[42] Forty-nine per cent w/w liquid containing sodium, 1-undecyl 2-hydroxy 2-sodium ethoxymethylene carboxylate ethylene cycloimidinium 2-methylene carboxylate, Miranol Chemical Co., Inc., Irvington, N. J.

[43] Forty-seven per cent w/w liquid containing sodium 1-nonyl 2-lauryl sulfate 2-hydroxyethyl ethylene cycloimidinium 2-methylene carboxylate, Miranol Chemical Co., Inc., Irvington, N. J.

[44] Forty-six per cent w/w liquid containing 1-undecyl 2-undecyl sulfate 2-sodium ethoxymethylene carboxylate ethylene cycloimidinium 2-methylene carboxylate, Miranol Chemical Co., Inc., Irvington, N. J.

[45] Thirty-three per cent w/w liquid containing cetyl betaine, E. I. DuPont de Nemours & Co., Inc., Wilmington, Del.

[46] Thirty-three per cent w/w liquid containing a mixture of long chain betaines, E. I. DuPont de Nemours & Co., Inc., Wilmington, Del.

[47] Iodine-nonyl phenoxypolyoxyethylene ethanol complex, in liquid form and containing 20% available iodine, Antara Chemicals, Division of General Aniline and Film Corp., New York, N. Y.

[48] N(methyl heptyl colamino-formyl methyl)pyridinium chloride containing coupled iodine, in liquid form and containing 0.6% available iodine, Ruson Laboratories, Inc., Portland, Ore.

[49] Polyvinylpyrrolidone-iodine complex, in liquid form and containing 1% available iodine, Tailby-Nason Co., Inc., Dover, Del.

[50] Partially polymerized silver mannuride, Ion-Exchange and Chemicals Corp., New York, N. Y.

[51] Diacetate salt of bis (*p*-chlorophenyl diquanido)-hexane. Marketed as Hibitane by Ayerst Laboratories, New York, N. Y.

[52] Marketed as Coli-Mycin S by Warner-Chilcott Laboratories, Morris Plains, N. J.

Comparative Hydrolytic Rates of Some Tropine Esters

By J. M. PATEL and A. P. LEMBERGER

A study has been carried out on the chemical kinetics of the hydroxyl ion catalyzed hydrolysis of nor-atropine, tropine phenylacetate, tropine phenoxyacetate, tropine *p*-nitrobenzoate, atropine ethylbromide, and atropine benzylchloride. The purpose of the study was to observe the effects of various acid moieties in tropine esters on overall reaction rate. The experimental results would seem to indicate that a number of factors may be involved, including steric, inductive, and hyperconjugation effects.

THE RELATIVE RATES of second-order alkaline hydrolysis of atropine (1), homatropine (2), atropine methylbromide, and homatropine methylbromide (3) have been reported previously. The purpose of this investigation was to study further the influence of inductive and steric factors on the hydrolytic cleavage of these esters. The kinetics of the hydroxyl ion catalyzed hydrolysis of nor-atropine were studied in order to establish hydrolytic rates for what might be considered the base compound. Tropine phenylacetate, tropine phenoxyacetate, and tropine *p*-nitrobenzoate were prepared and rates of hydrolysis determined. In addition, atropine ethylbromide and atropine benzylchloride were prepared and studied.

THEORY

Previous studies (1–3) have shown hydroxyl ion catalyzed hydrolysis to occur with tropine esters. Since nor-atropine, tropine phenylacetate, tropine phenoxyacetate, and tropine *p*-nitrobenzoate can exist as the free base or as the protonated form in solution, two hydrolytic pathways are possible. For convenience, hydrolysis of the free base will be designated Reaction 1, hydrolysis of the protonated form of the ester will be designated Reaction 2.

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In accord with the theoretical concepts employed by Higuchi, *et al.* (4), in their study on procaine, the reaction kinetics may be

$$-\log t_{1/2} = \log (OH^-) - \log [K_b + (OH^-)] + \log \left[\frac{k_1(OH^-)}{0.693} + \frac{k_2 \cdot K_b}{0.693}\right] \quad \text{(Eq. 1)}$$

where k_1 and k_2 are the second-order rate constants at high pH (Reaction 1) and low pH (Reaction 2), respectively, and K_b is the dissociation constant of the base.

