

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE POLYTECHNIC INSTITUTE OF BROOKLYN]

The Acid-Catalyzed Alcoholysis of β -Naphthyl EstersBY MORTON HARFENIST¹ AND RICHARD BALTZLY

The de-acylation of alcoholic functions by ester-interchange with a large excess of a lower alcohol is a procedure of some industrial importance. In the laboratory the process often offers a convenient and sparing equivalent of saponification and also, at times, leads to embarrassing complications when it is desired to keep an ester intact through certain manipulations. It seemed, therefore, desirable to explore further the conditions governing the rates of alcoholysis. This paper is concerned with the alcoholysis of phenolic esters, for which esters of β -naphthol are taken as typical, unhindered examples, with an acidic catalyst, such being generally preferable to alkaline catalysts when it is desired to operate with sensitive phenols.²

Experimental

The procedure used was chosen so as to give results readily applicable to practical conditions and so that the reaction would be kinetically of the first order. The samples of esters were allowed to react with solutions of hydrogen chloride in the exchange alcohol and the β -naphthol liberated was determined in aliquots by coupling with *p*-sulfonamidobenzene diazonium chloride, the concentration of dye produced being estimated photometrically.

Fifty ml. of a solution of hydrogen chloride in an alcohol was thermostated at least one hour in each of two 50-ml. flasks. Weighed amounts of ester, usually 40–120 mg., were added and the contents were mixed thoroughly. At convenient intervals 1-ml. aliquots were removed and added to 15-ml. portions of stock sodium acetate solution. It had been found that the esters underwent no significant change in such solutions during six hours at room temperature. To each diluted aliquot was added 1 ml. of "Diazo Reagent," the solutions were allowed to stand at least thirty seconds and then heated to the boiling point to destroy excess reagent. Three ml. of 6 *N* sodium hydroxide solution was then added and the solution was made up to 50 ml. with distilled water. The resultant orange or red solutions were read against blanks in photo-electric colorimeters using calibration curves. The dye, 1-(*p*-sulfonamidobenzeneazo)- β -naphthol, under alkaline conditions has intense absorption between about 420 and 540 $m\mu$, and there was no evidence of fading over several hours provided the solutions were protected from the atmosphere.

In the earlier part of the work a Klett-Summerson photo-electric colorimeter was used, with filter no. 470 (transmitting approximately 450–500 $m\mu$). When that instrument was no longer available, readings were made with a Cenco-Sheard spectrophotometer. Although this instrument is the more troublesome to handle, it was possible with both to reproduce readings within 0.5%. Values obtained with solutions containing over 0.64 mg. of β -naphthol (in 50 ml.) were found to be erratic and were discarded.

(1) From a thesis submitted by M. Harfenist to the School of Graduate Study of the Polytechnic Institute of Brooklyn in partial fulfillment of the requirements for the degree of Master of Science, May, 1946.

(2) Earlier literature in this field is reviewed by Minor, Doctoral Thesis, Bryn Mawr College (1917). Cf. also Waters, *J. Chem. Soc.*, 1014 (1936); Dasannacharya, *THIS JOURNAL*, **46**, 1627 (1924); Dasannacharya and Sudborough, *J. Indian Inst. Sci.*, **4**, 181 (1921); Patel and Watson, *ibid.*, **16A**, 55 (1933).

The alcohols used were initially "C. P." or "U. S. P." grade. The normal alcohols were dried by the method of Lund and Bjerrum.³ *i*-Propanol was refluxed with 50 g./liter of aluminum *i*-propoxide (Eastman Kodak Co. practical grade). All alcohols were distilled from the desiccant in all-glass apparatus immediately before use and were protected from moisture by aluminum chloride or "Drierite." The time of exposure during handling was about ten seconds. These precautions in excluding moisture were found to be essential since traces of water slowed the alcoholysis considerably in solutions of moderate hydrogen chloride concentration, whereas in very dilute or with more concentrated acid (*ca.* 1 *N*) the effect of water was much less.⁴

It had been expected that in the slower reactions complications might ensue from the reaction: $\text{ROH} + \text{HCl} \rightleftharpoons \text{RCl} + \text{H}_2\text{O}$ producing a loss of total acid and a reduction in activity of that remaining. Such a phenomenon, which would be indicated by a drift of the constant, *k*, to lower values during the course of a run, was not observed with the concentrations used (0.006 to 4 *N*).

