

values for 1 9.59 and 2 6.87 agree well with those given in the literature, 9.83<sup>7</sup> and 7.0,<sup>8</sup> respectively.

When ethanol is added the  $pK_a$ -values increase, at 50 % ethanol concentration the value for 1 is 10.54 and for 2 7.57.

The increase over the investigated interval seems to be almost linear, and thus added ethanol does not cause any abrupt change in the mode of dissociation of the two phenols, and the difference in acidity between them remains fairly constant.

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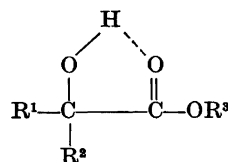
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## Investigations of Dithienylglycolic Esters. V. Hydrolytic Stability and Preparation of Some Esters of Glycolic Acids

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The hydrolytic stability of aryl substituted glycolates has received scant attention. Some data for esters of open-chain alkylamino alcohols have been reported by Kuznetsov and Rozinskaya.<sup>1</sup> They found that the rate of hydrolysis of alkylamino esters in an alkaline medium is higher than that of analogs containing no nitrogen. Knowledge of the hydrolytic stability is important for the elucidation of the structure-activity relationships of these atropin-like anticholinergic compounds. We have therefore synthesized and undertaken a study of the hydrolysis of some cyclic amino alcohol glycolates as well as their corresponding methyl esters<sup>2</sup> with the general structure



	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>
1	Ph	Ph	-CH <sub>3</sub>
2	3-Th <sup>a</sup>	3-Th	-CH <sub>3</sub>
3	Ph	2-Th	-CH <sub>3</sub>
4	3-Th	2-Th	-CH <sub>3</sub>
5	2-Th	2-Th	-CH <sub>3</sub>
6	Ph	Ph	Q <sup>b</sup>
7	3-Th	3-Th	Q
8	Ph	2-Th	Q
9	2-Th	2-Th	Q
10	2-Th	2-Th	3-Pip <sup>c</sup>
11	2-Th	2-Th	4-Pip <sup>c</sup>

<sup>a</sup> Th = thienyl. <sup>b</sup> Q = 3-quinuclidinyl. <sup>c</sup> Pip = piperidyl.

In order to determine the extent to which differences in reaction rates depend upon steric interaction from the alcoholic part of the esters, the intramolecular hydrogen bond between the hydroxyl and the carbonyl groups was studied by IR spectroscopy. The strength of the hydrogen bond will also reflect the various inductive effects within the esters.<sup>3</sup> A hydroxyl group hydrogen bonded to a carbonyl group increases the positive charge at the carbonyl

Table 1. Rate constants for hydrolyses of some aryl substituted glycolates  $R^1R^2C(OH)COOR^3$  in glycine-sodium hydroxide buffer system, (50 °C) at pH 9.32, and yields of synthesis 6, 7, 9, 10 and 11.

Compound	$k_{obs}/10^{-3} s^{-1}$	Yield/%
1	0.10	
2	0.28	
3	0.57	
4	0.77	
5	1.52	
6	0.17	70
7	0.30	73
8	1.26	
9	1.67	85
10	0.83	50
11	0.43	75

carbon atom which should favour an attack by hydroxyl ion.<sup>4</sup>

**Experimental.** Compounds 1–11 were synthesized according to Kadin and Cannon.<sup>5</sup> By using cyclohexane instead of heptane long periods of reflux time were avoided (7–24 h), and the reactions were completed within 30–60 min. The yields are given in Table 1. The rate constants given in Table 1 were obtained using Hestrin's method.<sup>6,7</sup> Hydrolyses were run at pH 9.32 and 50.0 °C in a glycine-sodium hydroxide buffer system (ionic strength=0.5) containing 10% methanol. 1 and 6 were also studied at pH 9.68 and 10.09. The initial concentrations of the esters were in the range 0.003–0.006 M. Aliquots were removed at certain intervals and measured spectrophotometrically. A Beckman Model B Spectrophotometer was used to follow the reaction. Absorbance readings ( $A_t$ ) were followed for one–two half-lives. It was shown that Lambert-Beer's law was obeyed. The pseudo-first order rate constant ( $k_{obs}$ ) was obtained by plotting  $\log(A_t)$  vs. time. All the plots were linear and the rate constants from the duplicate runs were in general reproducible within less than  $\pm 7\%$  of the average of the two runs.

**Infrared spectra** were run on a Perkin-Elmer Model 225 instrument. The solvent used was carbon tetrachloride, dried over activated molecular sieves. The temperature in the cell compartment was 37 °C and the cell path lengths were 3 and 10 mm. Concentrations were 0.006 M and 0.03 M, depending on the cell path length used.

The rate constants of compounds 1–5 are given by

$$k_{obs} = k_2[OH^-]$$

and for 6–11 by

$$k_{obs} = (k_1K_w + k_2K_E[OH^-]) / (K_E + [H^+])$$

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where  $k_1$ =second order rate constant for the protonated ester,  $k_2$ =second order rate constant for the basic form of the ester,  $K_w$ =thermodynamic ionic product of water,  $K_E$ =mixed dissociation constant of the ester.

A plot of  $\log k_{obs}$  vs. pH gives a straight line with a unit slope for 1. The hydrolysis for the other methyl esters is assumed to be first order with respect to ester and hydroxyl ion as well. The second order constant of the basic form of the amino alcoholic esters is approximately  $1 M^{-1} s^{-1}$  (and thus of the same magnitude as for the methyl esters). However, the pH range (9.32–10.09) is too narrow for calculations of the second order rate constant of the acid form.

