[Contribution from the Chemical Laboratory of Queens College]

CHEMICAL EFFECTS ACCOMPANYING HYDROGEN BONDING. III

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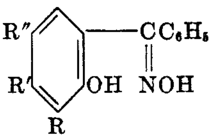
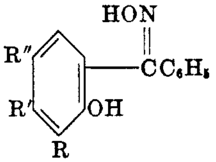
Received December 21, 1954

In earlier articles (1) we described the chemical behavior of the bonded oxime of 2-hydroxy-5-methylbenzophenone (I, R = R′ = H, R″ = CH_3) and its non-bonded isomer (II, R = R′ = H, R″ = CH_3), and reported enough work with the corresponding oximes of 2-hydroxybenzophenone (I and II, R = R′ = R″ = H) to show that the pattern of differences in behavior between the 2-hydroxy-5-methylbenzophenone oximes was also shown by the 2-hydroxybenzophenone oximes. We have now generalized these results by extending our study to include the two remaining *ortho* hydroxy benzophenones (2-hydroxy-4,5-dimethyl- and 2-hydroxy-3,5-dibromo-benzophenone) for which pairs of isomeric oximes have been reported, and by preparing and examining the hitherto unreported oximes of 2-hydroxy-5-bromobenzophenone. The results obtained with these three additional pairs of oximes parallel our earlier findings. The work with the five pairs of oximes makes available efficient general procedures for preparing the bonded oximes of *ortho* hydroxy benzophenones and for converting these oximes to their non-bonded isomers. It also provides new support for the currently accepted views about the mechanism of the Beckmann rearrangement by showing how these views can be applied to rearrangements hitherto considered to be abnormal, and it makes possible the assignment of configurations with a high degree of confidence to the many single oximes of *ortho* hydroxy acetophenones and benzophenones that are described in the literature. In the paragraphs that follow we summarize our results and attempt to account for the unusual behavior of the bonded oximes. In the experimental section, but not included in the discussion, will be found a number of specific observations that amplify or correct the reports on certain of the compounds included in our study that have been described previously.



I



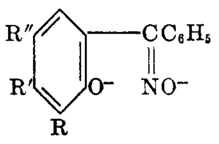
II

Formation of the bonded oximes I. Oxime formation in acid solution was examined with 2-hydroxy-5-methylbenzophenone but the procedure was not satisfactory for it led to a mixture of bonded oxime and hydroxy ketone. In a typical experiment in which the ratio of hydroxy ketone to hydroxylamine hydrochloride was 1.0:1.5, the product consisted of about 45% of the bonded oxime and 55% of the ketone. That this probably represents an equilibrium and not a slow rate of oximation was shown by an experiment in which the starting materials were the bonded oxime, hydroxylamine hydrochloride, and hydrochloric acid. This experiment furnished a mixture of essentially the same composition (46% oxime, 54% ketone) as that obtained from the ketone.

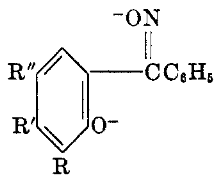
Oximation of 2-hydroxy-5-methylbenzophenone in alkaline solution gave much more satisfactory results. Treatment of the ketone with hydroxylamine and aqueous potassium hydroxide at room temperature furnished the crude bonded oxime (I, $R = R' = H, R'' = CH_3$) in quantitative yield. The crude bonded oxime prepared in this way is of good quality; it contains a few per cent of the non-bonded isomer which can be removed by taking advantage of its solubility in 5% aqueous sodium carbonate. The same procedure is applicable with equally good results to the other *ortho* hydroxy benzophenones that we have examined.

Conversion of the bonded oximes I to the non-bonded isomers II. With the bonded oximes readily available by oximation in alkaline solution, it was necessary for further work only to develop an efficient procedure for converting them to their non-bonded isomers. This conversion is effected by alkali. The rate of conversion is increased by increasing the concentration of the alkali and by increasing the temperature. High temperatures, however, lead to side reactions that lower the quality of the product. By operating with a high concentration and a large excess of alkali, it is possible to secure essentially complete conversion at room temperature in a reasonable time. Thus a solution of 10 g. of the oxime I ($R = R' = H, R'' = CH_3$) in 100 ml. of 3 *N* sodium methoxide solution furnishes the isomer II ($R = R' = H, R'' = CH_3$) in better than 90% yield in 75 hours at room temperature. The same procedure and a similar procedure using aqueous sodium hydroxide work equally well with the other bonded oximes.

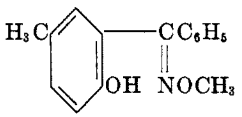
A reasonable interpretation of the transformation of a bonded oxime to its non-bonded isomer is that the isomerization takes place not with the oxime but with the doubly charged anion III and that the driving force is the repulsion of the two like charges. In the anion IV of the non-bonded oxime the charges are further apart than in the anion III and the dipoles are oppositely oriented. It is consistent with this interpretation that we have been unable to isomerize the bonded ether V from which the formation of a doubly charged anion is not possible.