Hydrogen chloride was obtained either from tanks or by addition of concentrated hydrochloric acid to sulfuric acid. In either case the gas was dried by passage over anhydrous aluminum chloride. The solutions in the various alcohols were titrated against standard alkali immediately before use.

"Diazo Reagent" was prepared by mixing equal volumes of two solutions, the one containing 2.90 g. of sodium nitrite in a liter, and the other containing 6 g. of sulfanilamide and 40 ml. of concentrated hydrochloric acid in a liter. The mixed reagent was allowed to stand at least thirty seconds before use, and was stable at least four hours at 30°. One ml. of this reagent is equivalent to nearly 3 mg. of β -naphthol so that at least a fivefold excess of diazonium salt was present in all couplings.

The sodium acetate solution contained 100 g. of "C. P." trihydrate per liter. Growth of molds was prevented by the addition of 5 ml. of chloroform.

Most of the esters used were prepared by refluxing β -naphthol with an excess of the appropriate acid chloride. The liquid esters were distilled to constant boiling-point and then analyzed. The solid esters were recrystallized from petroleum ether. The pivalate was the only one offering difficulties in the purification, but was finally freed from traces of β -naphthol. Ethyl β -naphthylcarbonate was prepared in poor yield from ethyl chloro-carbonate and sodium β -naphthoxide. The caproate, pivalate and ethyl carbonate appear to be new substances; data on them are presented in Table I.

TABLE I
ESTERS OF β -NAPHTHOL

Ester	M. p., °C.	Empirical formula	Analyses, %			
			Calcd.		Found	
			C	H	C	H
Pivalate	66–66.5	C ₁₁ H ₁₆ O ₂	78.91	7.07	78.80	7.10
Caproate	29.5 ^a	C ₁₆ H ₁₈ O ₂	79.30	7.49	79.55	7.50
Ethyl carbonate	34–35	C ₁₅ H ₁₈ O ₃	72.19	5.56	72.06	5.70

^a B. p., 170° (1 mm.).

Results

The values found for the pseudo-unimolecular reaction constant, *k*, at 25° are presented in Table II. As the thermostat temperatures were not always exactly at 25°, corrections were made for those figures obtained at other temperatures by

(3) Lund and Bjerrum, *Ber.*, **64**, 210 (1931).

(4) Cf. Kolhatkar, *J. Chem. Soc.*, **107**, 921 (1915).

TABLE II
 UNIMOLECULAR REACTION RATES FOR ALCOHOLYSES OF β -NAPHTHYL ESTERS IN VARIOUS ALCOHOLS AT 25°

β -Naphthyl ester	Alcohol	Detns.	Normality of HCl	$k \times 10^4 \times \text{min.}^{-1}$ (calcd. for N HCl)	
Acetate	MeOH	6	0.0981	378	± 11
			.0656		
			.00624		
Propionate	MeOH	6	.0656	238	± 8
			.02009		
			.006245		
Butyrate	MeOH	2	.0655	140	± 2
Caproate	MeOH	2	.0655	116	± 3
<i>i</i> -Butyrate	MeOH	4	.06556	54.9	± 1.1
			.006245		
Pivalate	MeOH	2	.931	2.71	± 0.02
Ethyl carbonate	MeOH	2	.931	0.950	$\pm .012$
Acetate	EtOH	2	.3430	91.2	± 2.2
Propionate	EtOH	2	.3430	50.7	± 1.1
<i>i</i> -Butyrate	EtOH	2	.3430	8.58	± 0.06
Acetate	EtCH ₂ OH	2	.382	87.6	± 1.0
Propionate	EtCH ₂ OH	2	.3098	45.8	± 0.4
Butyrate	EtCH ₂ OH	2	.3098	24.0	$\pm .3$
Caproate	EtCH ₂ OH	2	.382	23.3	$\pm .2$
<i>i</i> -Butyrate	EtCH ₂ OH	4	.310	7.30	$\pm .10$
			.263		
Pivalate	EtCH ₂ OH	2	1.974	0.210	$\pm .004$
Ethyl carbonate	EtCH ₂ OH	2	1.170	.187	$\pm .005$
Acetate	Me ₂ CHOH	4	0.626	5.43	$\pm .18$
			.572		
Propionate	Me ₂ CHOH	4	.572	2.62	$\pm .09$
			.369		
Butyrate	Me ₂ CHOH	2	.8785	1.36	$\pm .02$
Caproate	Me ₂ CHOH	2	.626	1.24	$\pm .04$
<i>i</i> -Butyrate	Me ₂ CHOH	4	2.020	0.300	$\pm .005$
			0.572		
Pivalate	Me ₂ CHOH	2	4.04	.00595	$\pm .00012$
Ethyl carbonate	Me ₂ CHOH	2	0.879	.0141	$\pm .0004$

