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Alkaline Hydrolysis of Some Local Anaesthetic Esters

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The alkaline hydrolysis of the following local anaesthetic esters has been studied: benzocaine, butyl benzocaine, tetracaine, procaine, panthesine and *o*-hydroxyprocaine.

The velocity constants are determined photometrically in water solution at 25.0, 35.0 and 45.0°C. The influence of substituents on the activation energy and the frequency factor is discussed.

A knowledge of the behaviour of the local anaesthetics on alkaline hydrolysis is of interest not only from a theoretical point of view but also practically. For example the deterioration of pharmaceutical preparations may be estimated and the possibility of heat sterilization predicted. Further, the duration and toxicity of intravenous injected preparations is said to be connected with the speed of hydrolysis by blood serum [1]. In the thesis of Terp [2] the hydrolysis of procaine influenced by procaine esterase is discussed. Obviously, other physical and chemical factors will also affect the physiological effect of local anaesthetics, *e.g.* their solubility. However, this property has not been studied in this work.

Some of the substances which we have studied have also been investigated by other authors. The purpose of most of the earlier investigations published has been to make clear the stability of pharmaceutical preparations under special conditions and the authors have not been interested in the kinetic problems from a theoretical point of view. Among these publications the following may be mentioned [3–8]. Only a few investigations have been found in the literature, where the kinetic aspects on the alkaline hydrolysis of local anaesthetic esters have been thoroughly studied. In Table 1 a survey of the results from other authors is found. The authors all have found, that the process in strongly alkaline solution is a bimolecular reaction and thus can be written

$$\text{ester} + \text{OH}^- \rightarrow \text{alcohol} + \text{acid}$$

and the velocity constant, k_2, is defined by the equation

$$\mathrm{d}x/\mathrm{d}t = k_2\,(\text{OH}^-)\,(\text{ester})$$

Table 1. Previous work.

Compound	k_2 lit/mole/min	Temp. °C	Medium	E kcal	A lit/mole/min	Ref.
Benzocaine	7.53×10^{-4}	25	85 % ethanol	20.00	11.50	9
	5.04×10^{-3}	25	56 % acetone	16.70	10.00	10
	1.14×10^{-3}	30	88 % ethanol	—	—	13
	2.52×10^{-1}	30	water	—	—	15
	1.85×10^{-1}	25	water	12.6	8.5	this work
Procaine	4.8×10^{-2}	40	60 % acetone	—	—	11
	6.6×10^{-1}	40	water	13.80	9.38	12
	7.84×10^{-1}	37	water	—	—	14
	3.14×10^{-1}	25	water	14.2	9.9	this work

In the table all the values of k_2 are given in litre/mole/min. In some of the investigations the hydrolysis has been studied at several temperatures so that the activation energy, E, and the frequency factor, A, could be calculated. In the calculations the Arrhenius formula has been used

$$k_2 = PZ \times e^{-E/RT}$$

and

$$\log (PZ) = A$$

A great number of investigations have been published, where esters of different kinds have been studied in this respect. To be mentioned are the following authors, namely Tommila [16], Tommila and Hinshelwood [10], Newling and Hinshelwood [17], Kindler [13], Jones and Robinson [18], Ingold and Nathan [9] *etc.*

Among the many local anaesthetic esters only benzocaine and procaine seem to have been kinetically studied, and thus the present work will elucidate the properties of some other of the most used local anaesthetic esters.

Many of the authors mentioned have studied the end products of the hydrolysis. Some have found that the first produced acid is later on broken down by decarboxylation, but this has only been found in acidic solutions. In the present work no further decomposition of the acid has been found, at least during the relatively short time the process has been followed. Hydroxy procaine is hydrolyzed to *p*-amino salicylic acid. Not even this rather unstable acid has been decomposed under the conditions and short time used by us.

METHODS

Some authors [1-3,6] have followed the ester hydrolysis by a chemical separation of one of the hydrolysis products, and then the amount of this substance or the ester left has been estimated, for instance photometrically. Another method being used is a titration of the hydroxyl ion. In order to make this method possible the amount of the reacting species must be rather great and this gives a rather high velocity. Further, the investigation has to be made in a suitable solvent as the water solubility of the esters is small. As solvent, acetone-water has been used by Tommila [16] and Armstrong [11], ethanol-water by Ingold [9] and Kindler [13].