III

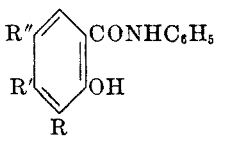


IV

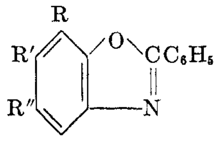


V

Beckmann rearrangement of the oximes. The non-bonded oximes II undergo a normal Beckmann rearrangement with phosphorus pentachloride or benzenesulfonyl chloride to yield anilides of substituted salicylic acids VI. The bonded oximes I with the same reagents yield benzoxazoles VII, a result which is amenable to ready interpretation in terms of the currently accepted views on the course of the Beckmann rearrangement.

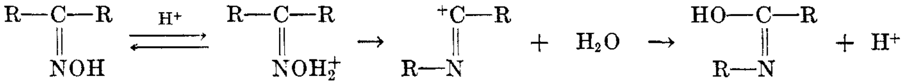


VI



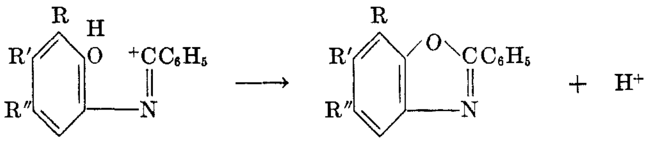
VII

The Beckmann rearrangement with acidic reagents is usually represented as involving the addition of a proton followed by the simultaneous loss of a molecule of water and the shift from carbon to nitrogen of the R group *trans* to the oximino hydroxyl group. The resulting carbonium ion and water yield the enolic form of the amide and a proton.



$$\begin{array}{c}R-C-R\\ \|\\ NOH\end{array} \overset{H^+}{\rightleftharpoons} \begin{array}{c}R-C-R\\ \|\\ NOH_2^+\end{array} \rightarrow \begin{array}{c}{}^+C-R\\ \|\\ R-N\end{array} + H_2O \rightarrow \begin{array}{c}HO-C-R\\ \|\\ R-N\end{array} + H^+$$

If a model of the carbonium ion intermediate that would be expected from a bonded *ortho* hydroxy benzophenone oxime is examined, it will be seen that this intermediate VIII is not limited to intermolecular reaction with a water molecule. An intermediate such as VIII could also undergo ring closure with loss of a proton to form a benzoxazole, and this intramolecular process would be expected to be favored.

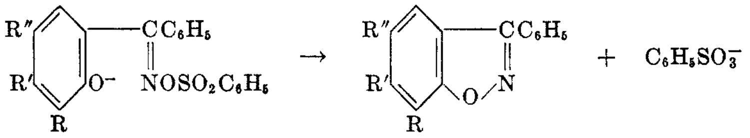


VIII

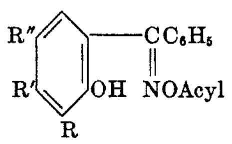
The rearrangement of the bonded oximes with benzenesulfonyl chloride and pyridine to yield benzoxazoles can be interpreted in similar fashion: the benzenesulfonate of the oxime dissociates to yield benzenesulfonate ion as the *trans* group migrates from carbon to nitrogen. The resulting carbonium ion intermediate is identical with that in the acid-catalyzed rearrangement and consequently the formation of a benzoxazole is again to be expected.

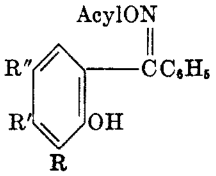
The rearrangement of the bonded *ortho* hydroxy benzophenone oximes just described occurs with *ortho* hydroxy aromatic ketoximes generally and the explanation given above is applicable, for example, to the many *ortho* hydroxy acetophenone oximes whose rearrangement to benzoxazoles is described in the literature. Similarly, *ortho* amino benzophenone oximes yield benzimidazoles on rearrangement. The interpretation of this process parallels that given above for the *ortho* hydroxy benzophenone oxime rearrangements.

The reaction of the bonded oxime of 2-hydroxy-5-methylbenzophenone (I, $R = R' = H, R'' = CH_3$) with benzenesulfonyl chloride takes a different course when 20% potassium hydroxide is used in place of pyridine: the principal product is the benzisoxazole (X, R = R′ = H, R″ = CH_3) rather than the benzoxazole (VII, R = R′ = H, R″ = CH_3) (1b). The formation of the benzisoxazole under these conditions can be interpreted as an intramolecular displacement within the anion IX that competes with the Beckmann rearrangement described earlier. It is to be expected that this same displacement could take place with the other bonded oximes I; but it does not take place to an appreciable extent when these other bonded oximes are treated with benzenesulfonyl chloride and 20% potassium hydroxide, and we have not attempted to find the modified experimental conditions necessary to effect the displacement with the other bonded oximes.


