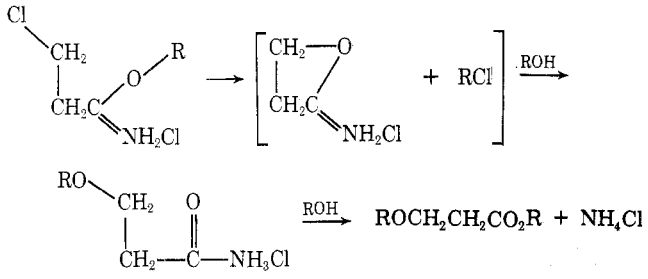
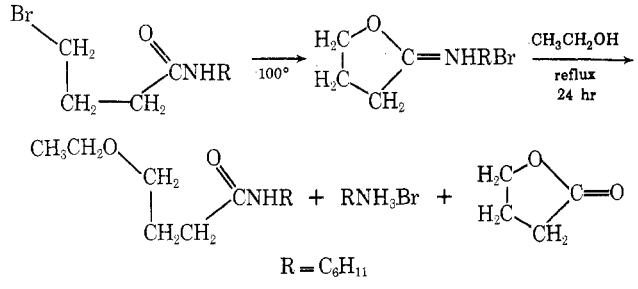
hydrochlorides.[10] The 3-chloropropionate esters, also observed as by-products in this work, would be expected based on the work of McElvain.[11]

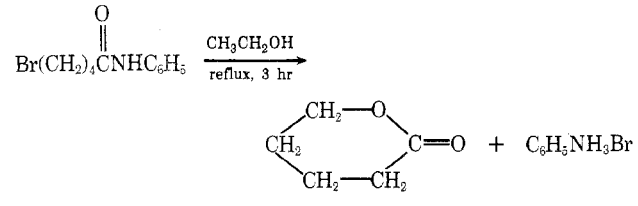
The high yields and mild conditions suggest a cyclic intermediate of the type shown. We have not attempted to define the mechanism other than by product identification; the following is postulation based on published isolations of alkyl β-alkoxypropionates from treatment of β-propiolactone with alcohols.[12,13]



There are mechanistic similarities to the work of Stirling,[14] wherein 4-bromo-*N*-cyclohexylbutyramide is cyclized to a stable, isolable five-membered cyclic imino ether, either thermally (100°) or in refluxing ethanol.



Ethanolysis of the imino ether hydrobromide, however, yields mainly 4-ethoxy-*N*-cyclohexylbutyramide, plus cyclohexylammonium bromide and butyrolactone. Also, the ethanolysis of 5-bromopentananilide is reported to yield valerolactone and anilinium bromide.[14] Differences in reactivity between four-, five-, and six-membered imino ether intermediates may account for the product differences.



Experimental Section

All chemicals were reagent grade, used as received. Nmr spectra were recorded on a Varian A-60A spectrometer by Dr. J. H. Fager, whose assistance is gratefully acknowledged. Melting points and boiling points are uncorrected.

Methyl 3-Methoxypropionate. Methyl 3-chloropropionimidate hydrochloride[15] (252 g, 1.6 mol) was combined with 1150 ml of dry ethyl ether and 320 g (10 mol) of methanol in a 2-l. 1NRB flask fitted with mantle, magnetic stirrer, thermometer, and condenser. The reaction mixture was heated at reflux for 6 hr. After standing for 2 days in the refrigerator, NH_4Cl was removed by filtration and the solution was stripped to remove solvents. Distillation yielded 102.8 g (53%) of methyl-3-methoxypropionate. A portion of the solid residue was recrystallized twice from ethyl ether containing a few drops of methanol, and the solid was identified as 3-chloropropionamide, mp 98.5–99.5° (lit.[16] mp 96–98°). The ester boiled at 45–48° (18 mm) [lit.[17] bp 55° (21 mm)], $n^{25}D$ 1.4035 (lit.[18] $n^{20}D$ 1.4030). Methyl chloride was detected in the reaction solution by vpc before work-up but was not isolated.