Structure-reactivity relationships may be discussed for the methyl ester series with respect to the aromatic  $\pi$ -systems involved.

A 2-thienyl group is known to display a stronger  $-I$ -effect than the phenyl and the 3-thienyl groups.<sup>8</sup> The trend of the  $k_{obs}$  values for the alkaline hydrolysis of the methyl esters is therefore in the expected direction (Table 1). A similar trend is noted for the corresponding quinuclidinyl esters with respect to the intramolecular hydrogen bonding ability of the hydroxy group,<sup>9</sup> i.e. the bonding becomes stronger as the  $-I$ -effect increases.

Ten Thijs and Janssen<sup>9</sup> have derived  $\sigma^*$  values for 2-thienyl and 3-thienyl groups to be 0.93 and 0.65, respectively. Using these values and  $\sigma^*=0.60$  for the phenyl group,<sup>10</sup> and assuming additivity of the parameter values,  $\log k_{obs}$  and  $\log(A''/A')$  ( $A'$  is the intensity of the weak IR band assigned to "free" hydroxyl stretch and  $A''$  is the intensity of the stronger band due to "bonded" hydroxyl stretch) were plotted (Fig. 1) against the sum of the  $\sigma^*$ 's ( $\sigma^*$ ) for the methyl esters of Table 1. The plots show reasonable linear dependencies upon the structural changes.

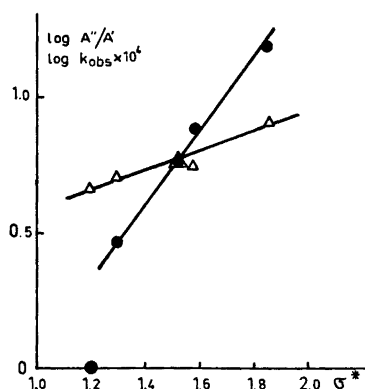


Fig. 1. Plot of  $\log A''/A'$  ( $\Delta$ ) and  $\log k_{obs} \times 10^4$  ( $\bullet$ ) of the methyl esters of Table 2 vs.  $\sigma^*$  (see text).

Thus it appears from Fig. 1 that both the variation in hydrolysis rate and the hydrogen bonding capacity are mainly due to the variation in the inductive effects of the aromatic and heteroaromatic substituents.

It should further be noted that the relative rate ratio of hydrolysis of, e.g., 2,2'-dithienyl/diphenyl for the methyl esters is comparatively large ( $\approx 15$ ) being of the same order of magnitude as that (33) of base catalyzed racemization of 2-thienylglycolic acid/phenylglycolic acid.<sup>11</sup> Those data should be compared with the rate factors of alkaline hydrolysis of 2-thenoate/benzoate<sup>12</sup> (1.02) and the *O*-nitration of 2-thenyl alcohol/benzyl alcohol<sup>11</sup> (0.5).

An investigation of 14 glycolates by IR spectroscopy in the OH- and CO-regions suggests that steric interaction from the alcoholic part is likely.<sup>3</sup> Structural variations in this part show that a change in "bulkiness" of the substituents may cause a change in the orientation of the CO-group relative to the  $\alpha$  hydroxy group in such a manner that an intramolecular hydrogen bond between these groups is conformationally favoured.

According to Meyerhöffer and Wahlberg<sup>13</sup> the  $pK_a$  values of the compounds 6–11 decrease in the series 6 > 7 ~ 9 > 8 > 11.\* Although similar data are unavailable for compound 10 it is likely that its  $pK_a$  does not exceed that of 6. For compound 6 the  $pK_a$  value corresponds to 3% protonated ester at 50.0 °C and pH 9.32. Thus for the remaining compounds of this series the contribution of the acid form ( $k_1$ ) must be even less, and the  $k_1$  term might be disregarded. The hydrolysis data can then be treated as being of the approximately pseudo first order. This suggests that the positive charge on the carbonyl atoms for the 2,2'-dithienylglycolate esters is in the order 9 > 10 > 11. Since the extent of the intramolecular hydrogen bonding also depends on the charge of the carbonyl group it is interesting to observe that a plot of  $\log(A''/A')$  vs.  $k_{\text{obs}}$  for these esters shows an approximately linear relationship (Fig. 2).

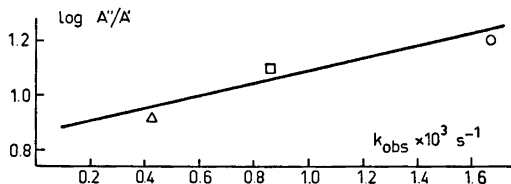


Fig. 2. The measure of intramolecular hydrogen bond strength,  $\log A''/A'$  vs.  $k_{\text{obs}}$ .  $\Delta$ , 1-methyl-4-piperidyl 2,2'-dithienylglycolate;  $\square$ , 1-methyl-3-piperidyl 2,2'-dithienylglycolate;  $\circ$ , 3-quinuclidinyl 2,2'-dithienylglycolate.

\* Estimated from the value of the corresponding diphenyl ester.<sup>13</sup>

In brief, the present work indicates that the hydrolysis rate of the diarylglycolates is influenced inductively by the aryl groups, and sterically by the alcoholic residue. The glycolic link further shows a relatively strong response upon changes of the inductive effects.

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