IX X

Behavior of the acyl derivatives of the oximes with bases. The acetates of the nonbonded oximes (XII, Acyl = CH_3CO) undergo ester interchange in aqueous ethanol in the presence of sodium carbonate or hydroxide to yield the nonbonded oximes and ethyl acetate which is then hydrolyzed. The presence of ethyl acetate is evidenced by its odor; the occurrence of ester interchange with an oxime ester was established many years ago by treatment of the *p*-phenylbenzoate of benzophenone oxime with bases in methyl alcohol. The products were methyl *p*-phenylbenzoate and benzophenone oxime (2).


XI

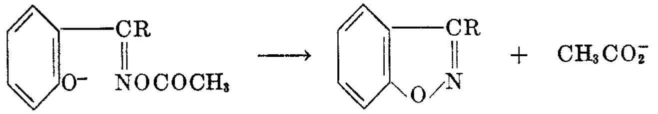

XII

The acetates of the bonded oximes (XI, Acyl = CH_3CO) also undergo ester interchange in aqueous ethanol on treatment with sodium hydroxide to yield the bonded oximes and ethyl acetate which then is hydrolyzed. On treatment of the bonded oximes in aqueous ethanol with sodium carbonate, ester interchange does not take place; instead the products are a benzoxazole VII and acetate ion. The difference in behavior of a bonded oxime ester on treatment with sodium hydroxide and with sodium carbonate corresponds to the change in mechanism of ester hydrolysis from O-acyl to O-alkyl cleavage as the basic reagent becomes weaker (3). The O-alkyl cleavage of an oxime ester such as XI would lead to an intermediate identical with the intermediate VIII in the Beckmann rearrangement of the corresponding oxime, and the formation of the benzoxazole VII is therefore to be expected. The rearrangement of a bonded oxime ester on attempted alkaline hydrolysis represents on this basis a new example of O-alkyl cleavage of an ester—a process that is probably better described here as an O-nitrogen cleavage.

The O-alkyl cleavage of esters of alcohols is favored by steric hindrance to the customary O-acyl cleavage, and by increased acid strength of the acid from which the acyl group in the ester is derived. Both of these effects operate in the bonded oxime esters XI. When the sterically hindered 2,4,6-trimethylbenzoate (XI) [$R = R' = H, R'' = CH_3$, Acyl = 2,4,6-$(CH_3)_3C_6H_2CO$] is treated with sodium carbonate or sodium hydroxide it furnishes the benzoxazole VII ($R = R' = H$, $R'' = CH_3$); the corresponding non-bonded 2,4,6-trimethylbenzoate VII [$R = R' = H, R'' = CH_3$, Acyl = 2,4,6-$(CH_3)_3C_6H_2CO$] is unaffected by the same reagents under the same conditions (1b). The bonded oximes I on treatment with benzenesulfonyl chloride as described above furnish the benzoxazoles VII directly, the intermediate benzenesulfonate rearranging too rapidly to permit its isolation.

Nothing of what has just been written, however, accounts for the difference in behavior of the bonded and non-bonded oxime acetates on treatment with sodium carbonate. One can suggest that O-nitrogen cleavage will be favored by substituents in the oxime that can supply electrons and thus facilitate the dissociation of the acyl group as the anion; the *ortho* hydroxyl group can serve in this capacity. The fact that the non-bonded acetates do not undergo O-nitrogen cleavage suggests stereochemical restrictions on such an effect. This possibility is now being explored.

In addition to hydrolysis to an oxime and O-nitrogen cleavage leading to a benzoxazole, the reactions just described, a bonded oxime acetate should be capable of an intramolecular displacement to yield a benzisoxazole.



This process has been observed by Lindemann and co-workers who found that the acetates of a number of bonded *ortho* hydroxy benzaldehyde and acetophenone oximes on treatment in aqueous suspension with excess sodium carbonate or the calculated amount of sodium hydroxide gave benzisoxazoles (4). We have not observed the formation of benzisoxazoles from the bonded *ortho* hydroxybenzophenone oxime acetates that we have studied and we have not attempted to determine the experimental conditions that would favor the displacement reaction with these compounds.

Applications to other ortho hydroxy aromatic ketoximes. For the great majority of *ortho* hydroxy acetophenones and benzophenones described in the literature only a single oxime has been reported. For the most part, configurations have not been assigned to these single oximes. It is a safe assumption that these single oximes are the bonded isomers, for the bonded oximes are the first products of oximation in either an acidic or alkaline medium. This assumption can be checked by noting the behavior of the oxime when it undergoes a Beckmann rearrangement: bonded oximes will furnish benzoxazoles. (The rearrangement is best carried out with benzenesulfonyl chloride and pyridine or by preparing the oxime acetate and treating it with sodium carbonate; phosphorus pentachloride is not so satisfactory for the yields are poor, presumably as a result of the loss of material in the form of intractable phosphorus compounds.) On this basis most of the single oximes of the various *ortho* hydroxy aromatic ketones described in the literature are the bonded isomers, for the formation of benzoxazoles on rearrangement is the most characteristic reaction reported for this group of compounds.