Ethyl 3-Ethoxypropionate. Ethyl 3-chloropropionimidate hydrochloride (88.2 g, 0.5 mol) was dissolved in 204 g (5.8 mol) of absolute ethanol and heated slowly to 40° over 5 hr with stirring. Product formation was complete by vpc. After standing overnight, the reaction was heated to reflux to distil out ethyl chloride, of which 14 g (43% of theory) was collected in a Dry Ice trap and identified. After cooling, NH_4Cl was removed by filtration and the remainder of ethyl chloride and ethanol was stripped. The residual oil was vacuum distilled, yielding a single cut, bp 65–67° (17 mm), 68.8 g (92% [lit.[17] bp 75–77° (20 mm)], $n^{26}D$ 1.4066 (lit.[18] $n^{20}D$ 1.4071). The product contained about 5% ethyl 3-chloropropionate by nmr.

Registry No.—Methyl 3-methoxypropionate, 3852-09-3; methyl 3-chloropropionimidate hydrochloride, 21367-88-4; ethyl 3-ethoxypropionate, 793-69-9; ethyl 3-chloropropionimidate hydrochloride, 21367-89-5.

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Concerning Anionic Nucleophilic Attack upon a Carboxyl Anion

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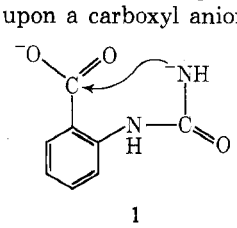
The rate of cyclization of *N*-(*o*-carboxyphenyl)urea in strongly basic solutions is first order in hydroxide ion concentration.[2,3] This observation was presented as evidence for anionic attack upon a carboxyl anion (1).[2,3] If mechanisms 2 or 3 were valid, then the rates would respectively decrease or remain constant with increasing hydroxide ion.[2,3] The base dependency of the ring closure could also be explained by a mechanism (Scheme I) in which rate-determining *collapse* of a tetrahedral intermediate is assisted by hydroxide ion. The rate law governing this mechanism (eq 1) shows first-order dependence on hydroxide ion if $k_{-1} \gg k_2K[OH^-]$. Therefore, anionic nucleophilic attack upon a carboxyl anion need not be in-



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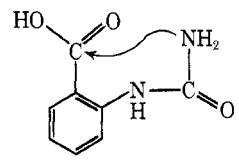

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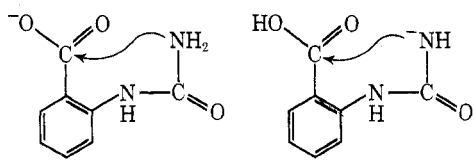

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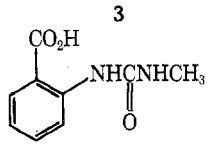


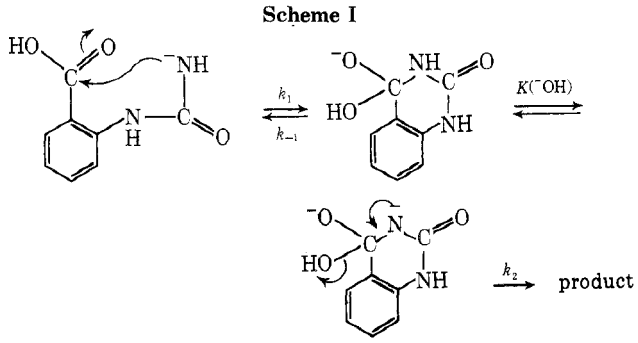
4

voked on the basis of previous data.[4] Because of this ambiguity and because of the uniqueness of mechanism 1,[5] we felt it important to test whether the alternative (or a kinetic equivalent) might be correct.

$$k_{obsd} = \frac{k_1 k_2 K [OH^-]}{k_{-1} + k_2 K [OH^-]} \quad (1)$$

Unlike the mechanism of Hegarty and Bruice,[2,3] Scheme I requires that the nucleophilic nitrogen of the starting material bear *two* hydrogens. Consequently, we examined 1-*o*-carboxyphenyl-3-methylurea (4), a compound lacking this property. The substrate was found to cyclize at a rate directly proportional to the hydroxide concentration (k_2 = 9.1 × 10^{-4} M^{-1} sec^{-1}, 30.0°, 0.6–1.0 M hydroxide). Moreover, the rate of cyclization is nearly the same (2.2 times as fast) as that of the corresponding nonmethylated urea. These observations eliminate Scheme I and support the contention that an intramolecular anionic nucleophile can indeed react with a carboxyl anion.[6]

