

Certain Physical and Physiological Properties of Stovaine and its Homologues.

By V. H. VELEY, F.R.S., and W. L. SYMES.

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I. INTRODUCTION.

The amino-alcohols of the general type $(\text{OH})\text{CCH}_3\text{RCH}_2\text{N}(\text{CH}_3)_2$ were originally obtained by Fourneau* by the reaction between the secondary or tertiary amines and the corresponding chlorhydrins $(\text{OH})\text{CCH}_3\text{RCH}_2\text{Cl}$ (R representing any hydrocarbon grouping). Their salts do not crystallise well, but if the hydrogen of the hydroxyl grouping be replaced by benzoyl, the derived salts, especially the hydrochlorides, can be obtained in a pure crystalline condition. Such salts produce local anæsthesia, the ethyl derivative, $\text{OBzC}\cdot\text{CH}_3\cdot\text{C}_2\text{H}_5\text{CH}_2\text{N}(\text{CH}_3)_2\text{HCl}$, or stovaine, being especially used in surgical practice. In a former communication by Veley and Waller,† the activities of stovaine, its methyl homologue, and cocaine were compared as regards their effect on the contractility of isolated muscle; it was shown that the toxic effects of the three drugs were all equal within the limits of experimental error, but the variation of effect by altering the concentration was rather less than that to be expected.

A few months later, Gros,‡ using a different method of excitation, namely, tetanic, obtained similar results as regards the equal activity of cocaine and stovaine, though the concentrations in the two cases were widely different, namely, $n/500$ to $n/1000$ (Veley and Waller) and $n/12\cdot5$ (Gros).

M. Fourneau recently sent to the former of us fine crystalline samples of stovaine and its homologues for the purpose of investigation; we desire to express our appreciation of his kindness and international courtesy.

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

† 'Roy. Soc. Proc.,' B, 1910, vol. 82, p. 147.

‡ 'Archiv f. Exp. Pathol. u. Pharmacol.,' Leipzig, 1910, vol. 62, p. 380.

The substances sent were—

- (i) Methyl stovaine,* $\text{OBzC}(\text{CH}_3)_2\text{CH}_2\text{N}(\text{CH}_3)_2\text{HCl}$;
- (ii) Ethyl stovaine, or stovaine, $\text{OBzC}.\text{CH}_3.\text{C}_2\text{H}_5.\text{CH}_2\text{N}(\text{CH}_3)_2\text{HCl}$;
- (iii) Amyl stovaine, $\text{OBzC}.\text{CH}_3.\text{C}_5\text{H}_{11}.\text{CH}_2\text{N}(\text{CH}_3)_2\text{HCl}$;
- (iv) Phenyl stovaine, $\text{OBzC}.\text{CH}_3.\text{C}_6\text{H}_5.\text{CH}_2\text{N}(\text{CH}_3)_2\text{HCl}$;
- (v) Benzyl stovaine, $\text{OBzC}.\text{CH}_3.\text{C}_7\text{H}_7.\text{CH}_2\text{N}(\text{CH}_3)_2\text{HCl}$; and
- (vi) The propyl ester of a dimethyl-amino-oxybenzoyl-isobutyric acid, $\text{OBzC}.\text{CH}_3.\text{COOC}_3\text{H}_7.\text{CH}_2\text{N}(\text{CH}_3)_2\text{HCl}$, which differs from stovaine in containing the grouping COOC_3H_7 in the place of the ethyl (C_2H_5) group. As regards the corresponding methyl ester, Fourneau† wrote:—"Il contient tous les groupements de la cocaine" (namely a tertiary amino, an oxybenzoyl, OBz, and a methylated carboxyl, COOCH_3 , grouping) "c'est d'ailleurs un anæsthésique puissant, mais l'accumulation des groupes acides autour de la fonction aminée détruit tellement la basicité de celle-ci que la molécule est très acide au tournesol." In other words, the salt may be regarded as intermediate, as regards its constitution, between stovaine on the one hand and cocaine hydrochloride on the other, though, as regards its properties, differing from both of them in giving an acid reaction; this point will be more fully discussed in the sequel.

II. PHYSICAL PROPERTIES.

The physical properties of the several compounds investigated are—(i) the densities of the salts themselves; (ii) the affinity value of Fourneau's salt, and, as to the physiological properties, their effects on (i) the contractility of isolated muscle, (ii) blood pressure, and (iii) respiration. The comparative effect of these drugs on nerve is dealt with as a separate subject in a further communication.

