

contained fluid. 10.0, fowl very unsteady, comparatively cold; abdomen ecchymosed. Fowl died during the night. *Post-mortem* examination showed ecchymosis of skin of abdomen and thorax, and effusion of blood into the pectoral muscle at the site of the puncture; the lungs were bright red and contained much blood-stained fluid.

On the Comparative Action of Stovaine and Cocaine as measured by their Direct Effect upon the Contractility of Isolated Muscle.

By V. H. VELEY, F.R.S., and A. D. WALLER, F.R.S.

(Received November 8,—Read December 9, 1909.)

It has been shown by Veley* that the affinity values of stovaine and cocaine by the methyl orange and borax precipitation methods are approximately equal. The method of measuring physiological activity of anæsthetic drugs, as described by Waller,† affords an independent control that can usefully be compared with affinity values.

Stovaine, sometimes called amyleine hydrochloride and originally prepared by Fournéau, has been successfully applied in recent years, especially for spinal anæsthesia, as also for general surgery and dentistry. As it is used for the same purposes and in doses of the same order as cocaine, the relative value of the two drugs has been compared in a series of memoirs or notices, more than 150 in number in various clinical journals. The general conclusions arrived at are: (1) as anæsthetics the drugs are of equal value, but stovaine produces vaso-dilatation, cocaine vaso-constriction; and (2) stovaine is less toxic than cocaine. The statement has even been made that stovaine does not produce any toxic effect.

Though, as stated above, the affinity values are approximately equal, yet the chemical constitution of the two compounds is wholly dissimilar. Stovaine is the hydrochloride of methyl ethyl dimethylamino-methyl carbinol benzoate $\text{HCIC}(\text{CH}_3)[\text{CH}_2\text{N}(\text{CH}_3)_2](\text{C}_2\text{H}_5)\text{OBz}$ and the base (molecular weight = 235), a benzoyl derivative of a diamino-tertiary amyl alcohol $\text{C}(\text{CH}_3)_2(\text{C}_2\text{H}_5)\text{OH}$ (Fournéau).‡

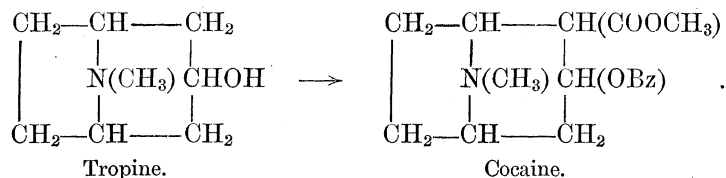
Cocaine (molecular weight of base = 303) is the methyl ester of benzoyl

* 'Trans. Chem. Soc.,' 1909, p. 763.

† 'Proc. Roy. Soc.,' June 24, 1909.

‡ 'Comptes Rendus,' 1904, vol. 138, p. 766.

ecgonine and derived from tropine by the replacement of the hydroxylic hydrogen by the benzoyl group, and of hydrogen by the methylated carboxylic group (Willstaetter*), thus:—



If stovaine and cocaine had not been used for identical purposes in surgery, no comparison would ever have been instituted in chemistry.

The crystalline samples of stovaine, kindly supplied by Messieurs Poulenc Frères, and of cocaine hydrochloride, by Messrs. Burroughs Wellcome & Co., had been tested and used for experiments on the affinity values by the methyl orange and borax precipitation methods. The solutions were made upon the same day of $n/10$ concentration, and subsequently diluted to $n/500$ and $n/1000$.

Simultaneous records were taken with the same pair of muscles as a "crucial" experiment.

Percentage calculated as base.		
$\left\{ \begin{array}{l} n/500 \\ n/1000 \end{array} \right.$	stovaine	0.0470 0.0235
$\left\{ \begin{array}{l} n/500 \\ n/1000 \end{array} \right.$	cocaine hydrochloride ...	0.0610 0.0305

From the records ($n/1000$ concentration, fig. 1, line 1) abolition took place in the following times: stovaine 22, cocaine 22.5 minutes, and the recovery in saline (at "sal," end of 1st, 2nd, and commencement of 3rd lines) was rather better in the case of cocaine than in that of stovaine.

On reversing the solutions it was found that too long a time would be required for total abolition, so solutions of double the strength were substituted.

The times required for abolition were then—stovaine 4 minutes and cocaine 5.5 minutes, and the subsequent recovery was rather better for the latter than for the former. It is evident that, judged by this method, there is no appreciable difference between these two drugs; the slight difference observed is rather in favour of cocaine being the less toxic.

Comparative experiments on nerve with solutions of stovaine and cocaine of the same molecular concentration also showed quite a trifling difference.

* 'Ber.,' 1891, vol. 34, p. 3108.