Acknowledgment. We are indebted to The Research Corporation for a grant to cover the cost of the analyses required in connection with this study.

EXPERIMENTAL

In order to save space, a given operation, e.g., treatment of an oxime acetate with base, is described in detail once. The same operation with other compounds is described only insofar as it varies from the original description.

THE OXIMES OF 2-HYDROXY-5-METHYLBENZOPHENONE (1a)

Oxime formation in acid solution is illustrated by the following experiment. A solution of 4.24 g. (0.02 mole) of 2-hydroxy-5-methylbenzophenone in 20 ml. of ethanol was mixed with a solution of 2.1 g. (0.03 mole) of hydroxylamine hydrochloride in 6 ml. of hot water. The resulting solution was heated under reflux for 2 hours, then rapidly cooled. Water and ether were added and the ether layer was separated. The bonded oxime was removed as its copper derivative ($C_{32}H_{28}CuN_2O_6$: Calc'd: Cu, 10.6. Found: Cu, 10.6) by shaking the ether layer with aqueous copper acetate; the ether on evaporation left the unreacted ketone. The copper derivative weighed 2.05 g., the recovered ketone, 2.2 g. The recovery amounted to 92% of the starting material and of the recovered material 42% was the bonded oxime (I, R = R′ = H, R″ = CH_3) and 58% was the hydroxy ketone. In a complementary experiment starting with 4.54 g. (0.02 mole) of the bonded oxime, 0.7 g. of hydroxylamine hydrochloride, 1.6 ml. of conc'd hydrochloric acid, and 5.2 ml. of water the recovery was 87%; 46% of the recovered material was the bonded oxime and 54% was the hydroxy ketone.

Oxime formation was studied under a variety of conditions and the following procedure was developed as the most efficient and convenient. To a solution of 27 g. (0.4 mole) of 85% potassium hydroxide in 115 ml. of water in a 500-ml. glass-stoppered Erlenmeyer flask, is added 21.2 g. (0.1 mole) of 2-hydroxy-5-methylbenzophenone. The resulting orange-red reaction mixture, which contains a substantial precipitate of the potassium salt of the hydroxy ketone, is chilled and 14.6 g. (0.2 mole) of hydroxylamine hydrochloride is added. The flask is left to stand stoppered at room temperature for 20 hours, then the contents are acidified by the addition of 3 *N* hydrochloric acid with stirring. The yield of crude oxime is quantitative.

The crude oxime is freed from a small amount of the non-bonded isomer by stirring for 30 minutes with 100 ml. of 5% sodium carbonate solution which dissolves the non-bonded oxime. The bonded oxime is crystallized by solution in hot benzene (2 ml. per gram) and addition of an equal volume of 70–90° ligroin. The yield of pure bonded oxime (I, R = R′ = H, R″ = CH_3) m.p. 137–138°, is 18.2–19.3 g., 80–85%. The loss is in the crystallization, and it is essential to use a heated funnel and to filter rapidly or the loss by crystallization in the funnel may be quite large.

The same procedure, modified when necessary by the use of mechanical stirring, is generally applicable to the preparation of the other bonded oximes I in comparable yields.

Conversion of anti 2-hydroxy-5-methylbenzophenone oxime (I, R = R′ = H, R″ = CH_3)

to the syn oxime (II, R = R′ = H, R″ = CH_3). The conversion of the bonded oxime to its non-bonded isomer can be shown by means of melting points and mixture melting points when one isomer predominates; mixtures of isomers can be separated by treatment with 5% sodium carbonate solution in which the non-bonded isomer dissolves cleanly and in which the bonded isomer dissolves only to the extent of about 0.2 g. per 100 ml.; and the absence of the bonded oxime can be shown by the failure to form a copper derivative with aqueous copper acetate. Since, however, it is always necessary to crystallize the conversion product in order to obtain completely pure material, the conversion while excellent for preparative purposes does not furnish results sufficiently accurate for a quantitative study of the effects of experimental conditions on the rate of conversion.

When the bonded oxime in 40% sodium hydroxide solution (2.5 g. of oxime in 100 ml. of a solution prepared by dissolving 40 g. of sodium hydroxide in 100 ml. of water) is boiled for 2 hours the conversion to the non-bonded oxime is complete, but the product is not of good quality and the yield of crude material averages only 67%. Decreasing the alkali concentration to 20% but otherwise operating as just described, the conversion is not complete in 2 hours.

At the temperature of the steam-bath with 2.5 g. of bonded oxime in 100 ml. of 20% sodium hydroxide, the product is principally the non-bonded oxime after 6 hours; after 8 hours the conversion is complete. Decreasing the alkali concentration to 10% results in incomplete conversion after 24 hours at the temperature of the steam-bath.