We have preferred to use a direct method also used by Higuchi [12,15] and others. All the esters studied in this work have a strong absorption in the UV. The acid formed has the maximum absorption shifted to another wavelength and the molecular extinction at this wavelength is lower than for the ester. Thus the concentration of the ester may be measured photometrically without separating it from the acid. The alcohol has a very low extinction in the same wavelength region. Thanks to the strong absorption, very low concentrations can be used, and thus water is suitable as a solvent.

Figs. 1—6 show the extinction curves of the esters and the corresponding acids. In the hydrolysis experiments all measurements are made at the wavelength where the extinction of the ester has its maximum. We have used the method given by Higuchi [12]:

A 0.1000 % water solution of the ester or its salt was warmed up to the temperature at which the hydrolysis was to be made. (Butyl benzocaine is sparingly soluble in water and in this case a saturated solution was made.) From this stock solution a certain volume was added to a solution of sodium hydroxide in water free from carbon dioxide. The volumes were so chosen that the concentration of the ester was 0.01000 % and the pH of the solution was exactly 12.00. This mixture was kept in one bottle in a water bath, the temperature of which was known within 0.1°. At different times samples were

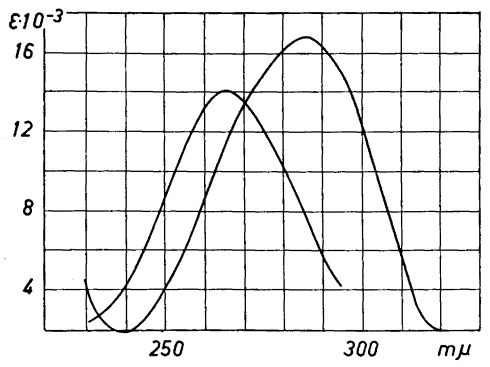


Fig. 1. Molecular extinction *vs.* wave length. Benzocaine (ε_{max} = 16 850 at 286 mμ) and *p*-amino benzoic acid (ε_{max} = 13 980 at 265 mμ). pH = 9.5

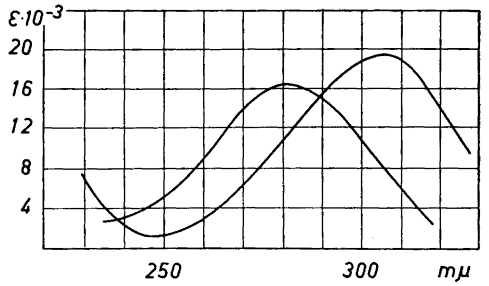


Fig. 2. Molecular extinction *vs.* wave length. Butyl benzocaine (ε_{max} = 19 450 at 305 mμ) and *p*-butyl amino benzoic acid (ε_{max} = 16 640 at 280 mμ). pH = 9.5

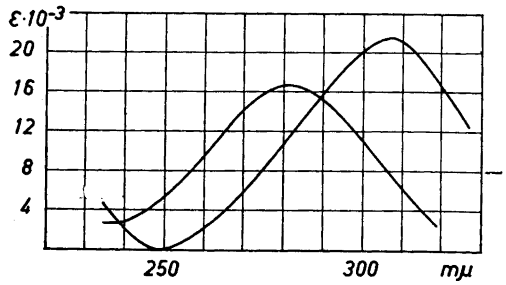


Fig. 3. Molecular extinction *vs.* wave length. Tetracaine (ε_{max} = 21 340 at 307 mμ) and *p*-butyl amino benzoic acid (ε_{max} = 16 640 at 280 mμ). pH = 9.5