Scheme I



Experimental Section

Materials. *N*-(*o*-Carboxyphenyl)urea was prepared from anthranilic acid and potassium cyanate.[7] 1-*o*-Carboxyphenyl-3-methylurea (4) was prepared from isatoic anhydride and methylamine.[8] The product was crystallized from wet acetone to give white crystals of mp 187–189° (lit.[8] mp 188–189°) and with a satisfactory elemental analysis. Cyclization of the methylurea in 6 *N* HCl to 3-methyl-2,4(1*H*,3*H*)-quinazolinedione was carried out by the procedure of Hayao, *et al.*[8]

Kinetics. A stoppered cuvette containing 3.00 ml of aqueous sodium hydroxide (0.6–1.0 *M*) was equilibrated at 30.0° for 20 min within the thermostated cell compartment of a Cary 14 spectrophotometer. A small amount (25 μl) of a methanolic solution of 1-*o*-carboxyphenyl-3-methylurea was then added to the cuvette (by means of a small stirring rod flattened at one end) such that the initial urea concentration in the cuvette was 2.6 × 10^{-4} *M*. The increase in absorbance at 332 nm was traced as a function of time until the reaction was completed. First-order plots were linear to greater than 2 half-lives.

Product Analysis. The spectrum of 3-methyl-2,4(1*H*,3*H*)-quinazolinedione in 1 *N* NaOH was shown to be identical with the "infinity spectrum" of a kinetic run under the same conditions.

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Registry No.—**2**, 610-68-4; **4**, 4141-12-2.

References and Notes

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(4) Indirect evidence, based on estimated rate constants, is presented in ref 3 against Scheme I.
(5) This reaction seems to be the only known example of an anionic nucleophilic displacement upon a carboxylate not involving a metal ion.
(6) A variation of Scheme I entails loss of the proton on the nitrogen bonded to the phenyl ring followed by formation of an *o*-quinoid-type intermediate. Attempts to test this mechanism were hampered by repeated failure to prepare 1-*o*-carboxyphenyl-1-methylurea and 1-*o*-carboxylphenyl-1,3-dimethylurea. Apparently, the compounds cyclize spontaneously during their preparation. This may be due to the 1-methyl group conformationally directing the 3 nitrogen into the proximity of the carboxyl group.
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Glyoxal Derivatives. VI. The Formation of Glycolates and the Acid-Catalyzed Decomposition of Glyoxal Acetals[1a]

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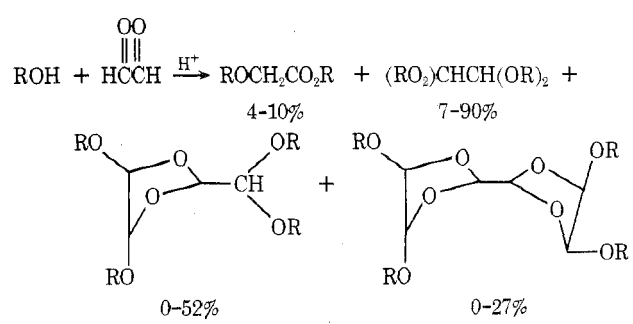
In our previous report[1a] we showed that aqueous glyoxal reacts with alkanols in the presence of acid catalysts to give glycolates, bisacetals, dioxolane, and bisdioxolane derivatives in varying yields depending upon the initial alcohol/glyoxal ratio. Although the yields of acetal-type



products could be controlled by the variation in the alcohol/glyoxal ratio, the yields of glycolates were relatively constant. In this report we describe the reaction of cyclohexanol to give glycolates in major amounts, and of other alcohols with glyoxal in which great differences in product type are observed depending upon reaction conditions. These observations plus a study of the hydrolysis and acid-catalyzed decomposition of glyoxal acetals allows us to suggest a mechanistic explanation for the differences observed.

Results

Unlike *all* of the other alkanols brought into reaction with glyoxal at 100–120°, cyclohexanol reacts to give gly-