

Basic Hydrolysis of Methyl Hippurate

By R. W. HAY* and P. J. MORRIS

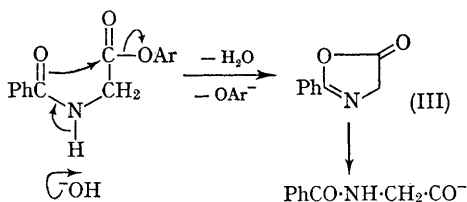
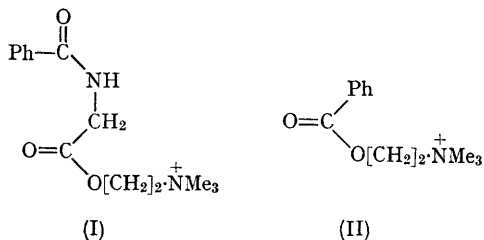
(Department of Chemistry, Victoria University of Wellington, Wellington, New Zealand)

It has been reported¹ that hippuric esters exhibit unusually high reactivities towards neutral and basic hydrolysis. The choline ester of hippuric acid (I) undergoes basic hydrolysis 20 times faster than benzoylcholine (II).¹ de Jersey, Kortt, and Zerner² have recently investigated the hydrolysis of *p*-nitrophenyl hippurate and have found that the ester has the abnormally high apparent rate-constant of 1.05×10^4 mole⁻¹ sec.⁻¹ for basic hydrolysis. They confirmed the presence of 2-

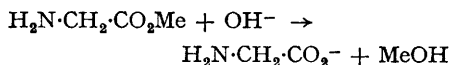
phenyloxazolin-5-one (III) as an intermediate in the hydrolysis.

At pH 11 the release of *p*-nitrophenol is virtually instantaneous while the intermediate has a half-life of *ca.* 14 sec. It is of interest to discover if neighbouring-group participation of this type is of importance in the hydrolysis of "nonactivated esters" with poor leaving groups, and we have therefore studied the basic hydrolysis of methyl hippurate. Some typical kinetic data obtained

using a pH-stat are summarized in the Table. For the basic hydrolysis of this ester $k = 103 \pm 1 \text{ mole}^{-1} \text{ min.}^{-1}$ at 25° and $I = 0.1\text{M}$. This



value may be compared with the rate constant for the basic hydrolysis of methyl glycinate



where $k = 79.2 \text{ mole}^{-1} \text{ min.}^{-1}$ at 25° and $I = 0.1\text{M}$.³ We conclude that the *N*-benzoyl substituent has little or no effect on the hydrolysis of amino-esters with poor leaving groups. Such a view is also supported by the observation of Zerner *et al.*² that there is no build up of an oxazoline intermediate during the hydrolysis of methyl hippurate.

TABLE

pH	$10^2 k_{\text{obs}}$ (min.^{-1}) ^a	$k_{\text{obs}}/[\text{OH}^-]$ ($\text{mole}^{-1} \text{ min.}^{-1}$)
10.40	3.381	103.0
10.60	5.302	101.9
10.80	8.535	103.5

(Chromatography of the reaction products showed that only hippuric acid was present and no glycine was formed. The amide linkage therefore remained intact under these conditions. The experimental infinity values were also consistent with one mole of base reacting with one mole of methyl hippurate.)

^a At 25° and $I = 0.1\text{M}$, the values of $[\text{OH}^-]$ are calculated from $\text{p}K_w = 13.9965$ and $\gamma_1 = 0.772$ obtained from the Davies' equation (ref. 4).

(Received, May 19th, 1967; Com. 489.)

¹ E. Wenger, H. Urheim, and M. Rottenberg, *Helv. Chim. Acta*, 1962, **45**, 1013.

² J. de Jersey, A. A. Kortt, and B. Zerner, *Biochem. Biophys. Res. Comm.*, 1966, **23**, 745.

³ R. W. Hay, L. J. Porter, and P. J. Morris, *Austral. J. Chem.*, 1966, **19**, 1197.

⁴ C. Davies, *J. Chem. Soc.*, 1938, 2093.