[Contribution from the Chemical Laboratory of Duke University]

THE ACYLATION OF ALDOXIMES. IV. THE BENZOYLATION OF *syn*, AND *anti* ALDOXIMES[1]

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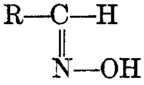
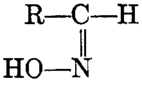
The purpose of this investigation has been to study the benzoylation of certain *syn*, and *anti* aldoximes in the presence of bases. Earlier investigators[2] have shown that *anti* aldoximes (II), as well as *syn* aldoximes (I), react with benzoyl chloride in the presence of aqueous alkali to give benzoyl *syn* derivatives (III), instead of the expected *anti* derivatives (IV) or nitriles. They reported[2] also that *anti* aldoximes give *syn* derivatives when the reaction with benzoyl chloride is carried out in pyridine solution, in spite of precautions to avoid isomeric change.



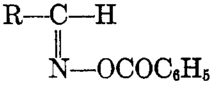
$$\begin{array}{l} R-C-H \\ \quad\| \\ \quad N-OH \end{array}$$

(I) *syn* (α)



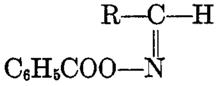
$$\begin{array}{r} R-C-H \\ \| \quad \\ HO-N \quad \end{array}$$

(II) *anti* (β)



$$\begin{array}{l} R-C-H \\ \quad\| \\ \quad N-OCOC_6H_5 \end{array}$$

(III) *syn* (α)



$$\begin{array}{r} R-C-H \\ \| \quad \\ C_6H_5COO-N \quad \end{array}$$

(IV) *anti* (β)

We have confirmed the result of the earlier investigators that *anti* aldoximes with benzoyl chloride in aqueous alkali give *syn* derivatives. Our results in pyridine solution, however, are not entirely in agreement with theirs, in that the product obtained in this solvent is largely or wholly nitrile. We have shown also that, although benzoyl *syn* derivatives are obtained from *anti* aldoximes and benzoyl chloride in the presence of aqueous alkali, nitriles are obtained when the reaction is carried out in a water-dioxane solution (or emulsion) of alkali. Similarly, nitriles are obtained when *anti* aldoximes are benzoylated with benzoic anhydride in an aqueous-dioxane solution (or emulsion) of alkali. The nitriles are formed presumably by the decomposition of intermediate benzoyl *anti* aldoximes (IV), which, although never isolated, would undoubtedly react with alkali or pyridine to give nitriles. It is well known that the corresponding acetyl *anti* aldoximes are decomposed by these bases to give nitriles.

In connection with the change of configuration that occurs during the benzoylation in the presence of aqueous alkali, it should be mentioned that an oil is first formed when the benzoyl chloride is added to the aqueous-alkaline solution of *anti* aldoximes. It seems likely that the change of configuration is in some way connected with the presence of this oil, since

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[1] Paper (III), J. Org. Chem., **5**, 68 (1940).

no change of configuration takes place when the benzoylation is carried out in the presence of a suitable solvent (dioxane).

The benzoylation of *anti* aldoximes in pyridine solution requires further comment. Preliminary experiments were carried out with three representative *anti* aldoximes, 3,4-methylenedioxy-, 3-nitro-, and 4-methoxybenzaldoximes, at 0° and at room temperatures, and in all cases high yields (70–90%) of nitriles were obtained; with the first two oximes, small yields (5–10%) of the *syn* derivatives were obtained under certain conditions, but no *syn* derivative was obtained from *anti*-4-methoxybenzaldoxime under the conditions studied. A more thorough study with *anti*-3,4-methylenedioxybenzaldoxime showed that when the benzoylation was carried out (either at 0° or at room temperatures) in the presence of a relatively small amount of pyridine, some (5–10% yield) of the *syn* derivative was formed, but when the benzoylation was carried out in the presence of a relatively large amount of pyridine, only nitrile was obtained. Also, it was found that the benzoylation of this *anti* aldoxime in the presence of a relatively small amount of pyridine together with a small amount of triethylamine gave only nitrile. Thus, at least with *anti*-3,4-methylenedioxybenzaldoxime, no change of configuration takes place when the benzoylation is carried out in a sufficiently basic solution.