At room temperature with 2.5 g. of the bonded oxime in 100 ml. of 20% sodium hydroxide, conversion is complete in 96 hours and the yield of crude non-bonded oxime averages 80%.

The conversion at room temperature is the most convenient process and it furnishes the cleanest product; side reactions are minimized and the reaction time is not excessive. To develop the most efficient operation, the concentration of the oxime was increased. This led to the following preferred procedure: A solution of 7.5 g. of the bonded oxime in 50 ml. of 20% sodium hydroxide is kept for 96 hours at room temperature. During this time the solution sets solid with a precipitate of the sodium derivative of the non-bonded oxime. Two hundred ml. of water is added and the clear solution is acidified with 25 ml. of conc'd hydrochloric acid diluted with 125 ml. of water. Mechanical stirring is desirable and the reaction mixture should be cooled sufficiently to prevent a temperature rise during the acidification. The precipitate is filtered and stirred with 750 ml. of 5% sodium carbonate solution in which it dissolves almost completely. The carbonate solution filtered and acidified with dilute hydrochloric acid furnishes 6.4–6.8 g. (85–90%) of the non-bonded oxime (II, R = R′ = H, R″ = CH_3) which melts at 134–136°, gives no precipitate with copper acetate, and is pure enough for most uses.

The same conversion can be effected even more smoothly with sodium methoxide. Using this reagent, the preferred procedure is to dissolve 10 g. of the bonded oxime in 50 ml. of 3 *N* sodium methoxide solution and to keep the solution at room temperature for 75 hours. Then 100 ml. of water is added and the clear solution is acidified with 100 ml. of dilute hydrochloric acid (1 part conc'd acid and 5 parts water). The precipitate of non-bonded oxime weighs 9.2–9.6 g. (92–96%), melts at 134–136°, and gives no precipitate with cupric acetate.

In both preferred procedures the conversion is complete in less than the specified time. Both procedures are generally applicable to the bonded oximes (I). We prefer the sodium methoxide procedure because it permits the use of higher concentrations of the bonded oximes and because the non-bonded oximes obtained on acidification become granular more quickly and are easier to handle.

THE OXIMES OF 2-HYDROXY-4,5-DIMETHYLBENZOPHENONE

Bartolotti and Linari (5) prepared 2-hydroxy-4,5-dimethylbenzophenone by an involved procedure from 3,4-dimethylphenyl benzoate, benzoyl chloride, and zinc chloride. The same chemists described two oximes made from the ketone. We found that the ketone can be prepared in more clean cut fashion by a Fries reaction with 3,4-dimethylphenyl benzoate and that the oximes are better prepared by the generalized procedure described above.

3,4-Dimethylphenol can be benzoylated in almost quantitative yield by the Schotten-Baumann procedure. The crude benzoate, crystallized from 1 ml. of methanol per gram of ester, furnishes the pure benzoate with a loss of about 10%. When 33.9 g. (0.015 mole) of the pure benzoate mixed with 25 g. of anhydrous aluminum chloride in a 500-ml. flask, open to the air and carrying a thermometer dipping into the solid, is placed in an oil-bath at 80° the heat of reaction carries the internal temperature to 100° and the mixture expands by frothing until it half fills the flask. The bath is removed until the exothermic reaction is complete, then replaced and heated so as to raise the temperature of the reaction mixture rapidly to 120° and then slowly to 140°. After 20 minutes at 140°, the mixture is cooled and decomposed by stirring with 75 g. of ice and 75 ml. of conc'd hydrochloric acid. The yield of crude ketone is quantitative. On crystallization from 100 ml. of ethanol it furnishes 22.5 g. (66%) of pure 2-hydroxy-4,5-dimethylbenzophenone as yellow crystals of m.p. 110–111°.

The bonded oxime of 2-hydroxy-4,5-dimethylbenzophenone (I, R = H, R′ = R″ = CH_3) was prepared in 95% yield in 0.1 mole quantity by the general procedure described for the oxime I (R = R′ = H, R″ = CH_3), save that the reaction was stirred for 3 hours and then left overnight. The oxime was crystallized with a 70% recovery from 5 ml. of benzene and 5 ml. of 70–90° ligroin per gram of crude material. The pure oxime melts at 141–142°. It is moderately soluble in the common solvents except ligroin and petroleum ether, very soluble in acetone. The ether solution shaken with copper acetate furnishes a khaki-colored copper derivative. When the bonded oxime in ether is treated with phosphorus pentachloride, the benzoxazole (see below) is formed in poor yield. The same benzoxazole is obtained in quantitative yield from the oxime and benzenesulfonyl chloride in pyridine.

On warming with excess acetic anhydride the bonded oxime dissolves and the oxime acetate crystallizes. Cooling the reaction mixture and decomposing the excess anhydride with water furnishes the crude acetate in quantitative yield. For analysis the acetate was crystallized from ethanol, in which it is sparingly soluble and from which it is obtained in colorless needles melting at 107–108°.