At relatively high hydroxyl ion concentration, where $OH^- >> K_b$, Eq. 1 reduces to

$$-\log t_{1/2} = \log (OH^-) + \log \frac{k_1}{0.693} \quad \text{(Eq. 2)}$$

Conversely, at low hydroxyl ion concentration, where $K_b >> OH^-$ it simplifies to

$$-\log t_{1/2} = \log (OH^-) + \log \frac{k_2}{0.693} \quad \text{(Eq. 3)}$$

It is apparent, then, that at high pH and at low pH the rate of hydrolysis should be directly proportional to hydroxyl ion concentration even though the mechanism of hydrolysis changes.

In the case of esters containing quaternary nitrogen, such as atropine ethylbromide and atropine benzylchloride, the mechanism of hydrolysis remains the same throughout the entire pH range.

EXPERIMENTAL

Materials.—Nor-atropine sulfate (K and K Laboratories) was recrystallized from ethanol and water.

TABLE I.—BUFFER SOLUTIONS USED

pH Range	Compn.
6.99–7.97	$M/15$ KH_2PO_4-Na_2HPO_4
8.03–9.89	$M/10$ H_3BO_3 + $M/10$ KCl + NaOH
10.01–10.51	$M/20$ $Na_2B_4O_7$-Na_2CO_3

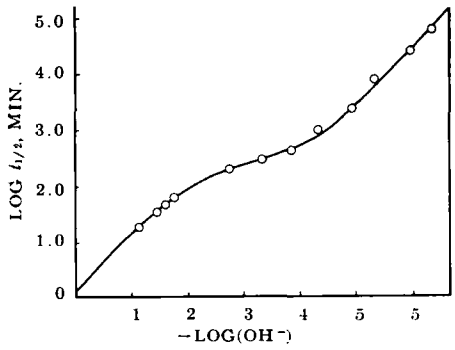

Fig. 1.—Half life of nor-atropine as a function of (OH^-) at 30°C. Solid line, theoretical; points, experimental.

Tropine phenylacetate, tropine phenoxyacetate, and tropine *p*-nitrobenzoate were prepared by reacting tropine hydrochloride with the appropriate acid chloride as described below. Phenylacetyl chloride was prepared according to the procedure of Auwers (5), phenoxyacetyl chloride was prepared according to the procedure of Rosenmund and Zetzsche (6), and *p*-nitrophenylacetyl chloride was obtained commercially.

A 2.0-Gm. quantity of the appropriate acid chloride was added to 2.5 Gm. of tropine hydrochloride in 20 ml. of dry chloroform. The reaction mixture was refluxed gently for 12 hours until evolution of hydrochloric acid ceased. The reaction mixture was extracted several times with water; the aqueous solution of ester salt was then made alkaline with 6% ammonia solution and immediately extracted with chloroform. Chloroform solutions were extracted four times with 5% hydrochloric acid solution, and the aqueous solution evaporated to dryness under vacuum (29°). The residue was dissolved in absolute ethanol, filtered, and anhydrous ether added until the solution just became hazy. Crystals which formed over 36 hours were filtered off and dried at 80°. The hydrochloride salt of the ester was recrystallized twice following the procedure outlined above and dried at 100°. Yields were poor but sufficient ester was obtained for hydrolytic studies.

Tropine phenylacetate hydrochloride, m.p. 197°.

Anal.—Calcd for $C_{16}H_{21}NO_2 \cdot HCl$: C, 64.96; H, 7.49; N, 4.73; Cl, 11.98. Found: C, 64.96; H, 7.50; N, 4.74; Cl, 12.06.

Tropine phenoxyacetate hydrochloride, m.p. 180°.

Anal.—Calcd. for $C_{16}H_{21}NO_3 \cdot HCl$: C, 61.63; H, 7.11; N, 4.49; Cl, 11.37. Found: C, 61.16; H, 7.02; N, 4.44; Cl, 11.55.