Densities of the Salts.—These were determined by displacement of toluene, using a specific gravity bottle of 10 c.c. capacity, rather more than 1 gramme of each salt being used; the necessary correction for air displacement was made, and each experiment performed in duplicate; a bottle of like capacity and nearly identical weight was used as a tare. It is not, of course, pretended that such determinations are of the order of accuracy which can be obtained in the case of liquids with a U form of pycnometer, but the curious absence of data for the densities of salts of organic compounds was

* For the sake of brevity, the words "homologue of stovaine" will be omitted in the case of the compounds (i), (iii), (iv), and (v); for the same purpose, compound (vi) will be designated in the text as Fourneau's salt.

† 'Journ. de Pharmacie et de Chimie,' June 1, 1908; also 'Bull. Soc. Chim.,' 1908, [4], vol. 3, p. 114; and *ibid.*, 1909, vol. 5, p. 239.

an inducement to arrive at some values. The following results were obtained in terms of water at 15°:—

Table I.

Salt.	S.G. 15/15.	Molecular weight.
Methyl stovaine	1·213 ₆	257·5
Ethyl „	1·207 ₆	271·5
Amyl „	1·106 ₀	313·5
Phenyl „	1·191 ₂	335·5
Benzyl „	1·178 ₀	349·5

(The variation in the results obtained in the duplicate experiments was in the fourth decimal place.)

It is evident from the above results that the densities, both for the paraffinoid and benzenoid derivatives, decrease with increase of molecular weight, but this decrease does not vary uniformly with each CH₂ group added to the molecule; the value of the amyl derivative is lower than that to be expected, but four determinations were made for the salt in the case of any error.

Affinity Value of the Base of Fournéau's Salt.—On account of the writer's results as to the acidity of the salt towards indicators the hydrolysis and affinity values were determined by the methyl-orange method* devised by the former of us. The hydrolysis found was 1 per cent. at dilution $V = 4 \times 10^3$; hence the affinity value of the base K_b can be calculated by Arrhenius' dilution formula and Kohlrausch's data for ionisation of water as

$$K_b = 0.99 \times 4 \cdot 10^3 \times 4.9 \cdot 10^{-15} / (0.01)^2 = 7.9 \cdot 10^{-8}.$$

The above value is comparable with that of glycine ethyl ester hydrochloride = $9.7 \cdot 10^{-8}$, and also for such comparison the affinity values (as determined by the borax method) of cocaine, stovaine, and methyl stovaine, whose hydrochlorides show no hydrolysis, are given below:—†

Base.	$K_b \cdot 10^{-7}$.
Cocaine	4
Stovaine (base)	1·5
Methyl stovaine (base).....	3·2

* 'Trans. Chem. Soc.,' 1908, vol. 93, pp. 652, 2114, 2122.

† 'Trans. Chem. Soc.,' 1909, vol. 95, pp. 763—766.

Fourneau's view that the accumulation of acidic groupings around the amino-function destroys the basic character of the latter is confirmed by quantitative measurements.

III. PHYSIOLOGICAL PROPERTIES.

A. *Contractility of Isolated Muscle.*

On dissolving in the usual manner in physiological tap-water saline solution, a turbidity resulted in the case of the salts of the higher molecular weight; this was due to the precipitation of the base by the alkali of the water, as previous investigations have shown that, though these compounds are not hydrolysed by water, yet a trace of the order of 1 per 10,000 of free alkali will cause separation of the base. But if such solutions are allowed to stand for some days, the turbidity slowly and almost completely disappears except in the case of benzyl stovaine.

The records obtained for all the compounds were similar in type, the only features worthy of note being (1) that the end or abolition point was often not very well defined, and (2) that the variation caused by alteration of concentration was less marked than for most other drugs.

The times required for abolition are collected together in the following table; in Column I the names of the compounds are given, in II, III and IV the concentrations in normality, and the same in percentage reckoned as base, and the times in minutes required for abolition. The temperature, unless otherwise stated, was $18 \pm 0.5^\circ$.

Table II.

I. Compounds.	II. <i>n</i> /1000.		III. <i>n</i> /500.		IV. <i>n</i> /300.	
	Percentage.	Time.	Percentage.	Time.	Percentage.	Time.
Methyl stovaine	0.022	mins. 23.5	0.044	mins. 18	0.077	mins. —
Stovaine	0.024	23.5	0.048	17.5*	0.081	6.5 (at 21°)
Amyl stovaine	0.028	—	0.056	24	0.093	9.0 (at 21°)
Phenyl stovaine	0.030	—	0.060	24	0.100	11.0
Benzyl stovaine	0.031	—	0.062	—	0.104	12.0 (at 20°)
Fourneau's salt	0.029	30	0.058	24	0.097	11.5

* Three determinations made at different times gave identical values.

