[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HOWARD UNIVERSITY]

The Action of Alkali on Acylated Ketoximes. II.[1] Steric Hindrance to Alkaline Hydrolysis

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Although chemists have not agreed upon the relative importance to be assigned to steric factors in chemical reactions, they have recognized the existence of hindrance in the alkaline hydrolysis of esters since the early experiments of Victor Meyer.[2] The acylated ketoximes are esters of organic acids and oximes and as such one would expect that their alkaline hydrolysis would be subject to hindrance when the acyl group involved was properly substituted. Since we were unable to find any data bearing directly on this point, and since we had need of specific information on it, we have examined the behavior toward alkali of the benzoates and 2,4,6-trimethylbenzoates of benzophenone oxime and the α-oxime of *p*-chlorobenzophenone. In addition, in order to make certain that configuration played no part, we included the benzoates and trimethylbenzoates of both oximes of *p*-methoxybenzophenone.

As our interest was in the existence of hindrance rather than in the exact amount of hindrance, we have not made quantitative studies of reaction rates but have, instead, contented ourselves with comparative tests. Our procedure consisted in determining first the conditions under which an oxime benzoate was completely hydrolyzed. We then made parallel runs with the benzoate and the corresponding trimethylbenzoate under these previously determined conditions. As was to be expected, hydrolysis was suppressed by hindrance for, without exception, the 2,4,6-trimethylbenzoates were unaffected by the treatment which served to hydrolyze the benzoates completely.

The structures of the oxime benzoates employed were established both by their method of preparation and by their hydrolysis. The structures of the oxime trimethylbenzoates followed with near certainty from their method of preparation, for it is known that oximes of the benzophenone type on treatment with pyridine and an acid chloride furnish acylated oximes and not rearrangement products unless the acid chloride is derived from a strong acid—*e. g.*, benzenesulfonic acid. 2,4,6-Trimethylbenzoic acid is of the same order of strength but somewhat weaker than benzoic acid so that a rearrangement in the preparation of the trimethylbenzoates seemed most improbable.[3] Since, however, our experiments with the trimethylbenzoates were meaningless unless these substances had the structures assigned them, we have hydrolyzed all the trimethylbenzoates by prolonged heating with alcoholic hydrochloric acid. This treatment furnished in each case trimethylbenzoic acid and the ketone from which the oxime was derived, showing that our starting materials were acylated ketoximes. This precaution was particularly necessary in the case of the β-oxime of *p*-methoxybenzophenone for it gave two isomeric products on treatment with 2,4,6-trimethylbenzoyl chloride. Both isomers on acid hydrolysis furnished *p*-methoxybenzophenone and 2,4,6-trimethylbenzoic acid and neither isomer was hydrolyzed by alkali. Presumably this is a case of dimorphism but it is not absolutely certain.

The fact that the hydrolysis of these acylated ketoximes is subject to hindrance is strong presumptive evidence that it proceeds through an addition reaction. An observation which we made during the hydrolysis of the benzoates has confirmed this and has enabled us to show the nature of the addend. When the benzoates were hydrolyzed by treatment in alcoholic solution with aqueous sodium hydroxide and the reactions were stopped by pouring into large volumes of water, the products were not oxime and sodium benzoate but oxime and ethyl benzoate. The isolation of the small amount of ethyl benzoate formed was not feasible under the conditions of our experiments. Consequently, in order to establish the formation of an ester in the alkaline reaction medium, we hydrolyzed the *p*-phenylbenzoate of acetoxime (I) using methyl alcohol and aqueous sodium hydroxide. This gave methyl *p*-phenylbenzoate (II). In our opinion the only reasonable interpretation of these facts is that the alkaline hydrolysis of acylated ketoximes under the condi-

(1) First paper, THIS JOURNAL, **57**, 1330 (1935).

(2) Meyer, *Ber.*, **28**, 1263 (1895). Compare Freudenberg, "Stereochemie," Franz Deuticke, Vienna, 1933, p. 462.

(3) The dissociation constants at 25° of benzoic acid and 2,4,6-trimethylbenzoic acid are 6.15×10^{-5} and 3.7×10^{-4}, respectively. "International Critical Tables," Vol. VI, McGraw-Hill Book Co., Inc., New York City, 1929, pp. 249, 295.

tions of our experiments proceeds through the, probably reversible, addition of alcohol followed by cleavage of the intermediate addition product—the reaction series (A).

$$(CH_3)_2{>}C{=}NOCOC_6H_4C_6H_5\text{-}p + CH_3OH \longleftrightarrow \underset{\text{I}}{}$$

$$(CH_3)_2{>}C{=}N{-}OC{-}C_6H_4C_6H_5\text{-}p \longrightarrow$$

$$\underset{OH\ OCH_3}{}$$

$$(CH_3)_2{>}C{=}NOH + \underset{\text{II}}{CH_3OCOC_6H_4C_6H_5\text{-}p} \quad (A)$$

The application of this mechanism to the alkaline hydrolysis and alcoholysis of carboxylic esters is sufficiently obvious to make specific comment unnecessary.