Tropine *p*-nitrobenzoate hydrochloride, m.p. 278° dec.

Anal.—Calcd. for $C_{15}H_{18}N_2O_4 \cdot HCl$: C, 55.14; H, 5.86; N, 8.57; Cl, 10.85. Found: C, 55.22; H, 5.84; N, 8.57; Cl, 11.11.

Atropine ethylbromide and atropine benzylchloride were prepared by refluxing atropine base with an excess of ethyl bromide or benzyl chloride in a vessel fitted with an air condenser. The reaction mixture was cooled and allowed to stand for 24 hours. The appropriate ester was recrystallized from anhydrous ether and dried at 100°.

Atropine ethylbromide, m.p. 176° dec.

Anal.—Calcd. for $C_{19}H_{28}NO_3Br$: C, 57.30; H, 7.10; N, 3.50; Br, 20.06. Found: C, 57.27; H, 6.90; N, 3.45; Br, 20.03.

Atropine benzylchloride, m.p. 220–221°.

Anal.—Calcd. for $C_{24}H_{30}NO_3Cl$: C, 69.30; H, 7.27; N, 3.37; Cl, 8.52. Found: C, 69.15; H, 7.30; N, 3.34; Cl, 8.59.

Buffer System.—To maintain hydroxyl ion concentration essentially constant at low pH values, the buffer solutions shown in Table I were used. For high pH, $Ba(OH)_2$ solution was used. Since the concentration of ester was kept low relative to the $Ba(OH)_2$ concentration, the pH remained

TABLE II.—

Compd.	$K_b \times 10^5$	Activation Energy Kcal./mole	Log Frequency Factor	Rate Constant L./mole/sec., 30°C.
Reaction 1				k_1
Tropine phenylacetate	7.4	11.3	5.41	1.8×10^{-3}
Tropine phenoxyacetate	4.7	8.8	5.43	0.11
Tropine *p*-nitrobenzoate	0.2	9.8	5.71	4.7×10^{-2}
Nor-atropine	11.7	7.1	3.07	8.8×10^{-3}
Atropine[a]	7.3	7.7	3.54	9.8×10^{-3}
Homatropine[a]	7.6	12.3	7.62	5.2×10^{-2}
Reaction 2				k_2
Tropine phenylacetate	...	5.4	3.00	0.13
Tropine phenoxyacetate	...	7.9	5.89	1.52
Tropine *p*-nitrobenzoate	...	11.0	7.98	1.05
Nor-atropine	...	6.9	4.59	0.42
Atropine[a]	...	12.0	8.54	0.25
Homatropine[a]	...	11.4	8.72	2.05
Quaternary Esters				k
Atropine methylbromide[a]	...	14.0	9.82	0.54
Atropine ethylbromide	...	10.7	7.38	0.47
Atropine benzylchloride	...	15.8	11.43	1.01
Homatropine methylbromide[a]	...	13.0	9.74	2.34

[a] Calculated from literature data (1–3).

essentially constant during the course of the reaction.

Procedure.—The desired quantity of buffer solution was placed in a thermostatically controlled bath at the desired temperature and allowed to reach temperature equilibrium. One milliliter of a solution containing sufficient ester to give the reaction mixture a concentration of approximately 1 mg./ml. was added and mixed by inverting the flask several times. The first sample of the reaction mixture withdrawn immediately was designated as the "0" minute sample and analyzed for residual ester. Progress of the reaction was followed by the withdrawal of samples at suitable time intervals and determination of residual ester concentration.

For nor-atropine, the method reported in the literature for atropine (1) and homatropine (2) was followed. For tropine phenylacetate, tropine phenoxyacetate, and tropine *p*-nitrobenzoate, carbon tetrachloride was used for extraction because extraction was incomplete with chloroform as the solvent.

