

Phenyl Ethyl Carbinol.—$C_6H_5.CH(OH).CH_2.CH_3$. This was successfully prepared by the Grignard reaction, using magnesium, ethyl bromide, a crystal of iodine as catalyst and benzaldehyde. The product was poured into water and collected with ether, the residue being fractionated at 26 to 28 mm. pressure. The pure alcohol boils at 210–211° at 760 mm., 105–110° at 28 mm. It is a colorless liquid with an aromatic odor.

Phenyl Ethyl Carbinol Acetate.—Acetylization of the alcohol proceeded readily using acetic anhydride, the product being collected as before. It is a colorless liquid with a very pleasant odor faintly resembling the carbinol, boiling point 225–225.5° C.

Phenyl Ethyl Carbinol Benzoate.—The Schotten Baumann reaction was unsuccessful in producing the benzoate but the latter was finally prepared by warming very gently a mixture of dry benzoyl chloride and the carbinol in molecularly equivalent quantities. Collected in the usual manner with ether, the ester is a thick viscous liquid boiling at 290–291° C. and possessing an exceedingly pleasant odor.

Mandelyl Acetate.—$C_6H_5.CH(OCO.CH_3).COOH$. The acetate was made according to the method of Anschütz and Böcker,[2] by heating acetyl chloride and mandelic acid together upon the steam-bath. The resulting syrupy liquid was dissolved in chloroform and precipitated in a freezing mixture with petroleum ether. The ester was crystallized with difficulty in shining white crystals melting at 80°. When recrystallized from water it contains water and melts at 60°.

Mandelyl Benzoate.—$C_6H_5.CH(OCO.C_6H_5)COOH$. Mandelic acid was benzoylated by the Schotten Baumann reaction in 10 per cent sodium hydroxide solution. The ester was precipitated by hydrochloric acid and recrystallized several times from hot water, as white crystals melting at 115–116° C.

In order to test the depressor or relaxing action of the esters so prepared, they were applied to active sections of rat intestines and the results recorded on the

[1] Rassow and Burmeister, *J. prakt. Chem.*, 84, 473 (1911).

[2] Anschütz and Böcker, *Ann.*, 368, 53 (1909).

kymograph. The muscle was suspended in a chamber filled with Locke's solution at 37°, and when peristaltic action was thoroughly established, 1 cc. of a solution of the ester was dropped into the chamber. A stream of oxygen which was kept bubbling through the cell served to distribute the solutions thoroughly. All liquid esters were made into 50 per cent solutions with alcohol, while the solid ones were made 20 per cent in alcohol.

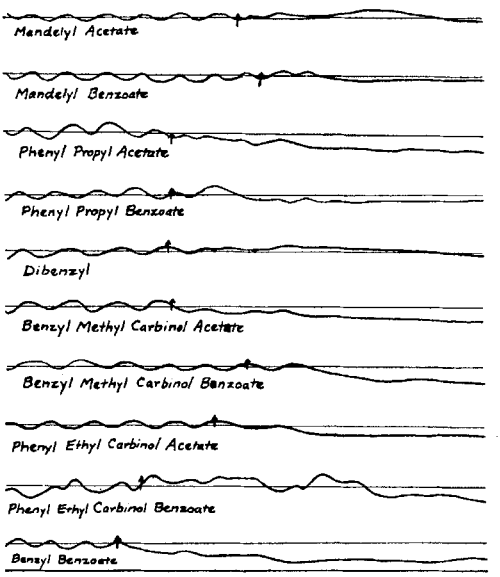

Chart I.

The results of the tests show that all the members of this series possess inhibitory or depressant action upon smooth muscle to about the same extent as does benzyl benzoate. It may be seen by the accompanying chart that in all cases the compounds caused cessation of peristaltic action, while in some instances there was a stretching of the muscle to a greater degree than when it was at the relaxed stage of the peristaltic movement.

COLLEGE OF PHARMACY,
UNIVERSITY OF WASHINGTON,
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CHEMICAL AND BIOLOGICAL ASSAY OF DRUGS.*

DIGITALIS STANDARDIZATION: UNDER ANESTHESIA.

BY J. B. BERARDI.

The action of drugs upon living organisms depends upon the state of the particular constituent parts, which go to make up the organisms. The state may be altered by seasonal variations, age, sex and previous administration of other drugs, etc. For example, when small doses of morphine are given in cases of broken compensation, the action of digitalis is altered. In some cases digitalis given in large doses prior to the administration of morphine produces no definite cardiac response, while in other cases, small doses of digitalis given after the administration of morphine produces full response.

The methods of standardization of digitalis, which are constantly receiving a great deal of consideration, utilize an animal which is anesthetized before standardization of the drug is carried out. The most commonly used is known as the Hatcher's cat method. In this method the preparation to be standardized, suitably diluted, is injected intravenously into an anesthetized cat.

Many objections have been raised to the use of these methods, the most outstanding one being that the death of the animal is produced by the anesthetic or

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