Apparently, no one has studied the reaction of *syn* aldoximes with benzoyl chloride in pyridine solution; it was probably considered obvious that the corresponding *syn* derivative would be formed. Contrary to what one might expect, however, we have found that *syn*-3,4-methylenedioxybenzaldoxime with benzoyl chloride in pyridine solution at room temperature gives partly *syn* derivative and partly nitrile, while *syn*-4-methoxybenzaldoxime with benzoyl chloride under similar conditions gives entirely nitrile. Since benzoyl *syn* derivatives are stable in pyridine, the nitrile is formed presumably by the decomposition of benzoyl *anti* derivatives; the formation of the latter from *syn* aldoximes obviously involves an inversion of configuration. Previously, inversion of configuration has been shown to occur in the presence of pyridine (and ether) during the reaction of *syn* aldoximes with phenylisocyanate (1). Since, in the reaction with phenylisocyanate, the presence of a stronger base, for example, triethylamine, prevents inversion, it seemed probably that inversion would likewise be prevented during benzoylation if the reaction were carried out in the presence of triethylamine; this has been found to be the case. The reaction of benzoyl chloride with either *syn*-3,4-methylenedioxybenzaldoxime or *syn*-4-methoxybenzaldoxime in pyridine solution in the presence of triethylamine (two to four equivalents) gives entirely the corresponding *syn* derivative.

The significant results obtained with *syn*- and *anti*-3-4-methylenedioxy benzaldoximes and benzoyl chloride in the presence of bases are summarized in Table I.

From these results it can be concluded that, although changes of configuration may occur under certain conditions of benzoylation of *syn*-, and *anti* aldoximes, no change of configuration takes place when the benzoylation is carried out in a sufficiently basic solution (conditions listed in 2 and 4 of Table I).

Finally, it should be pointed out that the formation of *syn* derivatives from *anti* aldoximes under certain conditions is not especially surprising, since the more stable configuration of aldoximes and their acyl derivatives is the *syn*. The formation of the relatively unstable *anti* derivatives (or nitriles) from *syn* aldoximes, however, is rather remarkable and may involve the formation of salt-like intermediates (1). The factors governing this inversion of configuration during the benzoylation of *syn* aldoximes in pyridine solution is being further studied.

TABLE I

PRODUCTS OF BENZOYLATION OF *syn*-, AND *anti*-3,4-METHYLENEDIOXYBENZALDOXIMES IN THE PRESENCE OF BASES

CONDITIONS	*syn* ALDOXIME	*anti* ALDOXIME
1. With aqueous alkali	*syn* derivative	*syn* derivative
2. With alkali in a water-dioxane solution or emulsion	*syn* derivative	(*anti* deriv.)[a] → nitrile
3. In pyridine solution at room temperature	Partly *syn* derivative, partly nitrile	(*anti* deriv.)[a] → nitrile, plus *syn* derivative,[b] in yields of 0–10%
4. In pyridine and triethylamine solution	*syn* derivative	(*anti* deriv.)[a] → nitrile

[a] *anti* Derivative not isolated.

[b] In the presence of a large excess of pyridine only nitrile is obtained.

EXPERIMENTAL

Benzoylation of syn *and* anti *aldoximes in the presence of alkali.*—In agreement with Brady and co-workers,[2] the corresponding benzoyl *syn* derivative was obtained when either the *syn*, or the *anti* isomer of 3,4-methylenedioxybenzaldoxime-, or of 4-methoxybenzaldoxime was treated with benzoyl chloride in the presence of aqueous sodium hydroxide; however, the yields of *syn* derivatives obtained from the *anti* aldoximes were lower than those obtained from the *syn* aldoximes.

Although *anti* oximes with benzoyl chloride and aqueous sodium hydroxide give *syn* derivatives, it has been found that only nitriles are obtained when the reaction is

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[2] See especially Brady and McHugh, *J. Chem. Soc.*, **127**, 2415 (1925).

carried out in the presence of alkali in an aqueous-dioxane solution or emulsion. Two cubic centimeters of benzoyl chloride dissolved in 25 cc. of dioxane was added, with shaking, to 2 g. of *anti*-3,4-methylenedioxybenzaldoxime dissolved in 25 cc. of 4 *N* aqueous sodium hydroxide solution at room temperature. The mixture was emulsified by shaking. The temperature rose to 60–70°. After standing for several hours, the mixture was evaporated almost to dryness in a current of air. Water was added to the residue, and, after the mixture was shaken, the solid was filtered off and washed with water. The solid was identified as 3,4-methylenedioxybenzonitrile by the mixture melting point method. The yield of nitrile was 60% of the theoretical amount. Fifteen per cent of the original oxime was recovered by saturating the filtrate with carbon dioxide in the usual manner. Similar results were obtained with *anti*-4-methoxy-, and *anti*-3-nitro- benzaldoximes.