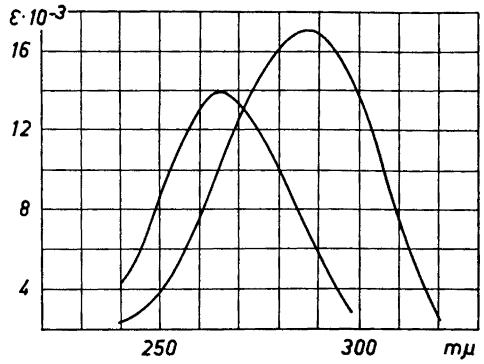


Fig. 4. Molecular extinction *vs.* wave length. Procaine (ε_{max} = 17 050 at 287 mμ) and *p*-amino benzoic acid (ε_{max} = 13 980 at 265 mμ). pH = 9.5

taken from the mixture and added to a borate buffer solution with a pH = 9.5, which was made according to the Swedish Pharmacopeia Ed. XI. The extinction of the resulting solution was measured with a Beckmann photometer model DU in 1 cm cuvettes.

In order to avoid the influence of the carbon dioxide of the air, some experiments were made in a slightly different manner. The reaction mixture was dispensed in a number of bottles closed with glass stoppers. The content of each bottle was used only for one measurement. However, it was found that the results from these experiments agreed with the other ones.

The reaction mixture contained about 30 times the theoretically necessary amount of sodium hydroxide to hydrolyse the total amount of ester. This means that the concentration of hydroxyl ions is hardly changed during the experiment. It was found that the pH of the solutions was diminished by 0.02 units at the end of the experiments. Thus, the reactions could be treated as monomolecular.

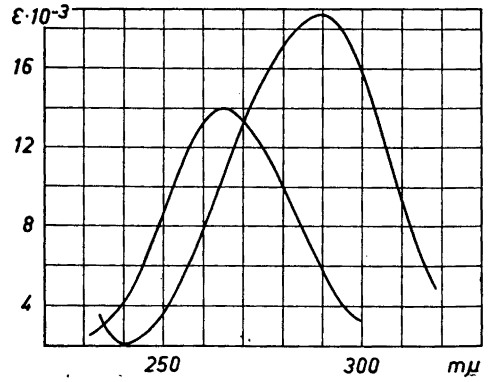


Fig. 5. Molecular extinction *vs.* wave length. Panthesine (ε_{max} = 18 680 at 289 mμ) and *p*-amino benzoic acid (ε_{max} = 13 980 at 265 mμ). pH = 9.5

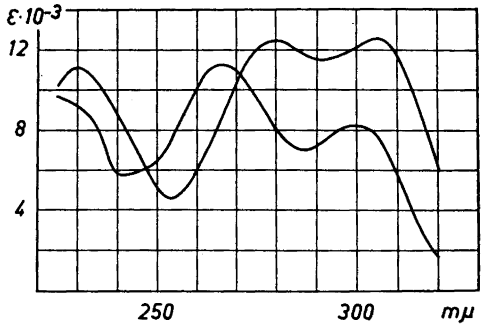


Fig. 6. Molecular extinction *vs.* wave length. Hydroxy procaine (ε_{max} = 12 550 at 305 mμ) and *p*-amino salicylic acid (ε_{max} = 8 290 at 300 mμ). pH = 9.5

Table 2. Hydrolysis of benzocaine. Starting conc. of ester = 6.054×10^{-4} mole/lit. λ = 286 mμ

Temp.	Time (min)	E_t	$E_t - E_s$	log (% ester left)
25°	0	1.020	0.563	2.0000
	65	0.955	0.498	1.9467
	120	0.905	0.448	1.9008
	210	0.845	0.388	1.8383
	240	0.835	0.378	1.8270
	315	0.762	0.305	1.7338
	"infin."	0.457	0.000	—
35°	0	1.020	0.563	2.0000
	30	0.970	0.513	1.9596
	55	0.934	0.477	1.9280
	135	0.805	0.348	1.7911
	180	0.760	0.303	1.7309
	"infin."	0.457	0.000	—
45°	0	1.020	0.563	2.0000
	15	0.960	0.503	1.9511
	40	0.885	0.428	1.8809
	60	0.828	0.371	1.8189
	82	0.773	0.316	1.7492
	120	0.730	0.273	1.6857
	225	0.572	0.115	1.3102
	340	0.509	0.052	0.9655
	"infin."	0.457	0.000	—

All the esters studied in this investigation were examined at 25.0, 35.0 and 45.0°C.

Chemicals. Commercial benzocaine, tetracaine hydrochloride, procaine hydrochloride, and panthesine methane sulfonate were used without any further purification.

