These data furnish several interesting comparisons.

First, as to the average number of each species of animal for a complete test. An average of 11.5 guinea-pigs were required for each test and 14.0 white mice for each test. This shows that very few more mice are needed for a test based on this series and part of this excess was, no doubt, due to absence of data as to the ratio between the doses for guinea-pigs and mice.

Second, as to the ratio between doses for the guinea-pig and white mouse in the various tests. The extremes in the 22 tests are 4 and 10 and the average of all the ratios is 6.7. If the four extremes (4, 10, 10, 10) are eliminated, the average is 6.25 which will be used in arriving at the following suggested standard doses for white mice when injected intraperitoneally.

	Standard M.L.D. for pigs.	Ratio.	Standard M.L.D. for mice.
F. E. Aconite	.000040 cc.	1 to 6.25	.00025 cc.
S. E. Aconite	.000010 Gm.	1 to 6.25	.00006 Gm.
Tr. Aconite	.00040 cc.	1 to 6.25	.0025 cc.
Aconitine	.00000008 Gm.	1 to 6.25	.00000050 Gm.

Third, as to the relative degree of accuracy between the pig and mouse methods. In the adjustment of Rx 749816 from 200% to standard the mouse test indicated the same accuracy as the guinea-pig test. The unknown solutions were known dilutions of previously tested Aconite preparations but were unknown to the person making the test. In five such tests by the mouse method two of the results were almost exactly correct while the other three were from 20% to 32% off. The average error was 18%. Only three such tests were conducted on guinea-pigs and the lowest error was 11%. The average error was 26%. These results on unknowns were not indicative of great accuracy and dependability by either method but the results on mice were even more accurate than those on pigs and the guinea-pig test has already been accepted as being the most dependable test available for aconite so the mouse test is apparently fully as accurate in this series of tests.

The data submitted should be of interest from an experimental standpoint and the greater economy which is evident in the new mouse method should commend it for practical commercial testing purposes where the cost of a guinea-pig assay is quite an item, especially if the lot is small.

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LOCAL ANESTHETICS OF THE AMINO ALKYL BENZOATES.*

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In spite of the vast amount of work which has been done on the physiological action of chemical compounds, there has been very little systematic grouping of facts and still less possibility of drawing general conclusions. Each experimenter

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has made a few compounds and studied their action but has made but few efforts or none to seek the relationships which exist between closely associated series of compounds. Another drawback has been the absence of co-relation between the work of different investigators. There has been some, of course, but the amount is very small compared to the total amount of investigation. This absence of coöperation was apparently fostered by the obvious fact that a goodly share of the workers were incited by a commercial interest in producing a new medicinal and were not at all interested in the furthering of pharmacological knowledge. The adverse criticism, which has lately been directed toward such commercialization of the ease with which chemical alteration can be brought about, is entirely just; what we want now is not more remedies but more insight into the relation between physiological action and chemical constitution. We know the pharmacology of but a very few compounds among the thousands of known substances; the spots which indicate where we have even imperfect knowledge are but minute dots on the whole field. We would undoubtedly accomplish most by enlarging these spots until definite and exact recognition of the function played by each group or radical is fully realized. It is with this idea in mind that we submit these few experiments.

One of the most important groups of local anesthetics is that of the alkyl amino-alkyl benzoates, several of which are successful commercially. A number of isolated studies have been made of the comparative action of the various members of this group and a few general conclusions reached, but only one or two apply to the alkyl groups. They are:

1. The alcohol from which the ester is derived may be primary, secondary, or tertiary. Branching of the chain decreases activity.
2. Increase of carbon atoms between the acyl and amino groups raises the action but, also, the toxicity.
3. The particular alkyl groups in the amino radical affect the activity, but in no apparently general way.
4. The presence of a double bond increases local anesthetic power.

No one has yet reported work on the simplest members of the group, probably because of the reputed inactivity of methyl derivatives compared with ethyl and higher. This should have no influence if one is merely investigating a means of developing new remedies, otherwise not. Furthermore, it is not clearly certain that methyl groups deserve this reputation. Methyl alcohol is certainly more potent than ethyl; methyl sulphate is very poisonous while ethyl sulphate is very much less so, and unpublished experiments of the writers would indicate that in other cases the lower radical is as potent or more powerful.