anti Aldoximes with benzoic anhydride in the presence of aqueous-dioxane mixtures of sodium hydroxide likewise give nitrile. To a solution of 2 g. of *anti*-3,4-methylenedioxybenzaldoxime in 50 cc. of 2 *N* sodium hydroxide was added slowly, with constant stirring, a solution of 3.5 g. of benzoic anhydride in 10 cc. of dioxane. After the mixture had stood for several hours, a 60% yield of nitrile was obtained. Some oxime was isolated from the filtrate in the usual manner. Similar results were obtained with *anti*-4-methoxy-, and *anti*-3-nitro- benzaldoximes.

Benzoylation of anti-*aldoximes in pyridine solution.*—Eastman's pyridine was dried over "Drierite" and distilled; the fraction boiling at 114–115° was collected for use. Eastman's benzoyl chloride was distilled under diminished pressure before use.

To 1 g. of *anti*-3,4-methylenedioxybenzaldoxime dissolved in 5 cc. of pyridine was added slowly 1 cc. of benzoyl chloride dissolved in 3 cc. of pyridine. The reaction was carried out both in an ice-bath and at room temperature. After standing for several hours, the mixture was poured on approximately 75 g. of ice. The precipitate that formed was filtered off and washed with water until free from pyridine. Some nitrile was obtained by working up the filtrate. The solid remaining in the funnel was washed with alcohol. The nitrile dissolved, leaving the relatively insoluble benzoyl *syn* derivative on the funnel; the nitrile was obtained by evaporation of the alcoholic solution. The yield of benzoyl *syn* derivative was 5–10%, while that of the nitrile was 70–75%.

When the reaction described above was carried out either in an ice-bath or at room temperature, using more than twice as much pyridine (20 cc.), only nitrile was obtained. Also, nitrile was the only product that could be isolated when 1 cc. of benzoyl chloride dissolved in 1 cc. of pyridine was added to 1 g. of *anti*-3,4-methylenedioxybenzaldoxime dissolved in a mixture of 2 cc. of pyridine and 2 cc. of triethylamine.

anti-3-Nitro-, and *anti*-4-methoxy- benzaldoximes were benzoylated in pyridine solution but no attempt was made to determine the effect of the relative amount of pyridine used. A 10% yield of the benzoyl *syn* derivative has been obtained from the former oxime, but no derivative has been obtained from the latter oxime. The yields of nitrile were 70–90% of the theoretical amounts.

Benzoylation of syn *aldoximes in pyridine solution.*—*syn*-3,4-Methylenedioxy-, and *syn*-4-methoxy- benzaldoximes were benzoylated in pyridine solution at room temperature, using purified reagents. The former oxime gave partly benzoyl *syn* derivative and partly nitrile, while the latter oxime gave apparently only nitrile. When the benzoylation of either *syn* aldoxime was carried out in the presence of two to four equivalents of triethylamine, however, the corresponding benzoyl *syn* derivative was obtained in yields of 60–80%; no nitrile could be isolated.

SUMMARY

1. A study has been made of the benzoylation of certain *syn*, and *anti* aldoximes in the presence of bases.

2. *anti* Aldoximes with benzoyl chloride, in the presence of aqueous alkali, give benzoyl *syn* derivatives, but, in the presence of a water-dioxane solution (or emulsion) of alkali, give nitriles. *anti* Aldoximes with benzoyl chloride in pyridine solution give largely or entirely nitriles; in the presence of triethylamine, nitrile is obtained.

3. *syn* Aldoximes with benzoyl chloride in pyridine solution give partly or entirely nitriles, but, in the presence of triethylamine, give entirely benzoyl *syn* derivatives.

4. From these results it is concluded that, although changes of configuration may occur under certain conditions, no change of configuration takes place when either *syn*, or *anti* aldoximes are benzoylated in a sufficiently basic solution.

Durham, N. C.

REFERENCE

(1) Rainsford and Hauser, *J. Org. Chem.*, **4**, 480 (1939).