Hydroxy procaine hydrochloride was synthesized from *p*-amino salicylic acid and β-chloroethyl diethylamine hydrochloride. The latter was synthesized according to Gough and King [20]. The acid was suspended in acetone and then β-chloroethyl diethylamine hydrochloride was added. The mixture was refluxed for 20 h. *Iso*propyl alcohol containing 10 % hydrogen chloride was then added to the filtered solution [19]. The precipitate was washed with acetone and recrystallized from ethanol. The melting point was 153.5—154°C. The water content was determined by K. Fischer titration to be 1.8 %.

Butyl benzocaine was synthesized from butyl bromide and benzocaine [21]. Its melting point was 68°C. The other chemicals used were of analytical grade.

RESULTS

The results of the experiments are reported in Tables 2—7. E_t is the extinction of the reaction mixture when added to the buffer solution. E_o, the extinction at the beginning of an experiment, was determined by measuring the ester in the same buffer solution but without any alkali. E_s, the extinction after "infinite" time, was determined by measuring the corresponding acid dissolved in the buffer solution.

Table 3. Hydrolysis of butyl benzocaine.

Starting conc. of ester = 4.190×10^{-5} (25°) mole/lit. $\lambda = 305$ mμ
4.370×10^{-5} (35°) »
4.113×10^{-5} (45°) »

Temp.	Time (min)	E_t	$E_t - E_s$	log (% ester left)
25°	0	0.815	0.453	2.0000
	70	0.756	0.394	1.9394
	125	0.730	0.368	1.9098
	225	0.700	0.338	1.8728
	275	0.683	0.321	1.8504
	350	0.661	0.299	1.8196
	465	0.622	0.260	1.7589
	"infin."	0.362	0.000	—
35°	0	0.850	0.473	2.0000
	70	0.730	0.353	1.8729
	120	0.690	0.313	1.8207
	225	0.629	0.252	1.7265
	275	0.583	0.206	1.6390
	350	0.560	0.183	1.5876
	465	0.514	0.137	1.4619
	"infin."	0.377	0.000	—
45°	0	0.800	0.445	2.0000
	60	0.668	0.313	1.8472
	115	0.630	0.275	1.7910
	215	0.500	0.145	1.5130
	265	0.475	0.120	1.4308
	340	0.434	0.079	1.2493
	"infin."	0.355	0.000	—

From the experimental results, the concentration of ester in each measurement could be calculated by the formula

$$\% \text{ ester left} = \frac{E_t - E_s}{E_o - E_s} \times 100$$

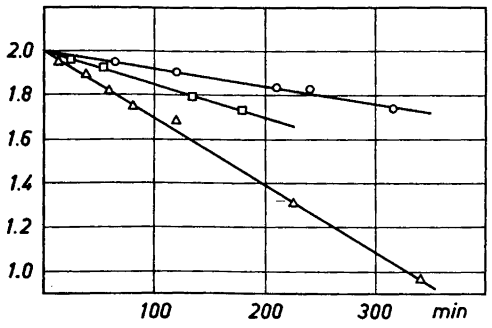


Fig. 7. Hydrolysis of benzocaine. log (% ester left) *vs.* time.

Table 4. Hydrolysis of tetracaine HCl.

Starting conc. of ester = 3.028×10^{-4} (25°) mole/lit. $\lambda = 307$ mμ
3.304×10^{-4} (35°) »
3.304×10^{-4} (45°) »

Temp.	Time (min)	E_t	$E_t - E_s$	log (% ester left)
25°	0	0.646	0.428	2.0000
	60	0.612	0.394	1.9640
	120	0.558	0.340	1.8890
	180	0.530	0.312	1.8627
	230	0.497	0.279	1.8142
	300	0.468	0.250	1.7665
	360	0.454	0.236	1.7415
	430	0.433	0.215	1.7010
	"infin."	0.218	0.000	—
35°	0	0.705	0.467	2.0000
	50	0.647	0.409	1.9424
	70	0.607	0.369	1.8977
	140	0.523	0.285	1.7855
	185	0.484	0.246	1.7216
	240	0.443	0.205	1.6425
	"infin."	0.238	0.000	—
45°	0	0.705	0.467	2.0000
	45	0.578	0.340	1.8622
	65	0.532	0.294	1.7990
	135	0.405	0.167	1.5534
	180	0.359	0.121	1.4135
	235	0.318	0.080	1.2338
	"infin."	0.238	0.000	—

