Conclusions and Summary

1. The variation in melting points given in the literature for naturally occurring aconitic acid is presumably due to admixtures of two or more definite forms of aconitic acid.

2. Repeated success in the recovery of an acid melting at 172–173° from several species of native plants, and its recovery in the same form from esters point rather clearly to the natural occurrence of an isomeric aconitic acid.

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THE RELATIONSHIP BETWEEN HYDROGEN-ION CONCENTRATION AND CHEMICAL CONSTITUTION IN CERTAIN LOCAL ANESTHETICS

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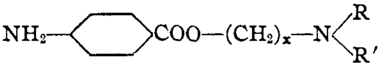
During the past twenty years a considerable number of local anesthetics of the general type (I), where R and R′ are alkyl or allyl groups and where x is any number greater than one, have been described and several have appeared on the market.



I

In an attempt to correlate the relationship between structure, physical properties and anesthetic efficiencies in these compounds, a large number of anesthetics of this type have been prepared.[1] They will be described in subsequent papers.

From recent work[2] it appears that in any study of the efficiency of local anesthetics, the hydrogen-ion concentrations of their aqueous solutions must be considered. Gros[3] found that the anesthetic efficiency of local anesthetics increases markedly as the hydrogen-ion concentration decreases and recent reports corroborate his findings.

In view of this effect of hydrogen-ion concentration on anesthetic efficiency, the hydrogen-ion concentrations of equimolecular solutions of the anesthetics were determined and are described in this communication. It was hoped that such data might incidentally be of some value as a means

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[1] The authors are indebted to The Abbott Laboratories for kindly furnishing quantities of β-diethylaminoethyl-*p*-aminobenzoate hydrochloride and borate, γ-di-*n*-butylaminopropyl-*p*-aminobenzoate hydrochloride and borate and the borates of β-diethylaminopropyl-*p*-aminobenzoate and β-*n*-butylallylaminoethyl-*p*-aminobenzoate.

[2] Copeland, *Brit. Med. J.*, **1925**, II, 547. Regnier, *Bull. sci. pharmacol.*, **31**, 513 (1924); **32**, 513 (1925). Abelin, *Biochem. Z.*, **141**, 458, 470 (1923). Protz, *Arch. exp. Path. Pharmakol.*, **86**, 238 (1920).

[3] Gros, *Arch. exp. Path. Pharmakol.*, **63**, 80 (1910); **67**, 127, 130 (1912).

of ascertaining the relationship between chemical constitution and the basicity of the amines.

Most of the compounds studied were the hydrochlorides of the amino alcohol esters of *p*-aminobenzoic acid. The two principal types of variation in the series were in the R and R′ groups (I) and in the number and arrangement of carbon atoms between the N and O atoms in the alcohol part of the molecule. The compounds before use were all very carefully purified from the proper solvent until successive crystallizations gave no change in melting point. In every instance the compounds were white and well crystallized.

In addition to this main study of the effect of structure on the hydrogen-ion concentrations of solutions of the local anesthetic hydrochlorides, the Sörensen (*P*H) values of a few salts other than the hydrochlorides were also determined.

The determinations of hydrogen-ion concentration were made with the use of the hydrogen electrode in series with a calomel electrode (saturated potassium chloride). The usual procedure was followed and equilibrium was considered to have been reached when there was no appreciable change in e.m.f. after ten minutes. Most of the solutions reached equilibrium quite readily, although some, notably the cyclohexanol derivatives, required nearly an hour.

Rigorous temperature control was not attempted. The room was kept as near to 25° as possible. Due to the high resistance of a few of the solutions, a sharp balance of the potentiometer was somewhat difficult in these cases, although fairly reliable results were obtained by using a rather sensitive galvanometer of the d'Arsonval type. The Sörensen values obtained may be considered as being accurate to about ±0.1 *P*H.

TABLE I

EFFECT OF CHANGES IN THE R AND R′ GROUPS ON THE SÖRENSEN VALUES OF 0.02 *N* SOLUTIONS OF THE HYDROCHLORIDES OF LOCAL ANESTHETICS; BASICITY CONSTANTS