With the existence of hindrance in the alkaline hydrolysis of acylated ketoximes thus established, we have made use of it in order to secure additional information about the two processes which take place when acylated benzoin oximes are treated with alkali. It has previously been shown[1] that acylated α-benzoin oximes (III) on treatment with alkali are cleaved to benzaldehyde, benzonitrile and the acid corresponding to the acyl group present, while the isomeric acylated β-benzoin oximes (IV) on similar treatment do not undergo cleavage but instead are hydrolyzed to oxime and acid.

$$\underset{\text{III}}{C_6H_5CH(OH){-}C(NOCOR){=}C_6H_5} \qquad \underset{\text{IV}}{C_6H_5CH(OH){-}C(RCOON){=}CC_6H_5}$$

To determine the effect of hindrance on these two processes we have examined the behavior toward alkali of the trimethylbenzoates of both benzoin oximes. The trimethylbenzoate of α-benzoin oxime (III, R = 2,4,6-$(CH_3)_3C_6H_2$—) on treatment with aqueous sodium hydroxide or alcoholic sodium carbonate cleaves, at least as readily as do the unhindered esters of this oxime, to benzonitrile, benzaldehyde and trimethylbenzoic acid. The trimethylbenzoate of β-benzoin oxime (IV, R = $(CH_3)_3C_6H_2$—) under the same conditions is unaffected. The application of these results to the acylated benzoin oximes is straightforward. Hydrolysis, here as in other acylated ketoximes, is the usual type of ester hydrolysis which proceeds through an addition reaction and which is stopped by hindrance. Cleavage, which is not affected by hindrance, obviously does not involve an addition reaction and must follow a quite different course.

The most probable course for the cleavage is one which is an application to the acylated α-benzoin oximes of the mechanism which Mills[4] has proposed for the action of alkali on aldoxime acetates. Stereoisomeric aldoxime acetates on treatment with alkali undergo cleavage to nitrile and acid or hydrolysis to aldoxime and acid. Mills has suggested that the first step in both cases is the loss of the aldehydic hydrogen atom as a proton. The resulting gap molecules will then, depending upon their configuration, either lose an acetate ion—cleavage—or undergo hydrolysis and regain a proton. This mechanism, applied to the acylated benzoin oximes with which we are dealing, involves the loss of the hydroxyl hydrogen atom as a proton from both isomers. It is in complete agreement with all the available facts insofar as the α-derivatives, those which cleave, are concerned. In the case of the β-derivatives we have already shown that the reaction involved is the usual type of ester hydrolysis proceeding through an addition reaction and we see no necessity for the assumption of the loss of a proton and the formation of gap molecules.

The essential difference between our point of view and that of Mills is that while Mills regards configuration as determining the behavior of the gap molecules once they are formed, we regard configuration as determining the ease of formation of the gap molecules. These alternatives can be tested by making use once more of the trimethylbenzoate of β-benzoin oxime (IV, R = 2,4,6-$(CH_3)_3C_6H_2$—). If configuration determines the behavior of the gap molecule, then this trimethylbenzoate should be unaffected by any alkaline treatment. If, however, configuration simply determines the ease of formation of the gap molecule then, since hydrolysis is stopped by hindrance, this trimethylbenzoate should cleave if the alkaline treatment is made sufficiently drastic. This latter is the case. The trimethylbenzoate of β-benzoin oxime, which is unaffected by the treatment which serves to cleave its α-isomer, is itself cleaved by alcoholic sodium hydroxide.

Experimental

The acylated oximes were prepared by mixing cold pyridine solutions containing equivalent amounts of oxime and acid chloride, allowing them to stand for twenty-four hours at room temperature and then pouring them onto ice and dilute hydrochloric acid. The benzoates solidified promptly; the trimethylbenzoates were generally obtained as oils which crystallized only after they had been dissolved

(4) Mills, *Chemistry and Industry*, **51**, 750 (1932).

TABLE I

Substance, benzoate	Crystallized from	M. p., °C.	Analyses, % Calcd. C	Calcd. H	Found C	Found H
Benzophenone oxime 2,4,6-trimethyl-	Ethanol	136–137	80.46	6.1	80.8	6.3
p-Chlorobenzophenone α-oxime	Ethanol	114–115	71.55	4.2	72.0	4.4
p-Chlorobenzophenone α-oxime 2,4,6-trimethyl-	Ethanol	101–102	73.1	5.3	73.1	5.2
p-Methoxybenzophenone α-oxime	Ethanol	115–116	CH_3O,	9.35		9.29
p-Methoxybenzophenone β-oxime	Ethanol	85–86	CH_3O,	9.35		9.47
p-Methoxybenzophenone α-oxime 2,4,6-trimethyl-	Ethanol–water	102–103	CH_3O,	8.31		8.48
p-Methoxybenzophenone β-oxime 2,4,6-trimethyl-	Ethanol	120–121			CH_3O,	8.36
		75	CH_3O,	8.31	CH_3O,	8.22
Acetoxime *p*-phenyl-	Ether	132–133	75.9	5.9	75.45	5.7

in ether and shaken thoroughly with dilute acid. The solvents used for purification, with the melting points and analyses of the products, are given in Table I. The benzoate of benzophenone oxime has already been described.[5] A more detailed description of the trimethylbenzoates of the benzoin oximes is given later.