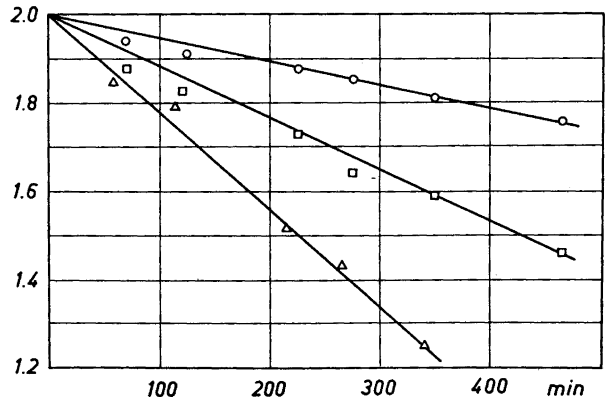


Fig. 8. Hydrolysis of butyl benzocaine. log (% ester left) *vs.* time.

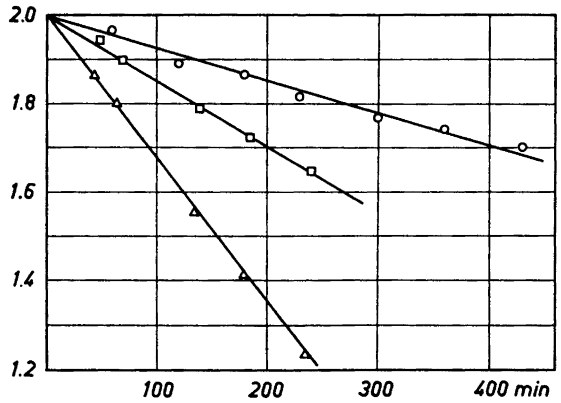


Fig. 9. Hydrolysis of tetracaine. log (% ester left) *vs.* time.

If the logarithm of this number is plotted against the time, straight lines should be obtained. These are found in Figs. 7—12. From the slope of the lines the velocity constant, k_1, may be calculated. k_1 refers to the "monomolecular" reaction:

$$k_1 \cdot t = \ln \frac{E_o - E_s}{E_t - E_s}$$

or

$$\frac{k_1 \cdot t}{2.303} = 2 - \log (\% \text{ ester left})$$

However, the reaction rate is

$$dx/dt = k_1 (\text{ester}) = k_2 (\text{ester}) (OH^-)$$

where k_2 is the bimolecular reaction rate constant. Thus the following equations are valid

$$k_2 = k_1/(OH^-)$$

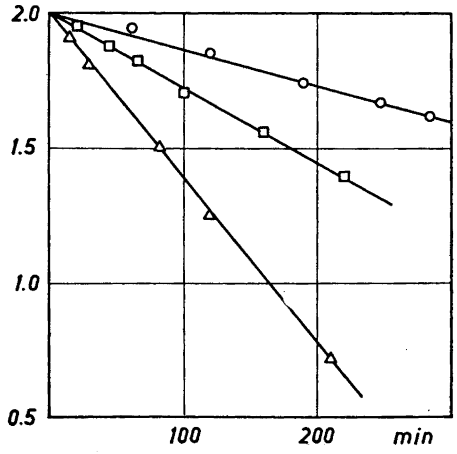


Fig. 10. Hydrolysis of procaine. log (% ester left) *vs.* time.

Table 5. Hydrolysis of procaine HCl.