applying the Arrhenius equation, taking the activation energy as 12,700 calories per mole (this being the average of those obtained in a number of the reactions). This correction came to 0.6% for a 0.1° difference in temperature. The figures given for k are also calculated for 1 N hydrogen chloride on the assumption that k is proportional to the concentration of acid. This assumption is justified in dilute solutions such as were used with the more reactive esters and the lower alcohols. In the higher concentration range, which was necessary in the slower reactions in order that observations could be completed in a reasonable time-period, the activity of the catalyst is not strictly proportional to the concentration and the calculation to a 1 N basis may involve considerable error (up to 10%). While this fact is appreciated, the deviation from linearity is not a simple one and the points available were not sufficient to determine the curve. The values obtained were therefore averaged together in the belief that the results would be at least roughly comparable to the rest.

The values given for precision are to some extent artificial. What was done was to take the

average deviation of the individual results and add thereto the 0.5% estimated as the reproducibility inherent in the method. It is not believed that a more elaborate statistical method would be justified since errors are not likely to have random distribution, but have led probably to low results. Beyond the question of the linearity of k with $[HCl]$, discussed above, the experimental error of most probable consequence would be incomplete removal of water from the system, and this would lower the observed value of k . As a consequence of this method of indicating precision, some of the figures probably most accurate appear less precise than others very likely less reliable. For example, k for β -naphthyl acetate and propionate in methanol were determined in three duplicate runs each at different hydrogen chloride concentrations, all low. It is felt that the estimated error in these cases is a maximum and that the true value is not far from that reported. In other cases, with fewer observations and higher hydrogen chloride concentrations, the true value is certainly somewhat, and possibly considerably, higher than here reported.

Some rates of alcoholysis in propanol and *i*-

propanol were also determined at 40°, and these are presented in Table III. From these an ap-

TABLE III

UNIMOLECULAR REACTION RATES FOR THE ALCOHOLYSIS OF β -NAPHTHYL ESTERS IN *n*-PROPANOL AND *i*-PROPANOL AT 40°^a

β -Naphthyl ester	Alcohol	Normality of HCl	$k \times 10^3 \times \text{min.}^{-1}$ (calcd. for <i>N</i> HCl)
Acetate	EtCH ₂ OH	0.09238	233 \pm 3
Butyrate	EtCH ₂ OH	.1152	69.2 \pm 1.4
Caproate	EtCH ₂ OH	.1152	64.4 \pm 1.3
Pivalate	EtCH ₂ OH	1.526	0.725 \pm 0.008
Ethyl carbonate	EtCH ₂ OH	1.526	.639 \pm .01
Acetate	Me ₂ CHOH	0.720	15.1 \pm .7
Propionate	Me ₂ CHOH	.4041	7.77 \pm .05
Butyrate	Me ₂ CHOH	.720	3.80 \pm .04
Caproate	Me ₂ CHOH	.385	3.55 \pm .06
<i>i</i> -Butyrate	Me ₂ CHOH	.720	0.849 \pm .008
Pivalate	Me ₂ CHOH	1.843	.0260 \pm .0004
Ethylcarbonate	Me ₂ CHOH	1.843	.0477 \pm .0002

^a All determinations were made in duplicate.

proximate evaluation of the activation energy was possible (Table IV) using the integrated form of the Arrhenius equation. Observations at a third