We have selected the simplest ester of this class, dimethylamino methyl benzoate $(CH_3)_2.N.CH_2.OOC.C_6H_5$ and plan to compare it with (a) other dialkyl derivatives, (b) compounds with larger number of CH_2 groups between nitrogen and carboxyl, (c) those made with substituted benzene nucleus, and (d) those formed by alkyl or aryl substitution of hydrogen in the CH_2 group. Examples of these would be:

(a) $(C_2H_5)_2.N.CH_2.OOC.C_6H_5$ (c) $(CH_3)_2.N.CH_2.OOC.C_6H_5OH$
(b) $(CH_3)_2.N.CH_2.CH_2.OOC.C_6H_5$ (d) $(CH_3)_2.N.CH(CH_3).OOC.C_6H_5$

In these experiments representatives of the first two variations have been made and examined. Dimethylaminomethyl benzoate has not as yet been obtained.

Diethylamino Methyl Benzoate.—This was prepared by benzoylating diethyl-

amino methyl alcohol by the Schotten Baumann reaction, in 15 per cent sodium hydroxide solution. It is a liquid boiling at 195–200° at 88 mm., soluble in alcohol, ether, or olive oil but insoluble in water. Attempts to form crystalline salts were unsuccessful. Per cent of nitrogen: calculated 6.76; found 6.44, 6.43.

The diethyl amino methyl alcohol was prepared in the same way that Henry[1] prepared the corresponding dimethyl compound by the action of formaldehyde upon diethyl amine. It is an oily liquid soluble in water, specific gravity 0.8529 at 0° C., and with characteristic piercing odor.

Dimethyl Amino Ethyl Benzoate Hydrochloride.—This compound was prepared by sealing equivalent parts of dimethylamine and β-chlorethyl benzoate in a Carius tube and allowing to stand at room temperature for a number of days. Gradually there were formed in the tube lustrous plates which melted at 147° C. and were soluble in water. According to a German patent[2] these have a melting point of 148° C.

The β-chlorethyl benzoate was prepared by heating on a water-bath equivalent parts of ethylene chlorhydrin and benzoyl chloride, and distilling the product, collecting that portion which boiled at 254–255° C.

Diethyl Amino Ethyl Benzoate Hydrochloride.—A similar method was used as for the dimethyl compound, employing diethylamine in place of the corresponding dimethyl compound. The hydrochloride crystallized out, after heating for twelve hours at 100–120°, in lustrous plates, soluble in water and melting at 224° C.

The three preparations were tested for local anesthetic action by application to the cornea of a rabbit. Ten per cent solutions of the compounds were made and at ten minute intervals for fifty minutes the conjunctival sac was filled with the solution. Ten minutes after each application the activity was tested by touching the cornea lightly with the point of a pencil, being careful to avoid touching the eyelid or a hair. If the contact caused winking there was no apparent anesthesia but if no winking occurred the substance was considered at least partially active. In this case the cornea was stroked with the pencil, the action being complete if no reaction occurred.

Diethyl amino methyl benzoate in olive oil gave partial local anesthesia after forty minutes and this was complete after fifty minutes. However, the preparation caused the formation of pus which disappeared in twelve hours, the irritation probably being due to the alkalinity of the free base.

The hydrochloride of dimethyl amino ethyl benzoate, in 10 per cent solution in normal salt, gave slight partial anesthesia after thirty minutes but this did not become more pronounced. There was no evidence at any time of irritation.

Diethylamino ethyl benzoate hydrochloride, in similar solution gave slight anesthesia after twenty minutes and complete partial anesthesia after thirty minutes, but became no stronger. There was no evidence at any time of irritation.

All three of these compounds, therefore, possess activity but none of them was more than moderately anesthetic, even with high concentration, and diethyl amino methyl benzoate was quite irritating. The ethyl group seems more active than the methyl.

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