The general conclusion to be drawn from these results is that the substitution of the ethyl grouping in stovaine by the amyl, phenyl, benzyl, and

(COOC_3H_7) groupings produces a decrease of rate of action while that of methyl is less marked, the differences observed being within the limit of experimental error. As regards the amyl, phenyl, and benzyl derivatives, it is possible that the differences observed may be due to the precipitation of the bases as pointed out above.

B. *Effect on Blood-pressure and on Respiration.*

Though it was not possible to carry out, *in vivo*, a complete investigation into the physiological action of these bodies, it nevertheless seemed of interest to employ some of the material at our disposal for the purpose of comparing their respective effects, with those of cocaine, on the circulation and respiration of the mammal.

The number of observations is not large enough to warrant close quantitative estimation of their individual toxicities, but suffices to enable comparison of the type and (to some extent) of the degree of their effects.

In all cases the animals employed were cats, under complete anaesthesia, and the drugs were administered by injection into the saphenous vein.

Cocaine.

As is well known, cocaine in sufficiently small doses is a cardiovascular and respiratory stimulant. On cats with intact central nervous system, blood-pressure was raised by doses of 0.05—0.7 mgrm. per kilo. body weight, lowered by larger doses; whilst on a completely pithed cat injections produced no fall in doses up to 1.9 mgrm. per kilo. On the respiratory movements, the depressant action of the drug has appeared with smaller doses than on the blood-pressure.

Stovaine and Methyl Stovaine.

These drugs have not, with us, raised blood-pressure or stimulated respiration in any dose. Small doses, when effective, led to fall of blood-pressure of varying amount and duration, together with a momentary pause in respiration, which was followed by a rhythm of greater frequency and smaller amplitude than that before injection. A single (first) dose of stovaine amounting to 5 mgrm. per kilo. has proved fatal, but provided that the initial doses were small, single injections amounting to three times as much did not cause death, and a total dose of 40 mgrm. per kilo. can be tolerated. With methyl stovaine an initial (single) dose of 8.4 mgrm. per kilo. did not produce any obviously dangerous effect. As on muscle* and on

* Veley and Waller, *loc. cit.*

nerve,* these drugs have also on the circulation and on the respiration similar and approximately equal effects, methyl stovaine being, if anything, slightly the less active of the two.

Amyl Stovaine.

In comparison with the two preceding drugs, small doses of amyl stovaine have produced (molecule for molecule) a greater fall of blood-pressure, but distinctly less interference with respiration.

Initial doses of 5·8 and 9·3 mgrm. per kilo. were well tolerated, and 41 mgrm. per kilo. has failed to kill. The effects are neither in type nor in degree, those of an acutely toxic drug. We have found amyl stovaine to be a powerful local anæsthetic.*

Phenyl Stovaine and Benzyl Stovaine.