TABLE IV

ACTIVATION ENERGIES IN ALCOHOLYSES OF β -NAPHTHYL ESTERS WITH *n*-PROPANOL AND *i*-PROPANOL

β -Naphthyl ester	Alcohol	Activation energy, cal./mole
Acetate	EtCH ₂ OH	12,100 \pm 600
Butyrate	Same	13,000 \pm 800
Caproate	Same	12,400 \pm 800
Acetate	Me ₂ CHOH	12,700 \pm 900
Propionate	Same	13,400 \pm 900
Butyrate	Same	12,700 \pm 800
Caproate	Same	12,900 \pm 1100
<i>i</i> -Butyrate	Same	12,700 \pm 800

temperature would have been desirable, but, in our opinion, the presence of considerable experimental errors in the slower reactions would have made the increased accuracy produced by further measurements largely fictitious. Activation energies were not calculated for the reactions of β -naphthyl pivalate and β -naphthyl ethyl carbonate.

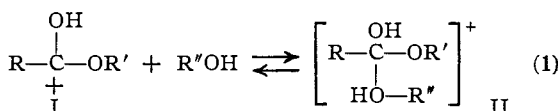
Discussion

Most of the variations in the value of k are at least qualitatively predictable on the basis of the modern theories of such reactions. All of the esters react most rapidly with methanol, considerably slower with ethanol and propanol and far slower with *i*-propanol, the difference between reaction rates in ethanol and propanol being rather small. There is a considerable fall in activity from the acetate to the propionate, less from the latter to the butyrate which is only slightly more reactive than the caproate. It is to be expected that further lengthening of the

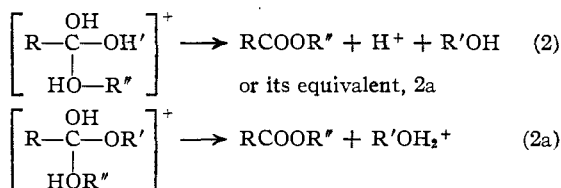
chain would produce still less effect. Substitution in the α -position by methyl groups slows the reaction far more, k for the *i*-butyrate being about one-fifth of k for the propionate, while the pivalate was about 1% as active as the propionate.

Similarly, the fact that the activation energies of the acetate, butyrate and caproate in propanol are approximately equal is in agreement with previous findings for similar reactions. It might, however, have been expected on steric grounds that reactions in *i*-propanol would show higher energies of activation. This phenomenon, together with the reversal in relative magnitude of the reaction rates of the pivalate and ethyl carbonate in the normal alcohols (methanol and propanol) on the one hand and in *i*-propanol, on the other, is understandable on consideration of the probable mechanism of the reaction.

The rate-determining step^b is presumably



the reaction-complex, II, subsequently losing a proton and the elements of an alcohol by equation 2



the concentration of I is a function of the total proton concentration and the basicity of the ester C=O relative to the strength of the other bases in the system, Cl⁻, R''OH and the ester —OR'. Both the concentration of I and the positive character of its central carbon atom will be influenced by resonance (or hyperconjugation) in the radical R. Thus, when R = OEt, CHMe₂ or CMe₃, I should be less capable of reaction. Further, α -substitution in R should hinder the formation of II sterically. Where the attacking alcohol is primary and subtends a relatively small angle in its approach, the effect of resonance in β -naphthyl ethyl carbonate is greater than the combined effect of resonance and hindrance in β -naphthyl pivalate (from aromatic chemistry we should expect an alkoxy group to have slightly greater effect than three methyl groups). With *i*-propanol it is evident that the steric effect is greater than with the primary alcohols, and the pivalate is the least reactive ester.

While the positive character of the ester carbon atom in I varies with the nature of R, so the oxygen of the solvent alcohol is more or less basic according to the nature of R''. *i*-Propanol should be a stronger base than *n*-propanol and thus,

(5) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, p. 262.

while the hindrance to addition in reaction I should be greater with *i*-propanol, the attractive force should also be greater. It was therefore to be predicted that the various influences at work would tend to compensate each other, although it could not have been predicted that the compensation would be so complete.