Second-order reaction rates of the quaternary salts, atropine ethylbromide, and atropine benzylchloride were followed by indicator photometry as described by Patel and Lemberger (3), using "Alizarin yellow R" solution for determining OH^- ions. It was found that the indicator was very sensitive to atmospheric oxidation; therefore 0.003 *M* sodium sulfite was added to the 0.00655 *M* $Ba(OH)_2$ solution, and the $BaSO_3$ formed acted as an antioxidant. The precipitated excess $BaSO_3$ was filtered off and the concentration of the hydroxyl ions was determined by titration.

RESULTS

Influence of Ester Concentration.—At constant temperature and hydroxyl ion concentration, the rate of hydrolysis of nor-atropine, tropine phenylacetate, tropine phenoxyacetate, and tropine *p*-nitrobenzoate was observed to be first-order with respect to ester in agreement with earlier studies (1, 2).

Influence of Hydroxyl Ion Concentration.—The effect of hydroxyl ion concentration on the rate of hydrolysis of nor-atropine (expressed in terms of half life in minutes of the ester) is illustrated in Fig. 1. Rate measurements were carried out for tropine phenylacetate, tropine phenoxyacetate, and tropine *p*-nitrobenzoate, one at high pH and one at low pH to obtain k_1 and k_2 for Reaction 1 and Reaction 2, respectively. K_b was determined from the pH of a half neutralized solution of the salt of the ester at 30°. These results are shown in Table II.

Temperature Dependency.—Figure 1 further verifies that above pH 12.0 the mechanism of

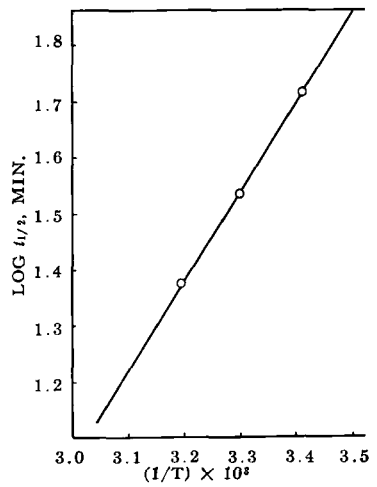

Fig. 2.—Temperature dependency of Reaction 1 for nor-atropine.

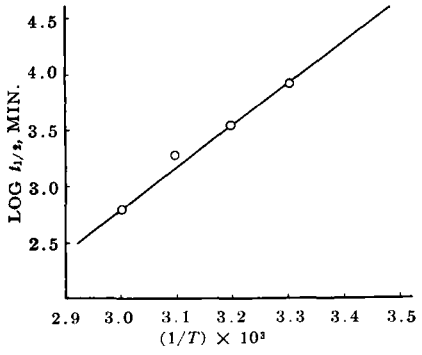

Fig. 3.—Temperature dependency of Reaction 2 for nor-atropine.

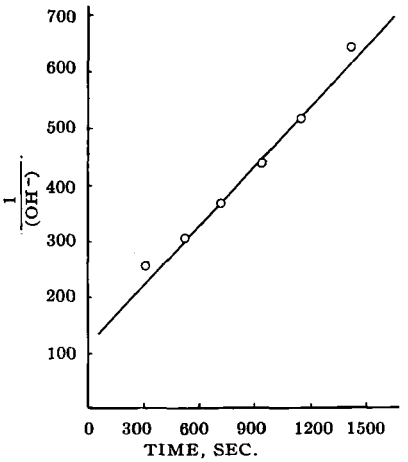

Fig. 4.—Typical bimolecular rate plot for the alkaline hydrolysis of atropine ethylbromide at 25.0°C. when alkali and ester are equal.

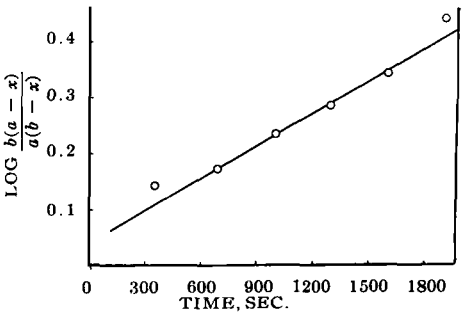

Fig. 5.—Typical bimolecular rate plot for the alkaline hydrolysis of atropine benzylchloride at 15.0°C. when alkali (*a*) and ester (*b*) are not equal.