Nature of grouping between the O and N atoms

		$=NCH_2CH_2O—$		$=N(CH_2)_2CH_2O—$		$=NCH(CH_3)$- $CH_2O—$		$=NCHCH_2CHO$ $CH_2CH_2CH_2$	
	R and R′ groups	*P*H	$K_b \times 10^6$	*P*H	$K_b \times 10^6$	*P*H	$K_b \times 10^6$	*P*H	$K_b \times 10^6$
1.	Dimethyl	...	.....	6.2	500	...	...	6.5	2000
2.	Diethyl	6.4	1250	6.7	5000	6.3	800	6.7	5000
3.	Di-*n*-propyl	6.1	310	6.4	1250	...	...	...	..
4.	Di-*iso*propyl	6.3	800	6.9	12000	...	...	...	..
5.	Di-*n*-butyl	5.0	2.0	5.6	32	4.9	1.2	...	..
6.	Di-*iso*butyl	4.4	0.125	4.5	0.20	...	...	...	..
7.	Di-*sec.*-butyl	5.2	5.0	5.4	12.5	...	...	...	..
8.	Di-*n*-amyl	4.6	0.32	4.7	0.50	...	...	...	..
9.	Di-*iso*-amyl	4.6	0.32	4.5	0.20	...	...	...	..
10.	*n*-Butyl allyl	5.3	8.0	5.5	20.0	...	...	...	..
11.	*n*-piperidyl	5.9	120	5.9	120.0	...	...	...	..

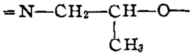
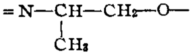
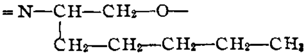
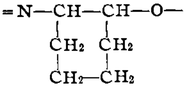
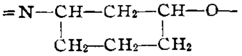
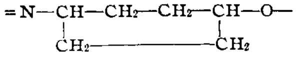
It was found expedient to use solutions of the anesthetics 0.02 N with respect to the amount of anesthetic base present. The solutions were prepared as needed by dissolving the compounds in distilled water.

The basicity constants, K_b, for each of the anesthetics were estimated from the Sörensen values by using the approximation developed by Clark,[4] $[\mathrm{H}^+]$ approximates $\sqrt{(K_w/K_b)\ [S]}$, where $[S]$ is the concentration of salt. The approximation approaches the facts in cases where the value of K_b is relatively small compared to $[S]$ and where the concentration of positive base ion approximates $[S]$.

The Sörensen values and the basicity constants calculated from them are given in Tables I, II and III.

TABLE II

EFFECT OF CHANGES IN THE NUMBER AND ARRANGEMENT OF THE CARBON ATOMS BETWEEN THE N AND O ATOMS ON THE SÖRENSEN VALUES OF 0.02 N SOLUTIONS OF THE HYDROCHLORIDES OF LOCAL ANESTHETICS; BASICITY CONSTANTS

	Nature of grouping between O and N atoms	Dimethyl		Diethyl		Di-*n*-butyl	
		PH	$K_b \times 10^6$	PH	$K_b \times 10^6$	PH	$K_b \times 10^6$
1	$=\mathrm{N{-}CH_2{-}CH_2{-}O{-}}$	...	....	6.4	1250	5.0	2.0
2	$=\mathrm{N{-}CH_2{-}CH_2{-}CH_2{-}O{-}}$	6.2	500	6.7	5000	5.6	32.0
3	$=\mathrm{N{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}O{-}}$	...	....	7.0	20000	...	....
4	$=\mathrm{N{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}O{-}}$	...	....	7.1	31000	...	....
5	 $=\mathrm{N{-}CH_2{-}\underset{\underset{\displaystyle CH_3}{\vert}}{CH}{-}O{-}}$	...	....	6.2	500	...	....
6	 $=\mathrm{N{-}\underset{\underset{\displaystyle CH_3}{\vert}}{CH}{-}CH_2{-}O{-}}$	...	....	6.3	800	4.9	1.2
7	 $=\mathrm{N{-}\underset{\underset{\displaystyle CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_3}{\vert}}{CH}{-}CH_2{-}O{-}}$	...	....	4.9	1.2	...	....
8	 $\begin{array}{l}=\mathrm{N{-}CH{-}CH{-}O{-}}\\ \qquad\ \vert\qquad\ \vert\\ \qquad\mathrm{CH_2\ \ CH_2}\\ \qquad\ \vert\qquad\ \vert\\ \qquad\mathrm{CH_2{-}CH_2}\end{array}$	...	...	(m. p., 216–217°)[a] 6.5	2000	...	....
9	 $\begin{array}{l}=\mathrm{N{-}CH{-}CH_2{-}CH{-}O{-}}\\ \qquad\ \vert\qquad\qquad\ \vert\\ \qquad\mathrm{CH_2{-}CH_2{-}CH_2}\end{array}$	(m. p., 183–185°) 6.5	2000	(m. p., 179–182°) 6.7	5000	...	....
10	 $\begin{array}{l}=\mathrm{N{-}CH{-}CH_2{-}CH_2{-}CH{-}O{-}}\\ \qquad\ \vert\qquad\qquad\qquad\ \vert\\ \qquad\mathrm{CH_2{-}{-}{-}{-}{-}{-}{-}{-}CH_2}\end{array}$	(m. p., 263–264°)[b] 6.7	5000	...	....	...	....
		(m. p., 220–222°)[b] 6.7	5000	...	...	...	...