Starting conc. of ester = 3.667×10^{-4} mole/lit. $\lambda = 287$ mμ

Temp.	Time (min)	E_t	$E_t - E_s$	log (% ester left)
25°	0	0.625	0.364	2.0000
	60	0.582	0.321	1.9453
	120	0.522	0.261	1.8555
	195	0.462	0.201	1.7421
	247	0.430	0.169	1.6668
	285	0.412	0.151	1.6179
	"infin."	0.261	0.000	—
35°	0	0.627	0.365	2.0000
	20	0.596	0.334	1.9615
	45	0.537	0.275	1.8770
	65	0.504	0.242	1.8215
	100	0.448	0.186	1.7046
	160	0.395	0.133	1.5615
	220	0.353	0.091	1.3967
	"infin."	0.262	0.000	—
45°	0	0.625	0.364	2.0000
	15	0.558	0.297	1.9116
	30	0.498	0.237	1.8136
	82	0.378	0.117	1.5070
	120	0.326	0.065	1.2518
	210	0.280	0.019	0.7177
	"infin."	0.261	0.000	—

Table 6. Hydrolysis of panthesine methane sulfonate.

Starting conc. of ester = 1.239×10^{-4} mole/lit. $\lambda = 289$ mμ

Temp.	Time (min)	E_t	$E_t - E_s$	log (% ester left)
25°	0	0.463	0.311	2.0000
	35	0.445	0.293	1.9741
	65	0.429	0.277	1.9497
	120	0.394	0.242	1.8911
	215	0.354	0.202	1.8126
	270	0.323	0.171	1.7402
	"infin."	0.152	0.000	—
35°	0	0.463	0.311	2.0000
	40	0.422	0.270	1.9386
	65	0.388	0.236	1.8802
	90	0.355	0.203	1.8147
	120	0.320	0.168	1.7325
	250	0.243	0.091	1.4663
	"infin."	0.152	0.000	—
45°	0	0.463	0.311	2.0000
	30	0.372	0.220	1.8497
	50	0.338	0.186	1.7767
	95	0.267	0.115	1.5679
	130	0.232	0.080	1.3931
	150	0.213	0.061	1.2926
	"infin."	0.152	0.000	—

Table 7. Hydrolysis of hydroxy procaine HCl.

Starting conc. of ester = 3.394×10^{-4} mole/lit. $\lambda = 305$ mμ

Temp.	Time (min)	E_t	$E_t - E_s$	log (% ester left)
25°	0	0.433	0.1745	2.0000
	60	0.426	0.1675	1.9823
	120	0.421	0.1625	1.9689
	240	0.407	0.1485	1.9299
	300	0.399	0.1405	1.9058
	360	0.391	0.1325	1.8802
	420	0.385	0.1265	1.8603
	480	0.379	0.1205	1.8392
	795	0.348	0.0895	1.7101
	840	0.344	0.0855	1.6902
	900	0.338	0.0795	1.6586
	"infin."	0.2585	0.0000	—
35°	0	0.433	0.1745	2.0000
	30	0.426	0.1675	1.9823
	60	0.417	0.1585	1.9582
	90	0.409	0.1505	1.9358
	120	0.399	0.1405	1.9059
	150	0.389	0.1305	1.8738
	180	0.378	0.1195	1.8352
	240	0.365	0.1065	1.7855
	270	0.358	0.0995	1.7560
	300	0.352	0.0935	1.7290
	330	0.346	0.0875	1.7002
	360	0.341	0.0825	1.6747
	420	0.332	0.0735	1.6245
	480	0.325	0.0665	1.5810
	"infin."	0.2585	0.0000	—
45°	0	0.449	0.1905	2.0000
	23	0.424	0.1655	1.9389
	40	0.403	0.1445	1.8900
	60	0.386	0.1275	1.8256
	83	0.369	0.1105	1.7634
	120	0.350	0.0915	1.6815
	150	0.336	0.0775	1.6094
	180	0.322	0.0635	1.5228
	210	0.311	0.0525	1.4403
	240	0.303	0.0445	1.3685
	270	0.297	0.0385	1.3056
	300	0.293	0.0345	1.2579
	330	0.289	0.0305	1.2044
	"infin."	0.2585	0.0000	—

or when pH = 12.00 and $(OH^-) = 0.01$

$$k_2 = 100\, k_1$$

k_2 is given in litre/mole/min. The results are surveyed in Table 8.