It is to be noted that although in all the systems studied unimolecular reaction kinetics should be observed, $[R''OH]$ was not the same for the different alcohols and consequently the conditions are not strictly comparable. It is not apparent how this could be avoided without introducing other uncertainties, and with low hydrogen ion concentration there should be considerable compensation. Where a higher alcohol is used $[R''OH]$ in equation 1 is lower than with methanol. On the other hand $[I]$ should be greater in nearly

the same proportion. With high concentrations of hydrogen chloride the amount of protonated alcohol which is not available for reaction in the sense of equation 1 subtracts significantly from the total alcohol concentration. This subtraction is, of course, most serious when $[R''OH]$ is initially low and the more so since this situation holds in the cases in which high hydrogen chloride concentrations had to be used.

Summary

The rates of hydrogen chloride-catalyzed alcoholysis have been determined for a series of β -naphthyl esters in methanol, ethanol, propanol and *i*-propanol.

A micro-method for the estimation of β -naphthol has been developed.

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Quinoline Derivatives from 3-Nitro-4-hydroxyquinoline¹

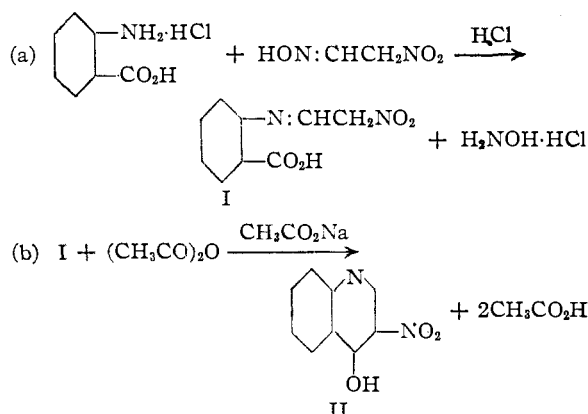
BY G. BRYANT BACHMAN, D. E. WELTON,² GLENN L. JENKINS AND JOHN E. CHRISTIAN

A search conducted in this Laboratory for new compounds suitable as antimalarial drugs has led to the preparation of a number of new 3,4-disubstituted quinolines from 3-nitro-4-hydroxyquinoline (II) as the primary intermediate. The synthesis of II itself was patented in 1922³ and involves the condensation of anthranilic acid hydrochloride with methazonic acid to yield 2- β -nitroethylideneaminobenzoic acid (I), which is subsequently dehydrated to II by acetic anhydride in the presence of sodium acetate. The yields of II

yields of I, reaction (b) gives only 30–45% yields of difficultly purifiable II. Reaction (b) has been subjected to further study by Musajo,⁴ who greatly simplified the experimental procedure for the isolation of II. Colonna⁵ attempted to synthesize the latter from methyl anthranilate through reactions similar to (a) and (b) but was unable to cyclize the intermediate methyl ester of I. We made an extensive study of reaction (b) but could convert I to II only by the anhydride-acetate combination previously employed. The alkali acetate catalyst was found to be essential to the reaction. Other metal salts are ineffective as catalysts, as are organic bases.

The preparation of 3-amino-4-hydroxyquinoline hydrochloride (III-HCl) by chemical reduction of II with metallic tin or stannous chloride in concentrated hydrochloric acid has been reported by other investigators.^{4,5} We have found that reduction of II may easily be effected by low-pressure catalytic hydrogenation of a suspension of II and Raney nickel in water or alcohols containing ammonia or organic amines. These bases greatly accelerate the reaction rate by increasing the solubility of II through salt formation. The resultant 3-amino-4-hydroxyquinoline (III) was not isolated as the free base, since it is rapidly oxidized by atmospheric oxygen, but was converted to its stable hydrochloride, III-HCl, consistently isolated in 95–98% of the theoretical yield.

The heretofore unreported 5-methoxy derivatives of I, II and III-HCl were also prepared by



obtained by the patented method leave much to be desired; although reaction (a) gives 80–90%

(1) Delivered before the Symposium on Antimalarial Agents at the Atlantic City Meeting of the American Chemical Society, April, 1946.

(2) Present address: du Pont Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware.

(3) German Patent, 347,375 (to Badische Anilin- and Soda-Fabrik) Jan. 17, 1922.

(4) L. Musajo, *Gazz. chim. ital.*, **67**, 222–230 (1937).

(5) M. Colonna, *ibid.*, **67**, 46–53 (1937).