[a] This substance is an isomer of the product which melts at 163°, described by Osterberg and Kendall, THIS JOURNAL, **43,** 1370 (1921).

[b] These two products are geometric isomers.

TABLE III

VARIATIONS IN THE SÖRENSEN VALUES OF 0.02 N SOLUTIONS OF DIFFERENT SALTS OF LOCAL ANESTHETICS

Substance	Salt		
	Hydrochloride	Acetate	Borate
β-Diethylaminoethyl-*p*-aminobenzoate	6.4	7.1	8.1
γ-Diethylaminopropyl-*p*-aminobenzoate	6.7	...	8.2

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[4] Clark, "The Determination of Hydrogen Ions," Williams and Wilkins Co., **1922,** p. 337.

Discussion of Results

The results of the determinations of hydrogen-ion concentration of the various compounds show a surprisingly consistent relationship to structure. Consequently, the changes in the basicity of compounds of this type may also be directly correlated with the variations in chemical constitution, since the higher the basicity of a substance, the more firmly will the hydrogen ion be held to it.

A few simple relationships are at once apparent. The general tendency is for the basicity to decrease as the size of the R and R′ groups increases (Table I). The dimethylamino compounds, which are slightly less basic than the diethylamino, are exceptions but it is quite common for methyl derivatives to occupy an odd place in such a series. There are also some interesting variations among compounds containing isomeric R groups. Whereas the di-*iso*propylamino compounds are slightly more basic than the di-*n*-propylamino and the di-*iso*- and di-*n*-amylamino products are virtually the same, there is a distinct drop in the basicity of the di-*iso*butylamino compounds from that of their normal and secondary isomers. It is of interest that the basicities of the piperidyl and the *n*-butylallylamino compounds fall between those of the di-*n*-propylamino and di-*n*-butylamino derivatives, as would be expected.

Increasing the number of carbon atoms between the nitrogen and oxygen atoms has an effect just the reverse of increasing the size of the R groups, so long as these carbon atoms are in a straight chain (Table II, 1, 2, 3, 4). However, when carbon atoms are added as side chains, the basicity again decreases. This decrease is only slight when a methyl group is substituted for a hydrogen either on the carbon next to the oxygen or the one next to the nitrogen in the series having only two carbons between the oxygen and nitrogen atoms but is very marked with the *n*-amyl group on the carbon next to the nitrogen (Table II, 5, 6, 7).

The results with the cyclohexanol derivatives indicate that these compounds act as if the nitrogen and oxygen atoms were connected by two straight chains of carbon atoms and that the basicity is determined by the length of the shorter chain. In the diethylamino compound with the oxygen and nitrogen attached to adjacent carbon atoms, thus giving one chain of two carbon atoms and one of six, the hydrogen-ion concentration is practically the same as that of the simple straight-chain compound with two carbons separating the oxygen and nitrogen (Table II, 8; Table I, 2). The hydrogen-ion concentration of the diethylamino compound, having chains of three and five (Table II, 9), is the same as that of the diethylamino derivative with a straight chain of three carbons separating the oxygen and nitrogen (Table I, 2, second column), while the dimethylamino compounds in the same two series differ only slightly. Both geometric dimethylamino isomers, each with two chains of four carbons, are still more basic and the results are in line with the Sörensen values that would be expected of the dimethylamino compound with one straight chain of four carbon atoms between oxygen and nitrogen (Table II, 10).

It is very interesting that these last two geometric isomers (Table II, 10) have Sörensen values that are identical, although their solubilities in water, melting points and anesthetic efficiencies differ greatly.

The Sörensen values of salts formed from weaker acids than hydrochloric agree with those that might be expected. From the stronger bases such as *p*-diethylaminoethyl- and γ-diethylaminopropyl-*p*-aminobenzoate and the weaker acids, salts are formed which are stable in solution but which have Sörensen values higher than those of the hydrochlorides due to the fact that when the salts ionize, the positive ion dissociates into free base and hydrogen ion only to a limited extent, whereas there is a tendency for the negative ion to react with water to form molecules of acid and free hydroxyl ion. However, the acid still furnishes more hydrogen ion than does the positive salt ion, so the compound remains stable.

Attempts were made to dissolve the borates of γ-di-*n*-butylaminopropyl and β-*n*-butylallylaminoethyl-*p*-aminobenzoate in water in order to make determinations of the hydrogen-ion concentration. However, since these compounds are weak bases, their borates were not stable in solution, and quickly hydrolyzed with separation of the free base.

Summary

The hydrogen-ion concentrations of equimolecular solutions of the hydrochlorides of various local anesthetics have been determined.

The effects of changes in structure on the basicity of these compounds have been studied and a few general relations have been pointed out.

The hydrogen-ion concentrations of solutions of a few anesthetic salts formed from weaker acids have been determined and the stabilities of these salts have been discussed.

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