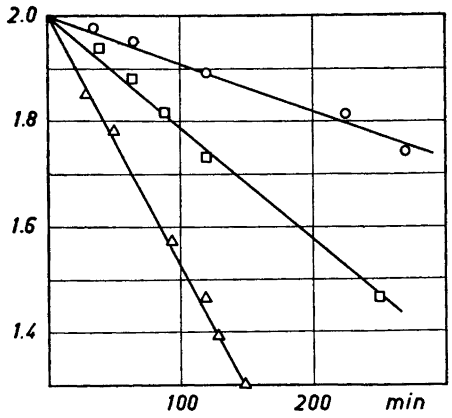


Fig. 11. Hydrolysis of panthesine. log (% ester left) *vs.* time.

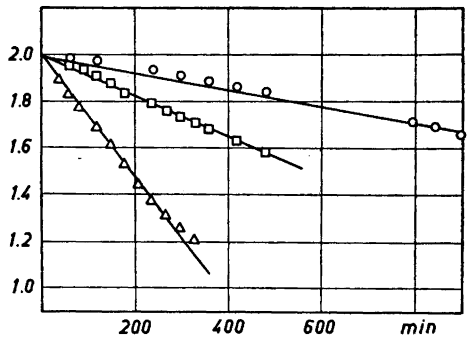


Fig. 12. Hydrolysis of hydroxy procaine. log (% ester left) *vs.* time.

The equation of Arrhenius is transformed to

$$\ln k_2 = \ln (PZ) - E/RT$$

or, when $\log (PZ) = A$

$$\log k_2 = A - \frac{E}{2.303\ RT}$$

Thus, if $\log k_2$ is plotted against $1/T$ a straight line should be obtained. The slope of the line, multiplied by 2.303 R, is the activation energy, E, and the intercept the frequency factor, A. In Fig. 13 these straight lines are shown. Table 9 shows the values obtained in this manner. The numbers are calculated by means of the method of least squares.

DISCUSSION

In alkaline medium the ester hydrolysis is due to the action of the nucleophilic reagent OH^- upon the carbon atom of the carbonyl group. This carbon atom has a partial positive charge due to the electrophilic character of the oxygen atom:

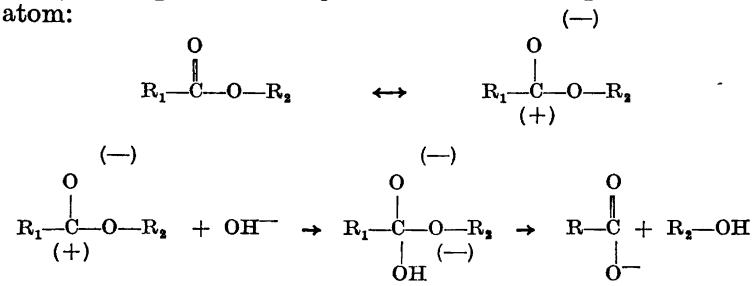


Table 8. Survey of results.

Name	k_2 lit/mole/min.		
	25.0°	35.0°	45.0°
Benzocaine	0.185	0.352	0.701
Butyl benzocaine	0.122	0.269	0.509
Tetracaine	0.173	0.344	0.743
Procaine	0.314	0.631	1.416
Panthesine	0.206	0.482	1.080
Hydroxy procaine	0.0825	0.204	0.613

By substitution in the acidic or the alcoholic part of the ester molecule the positive charge of the carbonyl carbon may be increased or decreased, which leads to a faster or slower hydrolysis. The ease with which the hydrolysis takes place may be expressed by the activation energy, E, of the process. A high value of E means a slow reaction and a low value of E means a fast reaction (provided that the value of the frequency factor A is unchanged).

The facts presented in this work are still too few to draw definite conclusions. However, it seems to be possible to make some preliminary observations.