Anal. Calc'd for $C_{17}H_{17}NO_3$: N, 4.94. Found: N, 5.15.

The acetate dissolved in warm ethanol is quantitatively hydrolyzed to the bonded oxime by the addition of excess 5% sodium hydroxide solution. When a solution of 1.0 g. of the acetate in 50 ml. of warm ethanol was treated with 10 ml. of 5% sodium carbonate solution, the addition of 50 ml. of water after 10 minutes precipitated 0.7 g. (90%) of benzoxazole (VII, R = H, R′ = R″ = CH_3). For analysis the product was crystallized from ethanol in which it is sparingly soluble and from which it crystallizes in fine needles melting at 167–168°.

Anal. Calc'd for $C_{15}H_{13}NO$: N, 6.28. Found: N, 6.68.

The bonded oxime was converted to the non-bonded isomer by sodium hydroxide (quantitative) or by sodium methoxide (95%) using the preferred procedures described above. The non-bonded oxime (II, R = H, R′ = R″ = CH_3) is moderately soluble in the common solvents, but is appreciably less soluble than its bonded isomer. It is conveniently crystallized from 12 ml. of ethanol per gram with a 70% recovery of the pure product of m.p. 173–174°. The oxime in ether solution does not form a copper derivative with copper acetate. The oxime is quantitatively acetylated by dissolving it in excess warm acetic anhydride. The acetate, crystallized from ethanol, melts at 155–156°.

Anal. Calc'd for $C_{17}H_{17}NO_3$: C, 72.1, H, 6.0.
Found: C, 72.0, H, 6.2.

The non-bonded acetate dissolved in warm ethanol and treated with 5% sodium hydroxide or 5% sodium carbonate as described above for the bonded isomer, furnishes the non-bonded oxime in excellent yield.

The non-bonded oxime on attempted Beckmann rearrangement furnishes only intractable products. Neither phosphorus pentachloride, nor benzenesulfonyl chloride with pyridine, nor polyphosphoric acid (6) gave a rearrangement product that could be handled.

THE OXIMES OF 2-HYDROXY-5-BROMOBENZOPHENONE

The benzoate of *p*-bromophenol necessary for the preparation of 2-hydroxy-5-bromobenzophenone is obtained in quantitative yield by the Schotten-Baumann benzoylation of *p*-bromophenol. The crude benzoate can be purified with an 85% recovery by crystallization from 3 ml. of ethanol per gram of crude material.

The conversion of *p*-bromophenyl benzoate to 2-hydroxy-5-bromobenzophenone by the Fries reaction is not clean: the product is a mixture of hydroxy ketone and unchanged ester whose separation by crystallization is so tedious and is accompanied by such large losses that it is better to subject the mixture to alkaline hydrolysis and separate the resulting mixture of hydroxy ketone and *p*-bromophenol. Increasing the temperature at which the Fries reaction is run gives a product free of unchanged ester, but at the cost of contamination with decomposition products. The most satisfactory procedure follows. A mixture of 27.8 g. of ester and 17.7 g. of aluminum chloride was heated at 110° by means of an oil-bath until the mixture melted, and then was held at 150° for 15 minutes. The melt was allowed to cool (after first spreading it over the inner surface of the reaction flask with a stirring rod so as to facilitate the subsequent decomposition) and was decomposed by stirring with ice and hydrochloric acid. The yield of the crude mixture of ester and hydroxy ketone melting from 80 to 90° was quantitative. The mixture was dissolved in 95 ml. of ethanol, a solution of 2 g. of sodium hydroxide in 10 ml. of water was added, and the whole was heated under reflux for an hour. Acidification with dilute hydrochloric acid and cooling furnished 12 g. (42%) of 2-hydroxy-5-bromobenzophenone as yellow crystals melting at 111–112°. Crystallization of a sample from ethanol for analysis did not raise the melting point.

Anal. Calc'd for $C_{13}H_9BrO_2$: C, 56.3, H, 3.25.
Found: C, 56.0, H, 3.5.

The bonded oxime (I, R = R′ = H, R″ = Br) was prepared in quantitative yield by the general procedure described above. The oxime was purified for analysis by crystallization from benzene and ligroin (70–90°) and from ethanol-water. The pure product melts at 155–156°.

Anal. Calc'd for $C_{13}H_{10}BrNO_2$: C, 53.4, H, 3.4.
Found: C, 53.2, H, 3.5.

The oxime in ether solution furnishes a khaki-colored copper derivative on treatment with copper acetate. On treatment with phosphorus pentachloride, or benzenesulfonyl chloride, or polyphosphoric acid the oxime furnishes the benzoxazole (see below).

With acetic anhydride the oxime furnishes the oxime acetate, which is purified by crystallization from ethanol in which it is only sparingly soluble. The pure acetate, which turns yellow on exposure to sunlight, melts at 115–116°.