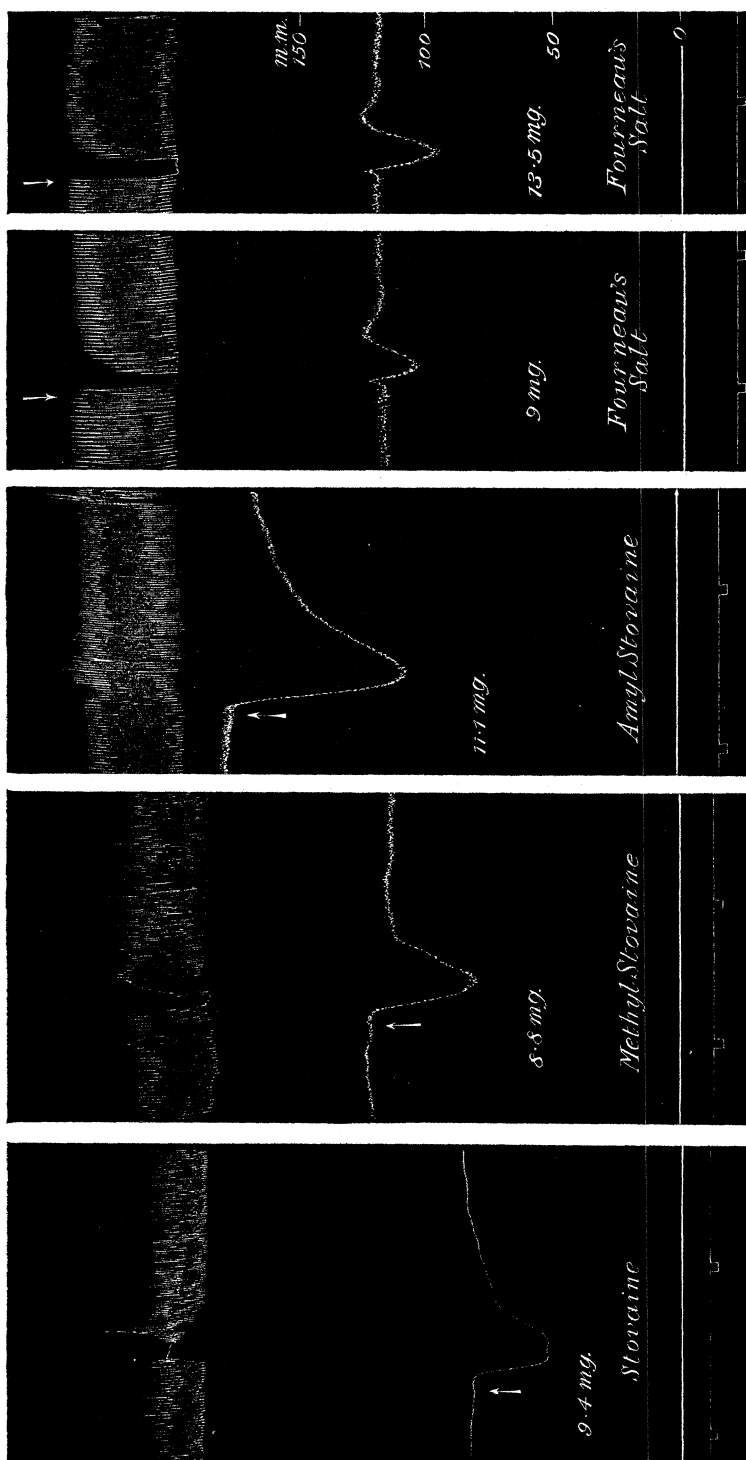
Only one observation was made in each case. With phenyl stovaine a brief rise of blood-pressure preceded the invariable fall, and both drugs produced some dyspnœa. With benzyl stovaine Traube-Hering and Cheyne-Stokes rhythm was noticed in the blood-pressure and respiration respectively. Both drugs are powerful local anæsthetics, but offer no advantage over amyl stovaine.

Fourneau's New Salt.

As already pointed out, this body is (in chemical structure) intermediate between cocaine and stovaine. In its effects, on injection, it also resembles both these drugs, the latter more closely than the former. Small doses may (or may not) produce a trifling initial rise of blood-pressure, but any such rise is small in comparison with the slight fall that invariably follows it. This fall is less than that caused by equivalent doses of the preceding drugs. On respiration, its effect closely resembles that of stovaine and of methyl stovaine, but the momentary pause is followed by closer return to the normal rhythm. Its effects on blood-pressure and on respiration are therefore less marked than those of cocaine, stovaine, and the homologues of the latter. As elsewhere† stated, it is a powerful local anæsthetic.

* *Vide infra*, p. 426.

† *Infra*, p. 427.



Effect of intravenous injections on respiration and on arterial pressure. Each injection is signalled by an arrow. Time tracing shows minutes. For other details consult Table III.

Table III.—*Cf.* Fig.

Drug.	Weight of animal.	Mean arterial pressure.		Ratio of fall to original pressure.
		Before injection.	After injection.	
	kgm.	mm. Hg.	mm. Hg.	Per cent.
Stovaine (9·4 mgrm.).....	3·7	80	52	35
Methyl stovaine (8·8 mgrm.)	3·3	122	82	33
Amyl stovaine (11·1 mgrm.).....	2·8	176	108	39
Fourneau's new salt (9·0 mgrm.).....	3·0	116	106	9
" (13·5 mgrm.) ...	3·0	118	96	19

These results are shown in the records—Fig. 1.

The above doses of stovaine, methyl stovaine, and amyl stovaine are equimolecular to one another and to 11·6 mgrm. of Fourneau's salt. The effect of amyl stovaine is perhaps exaggerated by the smallness of the animal.

In short, on the central nervous system and on the circulation, Fourneau's salt is less active, and methyl stovaine is, at most, no more active, than stovaine. On the central nervous system, amyl stovaine is less active; on the circulation, its depression is somewhat greater in degree, though more gradual in onset.

These three bodies will be further investigated, on more nearly clinical lines, for the purpose of ascertaining whether their anæsthetic properties may fittingly be employed in medical and surgical practice.