The introduction of a butyl group causes, as expected, an electron releasing effect. This is apparent by a comparison of the activation energies of benzocaine and butyl benzocaine. Here the butyl group diminishes the positive charge of the carbonyl carbon and thus the activation energy is increased by

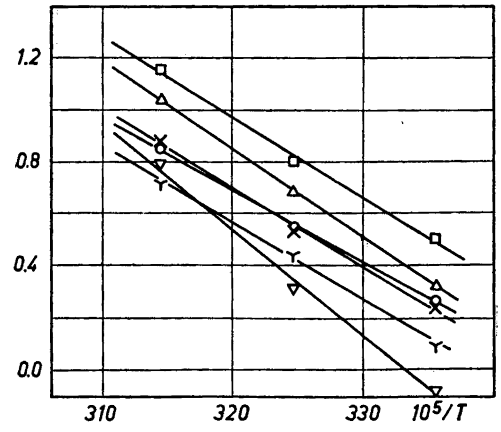
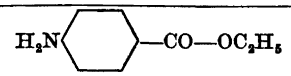
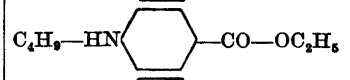
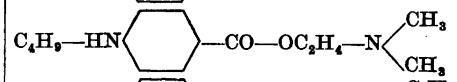
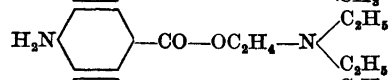
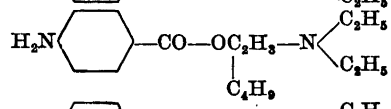
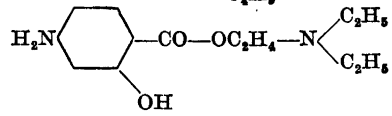


Fig. 13. (1 + log k_2) *vs.* 1/T.

Benzocaine	O	Procaine	□
Butyl benzocaine	Y	Panthesine	△
Tetracaine	×	Hydroxy procaine	▽

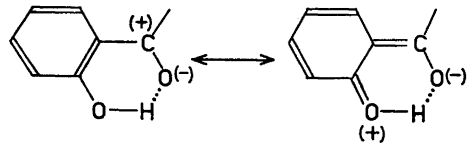
Table 9. Survey of results calculated from Fig. 13.

No.	Name	Formula	*E* kcal.	*A* lit/mole/min.
1	Benzocaine		12.6	8.5
2	Butyl benzocaine		13.5	9.0
3	Tetracaine		13.8	9.3
4	Procaine		14.2	9.9
5	Panthesine		15.7	10.8
6	Hydroxy procaine		18.9	12.8

0.9 kcal. A comparison of procaine and panthesine shows that the butyl group, when placed in the β-position of the alcohol, increases the E value by 1.5 kcal. In both cases the frequency factor is increased at the same time.

The introduction of a tertiary amino group in the alcoholic part of the ester has a rather vague effect. By comparing benzocaine and procaine it can be seen that the amino group increases E by 1.6 kcal, but by comparing butyl benzocaine and tetracaine it is found that there is an increase by only 0.3 kcal. At the same time there is a change in the frequency factor.

However, the introduction of a hydroxy group in the *ortho*-position in the benzene ring has the most striking effect. By a comparison of procaine and hydroxy procaine it is found that the OH group causes an increase in E by 4.7 kcal and in A by 2.9 units. The increase of the activation energy may be understood by the resonance effect, which is followed by an *o*-hydroxy group and which is visualized by the formula



(The dotted line represents a hydrogen bond.) By this resonance the charge on the carbonyl carbon is diminished.

The increase in A is opposite to the effect which is found in other cases of *ortho* substitution of esters of benzoic acid [9]. This effect may be understood by the following reasoning.

In esters of benzoic acid and *p*-amino benzoic acid there is a free rotation of the bond between the benzene ring and the carboxylic group. The reagent OH^- may rather easily attack the carbonyl carbon, which leads to hydrolysis. When there is an *ortho* group such as CH_3, Cl or NO_2 the carboxyl group will prefer to be in a plane which is perpendicular to the plane of the benzene ring. This means that the hydroxyl ion must attack from that side of the molecule which is opposite to the *ortho* substituent, and this fact makes the attack more difficult from steric reasons. This is indicated by a low value of A.

Ortho substitution by the hydroxy group seems to have an opposite effect. The hydroxy group is bound to the carbonyl group with a hydrogen bond, and thus the carboxyl group is held in the same plane as the benzene ring. The reagent OH^- will attack in a direction which is perpendicular to the benzene ring plane. From a steric point of view this attack seems to be easier than from another angle and this is indicated by a high value of A. However, at the same time there is a decrease in E.

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