Attempts to determine whether the 75 and 120° trimethylbenzoates of the β-oxime of *p*-methoxybenzophenone were dimorphous were inconclusive because the melts of these isomers did not crystallize satisfactorily on cooling.

Each of the above 2,4,6-trimethylbenzoates was hydrolyzed by boiling its alcoholic solution to which a small amount of concd. hydrochloric acid had been added, for from two to six hours. Water was then added, the solutions were made alkaline with carbonate and steam distilled. The distillates contained in each case the ketone from which the oxime was derived, while the residual alkaline liquid furnished on acidification 2,4,6-trimethylbenzoic acid.

Since the procedure in most of the alkaline hydrolysis experiments was similar, a generalized description will suffice for all but the exceptional cases. After preliminary experiments had shown the time required for complete hydrolysis of a benzoate, a solution of 1.0 g. of that benzoate in a definite volume of alcohol was prepared. At the same time a solution of 1.0 g. of the corresponding trimethylbenzoate was made up in the same volume of alcohol. To these solutions equal volumes of 5% sodium hydroxide solution were added. Then, after both solutions had been left for a time sufficient to hydrolyze the benzoate, half of the solution containing the trimethylbenzoate was poured into a large volume of water while all of the solution containing the benzoate was similarly treated. The precipitates thus obtained, after filtering and drying, were identified by melting points and mixed melting points. Finally, after a much longer reaction time, the remaining half of the solution of the trimethylbenzoate was poured into water and worked up. In every case the product from the benzoates (reaction time from thirty to ninety minutes) consisted of oxime produced by hydrolysis. The alcoholic solutions smelled strongly of ethyl benzoate. In every case the product from the trimethylbenzoates (reaction time from thirty minutes to twenty-two hours) consisted of unchanged starting material.

When a solution of 1.2 g. of the *p*-phenylbenzoate of acetoxime (I) in 90 cc. of methyl alcohol and 10 cc. of sodium hydroxide was poured into water after standing for one hour, there was obtained a quantitative yield of methyl *p*-phenylbenzoate (II) which was identified by comparison with an authentic specimen of that ester.[6]

The 2,4,6-trimethylbenzoate of α-benzoin oxime crystallizes splendidly from ether and petroleum ether or alcohol and water in clusters of small needles which melt irregularly at about 92°. The material undergoes cleavage on heating so that the melting point is not sharp. Even on standing the material cleaves to such an extent that it is not possible to secure acceptable analytical results. Carbon and hydrogen determinations are both inconsistent and low, presumably as a result of autoxidation of the benzaldehyde formed by cleavage. In the absence of analytical data the structure of the material is based on its alkaline cleavage to furnish benzaldehyde, benzonitrile and trimethylbenzoic acid and its hydrolysis, on standing in alcoholic solution with hydrochloric acid at room temperature, to furnish benzoin.

The 2,4,6-trimethylbenzoate of β-benzoin oxime crystallizes from ether and petroleum ether and melts at 151°. This material is quite stable and does not decompose on standing. (*Anal.* Calcd. for $C_{24}H_{23}O_3N$: C, 77.2; H, 6.2. Found: C, 77.25; H, 6.2.)

The trimethylbenzoate of α-benzoin oxime is completely cleaved to trimethylbenzoic acid, benzaldehyde and benzonitrile by shaking for fifteen minutes with an excess of 5% aqueous sodium hydroxide. Shaken for fifteen minutes in alcoholic solution with one mole of aqueous sodium carbonate the same cleavage occurs. Identification of the cleavage products was made by the method used in earlier work.[1] The trimethylbenzoate of β-benzoin oxime is recovered unchanged after the treatments just described. However, when it is treated in alcoholic solution with an excess of 5% aqueous sodium hydroxide for fifteen minutes, it is cleaved to benzaldehyde, benzonitrile and trimethylbenzoic acid.

Summary

The hydrolysis of acylated ketoximes by alkali in aqueous alcoholic solution proceeds through an addition of alcohol and can be stopped by the introduction of hindrance in the acyl group. The cleavage of acylated ketoximes of the benzoin type by alkali is not affected by hindrance. The mechanism of the cleavage process is discussed.

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(5) Chapman and Harris, *J. Chem. Soc.*, 809 (1933).

(6) Schlenk and Weickel, *Ann.*, **368**, 304 (1909).