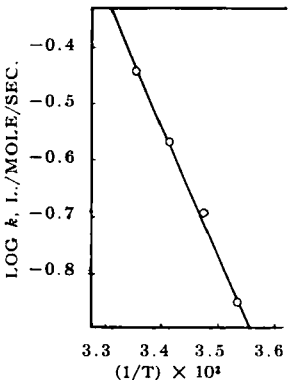

Fig. 6.—Arrhenius plot of the bimolecular rate constants for the alkaline hydrolysis of atropine ethyl bromide.

hydrolysis of these esters is that of Reaction 1, and that below pH 8.5 the mechanism is that of Reaction 2. Half lives were determined at different temperatures to study the temperature dependency of Reaction 1 and Reaction 2, respectively.

The logarithms of half life periods in minutes for these esters were plotted against the reciprocal of absolute temperatures and the straight line relationships obtained as illustrated in Figs. 2 and 3 indicate that the mechanism responsible for the ester hydrolysis is not altered by changes in temperature. The apparent activation energies were determined from the slopes of the plots and the frequency factors calculated from

$$k = se^{-\frac{E}{RT}}$$

The results are given in Table II.

Quaternary Salts.—The kinetics of the alkaline hydrolysis of the ester groups in atropine ethylbromide and atropine benzylchloride were determined by estimation of the slopes appropriate to the bimolecular rate expression

$$\frac{1}{a-x} = kt + \text{constant} \qquad \text{(Eq. 5)}$$

$$\log \frac{b}{a} \cdot \frac{(a-x)}{(b-x)} = \frac{kt\,(a-b)}{2.303} \qquad \text{(Eq. 6)}$$

$\frac{1}{a-x}$ was plotted against time when $a = b$ and $\log \frac{b}{a} \cdot \frac{(a-x)}{(b-x)}$ was plotted against time when $a \neq b$ where a and b are initial concentrations and $(a-x)$ and $(b-x)$ are concentrations at time intervals for the alkali and ester, respectively.

Hydroxyl ion concentration was calculated from the absorbance data.

Typical bimolecular rate plots for the hydrolysis of atropine ethylbromide and atropine benzylchloride are given in Figs. 4 and 5. Rate constants were determined at four different temperatures. Bimolecular rate constants are plotted against reciprocal of absolute temperature in Figs. 6 and 7. The rate constants at 30°, activation energies, and frequency factors are given in Table II.

DISCUSSION

Nor-atropine was studied extensively. The rather nice fit between the predicted relationship and the experimental points shown in Fig. 1 indicates that the hydrolytic Reactions 1 and 2 are mainly responsible for the hydrolysis of nor-atropine in aqueous solution. This behavior seems typical of the pattern of hydrolysis shown by other tropine esters reported previously (1–3). For this reason rate constants for hydrolysis of the other tropine esters reported here were determined at high (Reaction 1) and low (Reaction 2) pH only.

Of the esters listed in Table II tropine phenylacetate was observed to have the lowest hydrolytic rate for both Reactions 1 and 2. For convenience, hydrolysis rates of the other esters are compared to this compound. Thus, in Reaction 1 both atropine and nor-atropine hydrolyze approximately

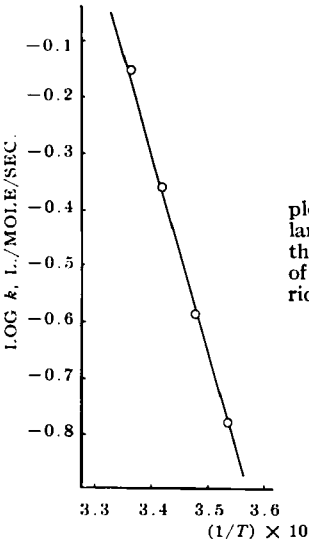

Fig. 7.—Arrhenius plot of the bimolecular rate constants for the alkaline hydrolysis of atropine benzylchloride.

five times faster than tropine phenylacetate; in Reaction 2 they are two and three times faster, respectively. This seems to indicate that replacement of one hydrogen on the nitrogen of nor-atropine with a methyl group to form atropine has virtually no effect on the rate of ester hydrolysis. With both these esters it is possible that the hydroxyl group in the acid moiety is responsible for an inductive effect on the carbonyl carbon. If this is true, the increase in positive character of the carbonyl carbon would facilitate hydrolysis of nor-atropine and atropine to account for the greater rate of hydrolysis relative to tropine phenylacetate.