Anal. Calc'd for $C_{15}H_{12}BrNO_3$: C, 53.9, H, 3.6.
Found: C, 53.35, H, 3.7.

With 5% sodium hydroxide, the acetate is hydrolyzed to the parent oxime in 87% yield; with 5% sodium carbonate, the acetate furnishes 2-phenyl-5-bromobenzoxazole (VII, R = R′ = H, R″ = Br) in 90% yield. The benzoxazole, which is quite soluble in the common solvents except ligroin, crystallizes well from methanol and melts at 110–111°.

Anal. Calc'd for $C_{13}H_8BrNO$: C, 56.9, H, 3.68.
Found: C, 56.5, H, 3.2.

Mixtures of the oxime acetate (m.p. 115–116°) and the benzoxazole (m.p. 110–111°) melt below 95°.

The bonded oxime was converted to its non-bonded isomer in 95% yield by sodium methoxide. The non-bonded oxime (II, R = R′ = H, R″ = Br) is very sparingly soluble in benzene and crystallization from that solvent furnishes the pure oxime, m.p. 172–173°.

Anal. Calc'd for $C_{13}H_{10}BrNO_2$: C, 53.4, H, 3.4.
Found: C, 53.4, H, 3.56.

The oxime in ether solution gives no precipitate with aqueous copper acetate. The oxime on treatment with benzenesulfonyl chloride and pyridine gave only intractable material. However, a Beckmann rearrangement did take place on treating the oxime with phosphorus pentachloride or with polyphosphoric acid. The product purified by crystallization from dilute ethanol melted at 224–225°.

Anal. Calc'd for $C_{13}H_{10}BrNO_2$: C, 53.4, H, 3.4.
Found: C, 53.0, H, 3.4.

The non-bonded oxime with acetic anhydride furnishes the acetate which is sparingly soluble in ethanol, ethyl acetate, and benzene. The pure acetate, m.p. 176–177°, is best obtained by crystallization from ethyl acetate-ligroin.

Anal. Calc'd for $C_{15}H_{12}BrNO_3$: C, 53.9, H, 3.6.
Found: C, 53.7, H, 3.7.

Mixtures of the acetate (m.p. 176–177°) and the corresponding oxime (m.p. 172–173°) melt below 160°. The acetate on treatment with excess 5% sodium hydroxide or sodium carbonate is hydrolyzed to the oxime in yields of over 85%.

THE OXIMES OF 2-HYDROXY-3,5-DIBROMOBENZOPHENONE

We were unable to secure the yields reported by Anschütz and Robitsek (7) for the preparation of 2-hydroxy-3,5-dibromobenzoyl chloride from the corresponding acid or those reported by Anschütz and Lowenberg (8) for the conversion of this acid chloride to 2-hydroxy-3,5-dibromobenzophenone. The following simplified procedure gives no better yields than those we obtained following the directions just cited, but it permits a considerable saving of time.

In a 250-ml. flask, 59 g. (0.2 mole) of 2-hydroxy-3,5-dibromobenzoic acid (dibromosalicylic acid) is covered with 50 ml. of ligroin (60–80°) and 42 g. (0.2 mole) of phosphorus pentachloride is added in one portion followed by 20 ml. of ligroin. A condenser is attached (ground glass joints are desirable) and the reaction mixture (protected from atmospheric moisture) is warmed on the steam-bath until the solids dissolve. This requires 20–30 minutes. The flask and contents then are chilled thoroughly and the acid chloride that crystallizes is collected on a sintered glass funnel, washed with ligroin, and dried by pressing between filter papers and by exposure to the air for 10–15 minutes.

The crude freshly prepared acid chloride, which weighs about 44 g., is transferred to a 250-ml. flask fitted with an adapter that connects with a condenser and also permits the introduction of a solid. The acid chloride is dissolved in 100 ml. of benzene, and 31 g. of aluminum chloride is added during 10 minutes followed by 25 ml. of benzene. The reaction mixture, which evolves hydrogen chloride and develops an orange color, is heated on the steam-bath for an hour, cooled, and decomposed with 100 g. of ice, 100 ml. of conc'd hydrochloric acid, and 100 ml. of water. The two-layer liquid is heated in an open beaker on the steam-bath until all the benzene is removed. As the benzene distils, the organic layer settles to the bottom of the beaker. The reaction mixture is cooled and the ketone which crystallizes is filtered, washed with water, and dried. The crude yield is 45 g. On crystallization from 100 ml. of glacial acetic acid, there is obtained 31 g. of pure 2-hydroxy-3,5-dibromobenzophenone, m.p. 121–122°, an over-all yield of 43% from dibromosalicylic acid.

The 2-hydroxy-x,x-dibromobenzophenone of unknown structure prepared by Cohn (9) by treating an alcoholic solution of 2-hydroxybenzophenone with excess bromine in chloroform, was shown to be identical with 2-hydroxy-3,5-dibromobenzophenone by preparing a small sample according to Cohn and comparing it with the product obtained from dibromosalicylic acid.