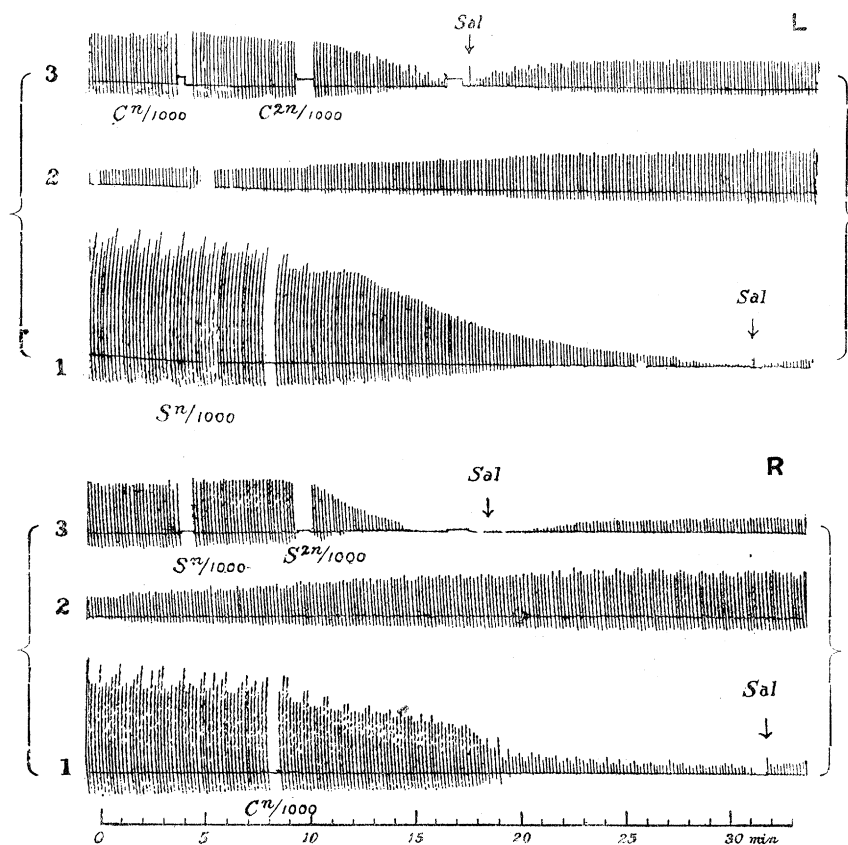


FIG. 1.—Stovaine and Cocaine.

Simultaneous record of two sartorius muscles, R and L; the former in cocaine $n/1000$, then in saline, then in stovaine $n/1000$ and $n/500$, finally in saline; the latter in stovaine $n/1000$, then in saline, then in cocaine $n/1000$ and $n/500$, finally in saline.—June 9, 1909. (The records read from left to right.)

The methyl analogue of stovaine or trimethyl dimethylamino-methyl carbinol benzoate $\text{HCIC}(\text{CH}_3)_3 \text{CH}_2\text{N}(\text{CH}_3)_2\text{OBz}$, derived from the tertiary butyl alcohol $\text{C}(\text{CH}_3)_3\text{OH}$, was also studied.

The sample, also supplied by Messieurs Poulenc Frères, had previously been found to have an affinity value slightly above that of stovaine.

In this case simultaneous records were made with a pair of muscles with solutions of different concentrations, namely :—

Percentage calculated as base.		
$n/500$	methyl stovaine	0.050
$n/1000$	„ „	0.025

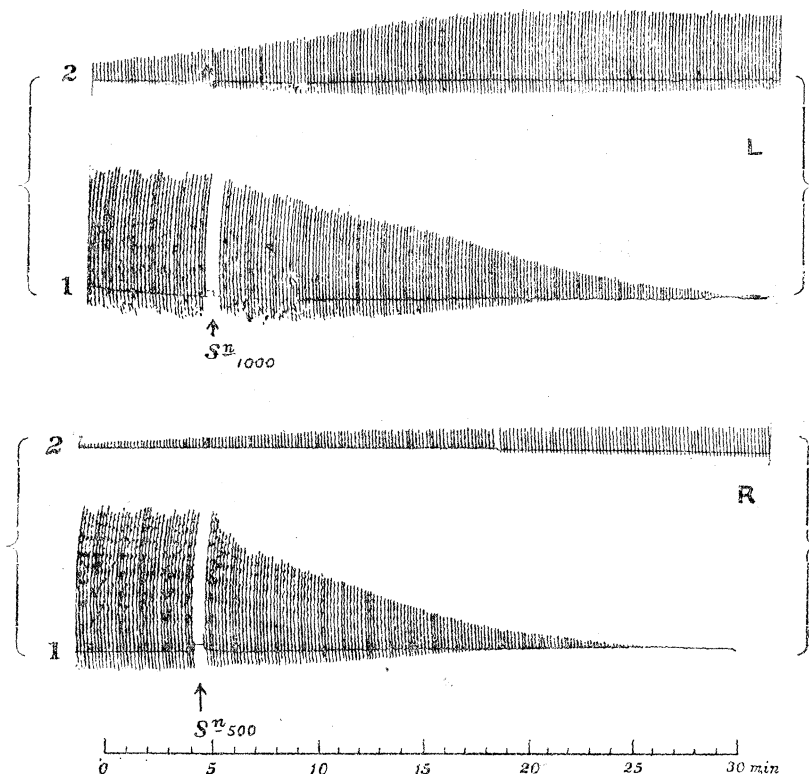


FIG. 2.—Methyl Stovaine.

Simultaneous record of two sartorius muscles, R and L, the former in $n/500$, the latter in $n/1000$ solution of methyl stovaine (in saline).

As appears from these records, abolition took place in the following times: 23.5 minutes for $n/1000$, and 18 minutes for $n/500$; the recovery in the former case was nearly complete, in the latter very incomplete.

It appears that, as regards the $n/1000$ solution, methyl stovaine does not differ materially from stovaine, the times of abolition and degree of recovery being almost identical. As regards the $n/500$ solution, though the time required for abolition is rather longer than might be expected, the degree of recovery is quite in accord with that of stovaine.

The general conclusion is, therefore, that the substitution of the ethyl group in stovaine by the methyl group produces no alteration in toxic effect, and this result is quite in accordance with the affinity values of the two substances in question.

The physiological activity of these drugs as compared with that of quinine, to which we have paid special attention, is as follows :—

Quinine	100
Stovaine	40
Methyl stovaine.....	40
Cocaine	40