In Reaction 1 tropine *p*-nitrobenzoate hydrolyzes approximately 25 times faster than tropine phenylacetate and in Reaction 2 eight times faster. The nitro group attached to the ester through the benzene ring seems to play a significant role in influencing hydrolytic rate. This has previously been observed (7, 8) and been attributed to the strong electron withdrawing tendency of the *p*-nitrobenzoyl group

TABLE III.—

Acid	Dissociation Constant, 25°C.	pKa
Phenylacetic	4.88×10^{-5}	4.31
Phenoxyacetic	5.56×10^{-5}	4.25
Tropic	7.50×10^{-5}	4.12
p-Nitrobenzoic	3.48×10^{-4}	3.46
Mandelic	4.29×10^{-4}	3.37

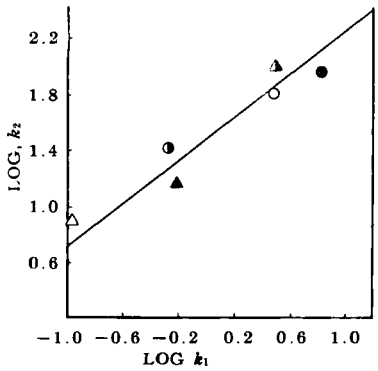

Fig. 8.—Plot showing the relationship of k_1 and k_2 of Reaction 1 and Reaction 2 for the following compounds at 30°C.: △, tropine phenylacetate; ▲, atropine; ◑, nor-atropine; ○, tropine *p*-nitrobenzoate; ⧋, homatropine; ●, tropine phenoxyacetate.

and the consequent formation of a highly positive center on the carbonyl carbon.

Homatropine is seen to hydrolyze 30 times faster than tropine phenylacetate by Reaction 1 and 15 times faster in the protonated form. This further confirms the inductive effect of the α-hydroxyl group in enhancing the positive character of the carbonyl carbon atom resulting in acceleration of the nucleophilic attack by hydroxide ion as reported previously (2).

As might be expected, if inductive effects are significant, the relative rates of hydrolysis of these esters should parallel the dissociation constants of the respective acids. Table III shows that this is mostly true. An exception is noted in the case of tropine phenoxyacetate whose rate of hydrolysis is 60 times faster by Reaction 1 and 11 times faster by Reaction 2 than the reference ester. These rates seem unusually high, considering that the dissociation constants of the acids are almost equal. It is possible that some other factor such as a steric effect may be involved, thus causing a greater hydrolytic rate than anticipated.

These observations are also apparent from the plot of log k_1 against log k_2 shown in Fig. 8. It can be seen that as polarity of the acid increases, the rate constants k_1 and k_2 increase. Similar observations have been made by Roberts and Moreland (9) in which they studied the electrical effects of substituted groups in saturated systems. They found that as the polarity of the acid increased, the effect of hydrolysis of its esters increased. It is also evident from Fig. 8 that the effect of polarity is more predominant in case of Reaction 1 than in Reaction 2, which would indicate that inductive effects are more prominent in hydrolysis of the base form of the ester.

The bimolecular rate of reaction of the quaternary nitrogen esters is of the same order of magnitude as the rate for the protonated form. Previous authors (3, 10) attribute this to the positive charge atmosphere which attracts hydroxyl ions to the vicinity of the carbonyl carbon in esters of esters of this type. Of the quaternary salts atropine methylbromide and atropine ethylbromide hydrolyze at approximately the same rate. There is some question whether the increased rate observed in atropine benzylchloride is truly significant. If so, it could perhaps be attributed to a steric facilitation by the relatively large benzyl group.

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