Anschütz and Lowenberg (8) described the preparation of a labile oxime (m.p. 175°) from 2-hydroxy-3,5-dibromobenzophenone, hydroxylamine hydrochloride, and sodium carbonate. They reported that this labile oxime resolidified after melting to yield a stable isomer of melting point 199–201°. We prepared the bonded oxime (I, $R = R'' = Br$, $R' = H$) in quantitative yield by our general procedure. The oxime is purified with a 70% recovery by crystallization from chloroform (20 ml. per g.) and ligroin (15 ml. per g.). It melts at

201–202°, but the melting point varies with the rate of heating and is accompanied by some decomposition for the melt is always yellow.

Anal. Calc'd for $C_{13}H_9Br_2NO_2$: C, 42.05, H, 2.4.
Found: C, 42.43, H, 2.8.

The material acquires a charge very readily when dry and is inconvenient to handle. In ether solution the oxime furnishes a khaki-colored copper derivative on shaking with copper acetate. On treatment with phosphorus pentachloride, benzenesulfonyl chloride, or polyphosphoric acid, the oxime furnishes a benzoxazole (see below).

The bonded oxime is acetylated by warming with acetic anhydride. The resulting acetate is sparingly soluble in ethanol and, after crystallization from that solvent, melts at 159–160°.

Anal. Calc'd for $C_{15}H_{11}Br_2NO_3$: C, 43.6, H, 2.66.
Found: C, 43.7, H, 2.96.

The acetate on treatment with 5% sodium hydroxide is hydrolyzed to the bonded oxime in almost 90% yield. With 5% sodium carbonate, the acetate furnishes 2-phenyl-5,7-dibromobenzoxazole (VII, $R = R'' = Br$, $R' = H$) in better than 90% yield. The benzoxazole is very sparingly soluble and crystallizes from ethanol in fine needles that melt at 175–176°.

Anal. Calc'd for $C_{13}H_7Br_2NO$: C, 44.2, H, 2.0.
Found: C, 43.9, H, 2.2.

Mixtures of the acetate (m.p. 159–160°) and the benzoxazole (175–176°) melt below 150°.

The conversion of the bonded oxime to its non-bonded isomer requires minor modifications because of the sparing solubility of the sodium derivatives involved. The conversion can be brought about in 90% yield by dissolving 2.0 g. of the bonded isomer in 25 ml. of 3 *N* sodium methoxide, allowing the solution to stand at room temperature for a week, and then working up in the usual fashion. However, in occasional runs a sodium derivative precipitates before all of the bonded oxime has dissolved; the precipitate encloses some of the undissolved bonded oxime and prevents complete conversion. It is possible to bring about complete solution by warming the reaction mixture for a few minutes, but it is preferable to add the bonded oxime to the sodium methoxide solution, hold the reaction mixture at its boiling point on a steam-bath for 7 hours, leave overnight, and work up the next day. The resulting non-bonded oxime (II, $R = R'' = Br$, $R' = H$) after crystallization from chloroform (20 ml. per g.) and ligroin (20 ml. per g.) melts at 170–171° to an opaque yellow liquid that does not become completely clear until the temperature reaches 200°.

Anal. Calc'd for $C_{13}H_9Br_2NO_2$: C, 42.05, H, 2.43.
Found: C, 42.65, H, 2.8.

The melting point of the non-bonded oxime varies with the rate of heating, and melting is apparently accompanied both by partial decomposition (yellow color) and partial conversion to the bonded isomer. Mixtures of the bonded and non-bonded oximes soften on heating to 160° and melt by 165°. The non-bonded oxime furnishes a copper derivative when its ether solution is shaken with aqueous copper acetate.

Attempts to rearrange the non-bonded oxime with benzenesulfonyl chloride gave sticky products that could not be handled. The Beckmann rearrangement was therefore carried out with polyphosphoric acid and furnished 2-hydroxy-3,5-dibromobenzanilide whose melting point, 137–138°, was not lowered by admixture with an authentic sample of the anilide prepared from 2-hydroxy-3,5-dibromobenzoyl chloride and aniline (7).

The non-bonded oxime furnishes an acetate on treatment with acetic anhydride. The acetate, after crystallization from benzene-ligroin, melts at 155–156°.

Anal. Calc'd for $C_{15}H_{11}Br_2NO_3$: C, 43.6, H, 2.66.
Found: C, 43.86, H, 2.77.

Mixtures of the bonded (m.p. 159–160°) and non-bonded (155–156°) acetates melt below 150°. The non-bonded acetate on treatment with 5% sodium hydroxide or sodium carbonate solution furnishes the non-bonded oxime in excellent yields.

SUMMARY

The chemical behavior of five pairs of isomeric bonded and non-bonded *o*-hydroxybenzophenone oximes is summarized and an attempt is made to interpret the unusual behavior of the bonded oximes and their esters.

FLUSHING 67, NEW YORK

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