[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

SYN-ANTI ISOMERISM OF *p*-CHLOROBENZALDOXIME WITH BORON FLUORIDE[1]

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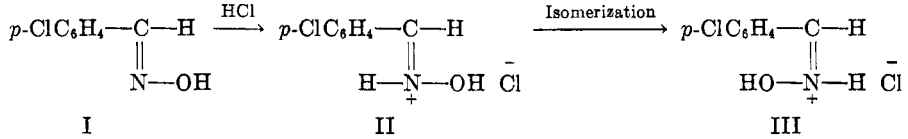
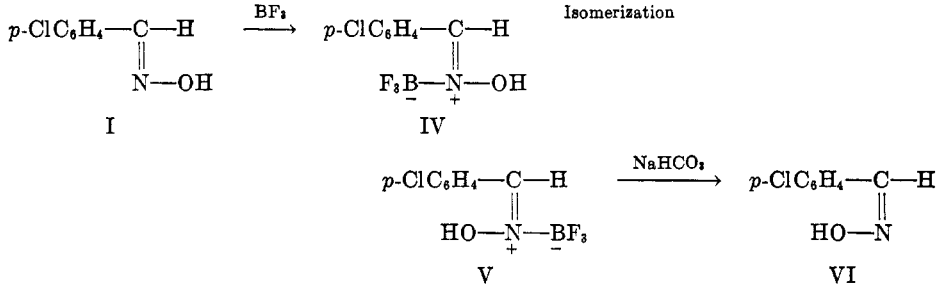
Received June 27, 1955

It is well known (1, 2) that *syn*-aromatic aldoximes, which are obtained from aromatic aldehydes and hydroxylamine, may be converted to their *anti*-isomers through the hydrochloride salt. For example, *syn-p*-chlorobenzaldoxime (I) is converted to its *anti*-isomer on saturating an ether solution of the *syn*-aldoxime with hydrogen chloride at room temperatures and treating the resulting precipitate with sodium carbonate (3). Presumably the *syn*-hydrochloride (II) is first formed and then is isomerized to the *anti*-hydrochloride (III). Actually Brady and Dunn (4) have shown that the *syn* salts of certain benzaldoximes may be precipitated at 0° or lower, and then converted to the *anti* salts at higher temperatures.



I II III

In the present investigation *syn-p*-chlorobenzaldoxime (I) was similarly converted to the *anti*-aldoxime (VI) by means of boron fluoride. This was accomplished by saturating a benzene solution of the *syn*-aldoxime with this reagent at room temperatures (25–35°) and treating the resulting precipitate with sodium bicarbonate solution. The over-all yield of *anti*-aldoxime (VI) from the *syn*-isomer (I) was 93–98%. Presumably the *syn*-aldoxime was first converted to its N-coordination complex (IV) which then isomerized to the N-coordination complex of the anti-aldoxime (V).

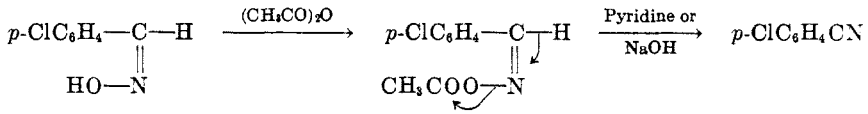


I IV V VI

The aldoxime obtained in this manner was shown by the mixture melting point method to be identical with that produced through the hydrochloride salt which may be regarded as the authentic specimen. Moreover, the *anti* configuration (VI) for the aldoxime liberated from the boron fluoride complex was con-

[1] Supported in part by the Office of Ordnance Research, U. S. Army.

firmed by acetylation to form VII followed by β-elimination with pyridine to give *p*-chlorobenzonitrile in high yield (5). The acetyl derivative of the original *syn*-aldoxime was stable towards pyridine under similar conditions. The *anti*-acetyl derivative (VII) also was converted to nitrile with sodium hydroxide but the yield was considerably lower that that obtained with pyridine. The pyridine method for distinguishing between *syn*- and *anti*-aldoximes is generally more quantitative than the usual one employing sodium carbonate or sodium hydroxide (5).

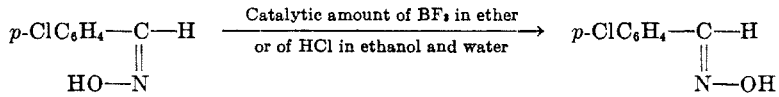


VII

It should be mentioned that the *anti*-aldoxime (VI) prepared through the hydrochloride salt was shown to be converted by boron fluoride to the *anti*-N-coordination complex (V) from which the *anti*-aldoxime (VI) was recovered on subsequent treatment with sodium bicarbonate.

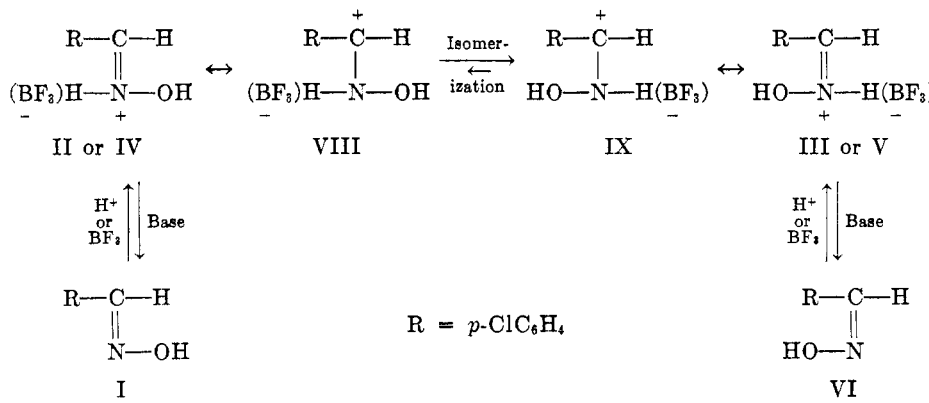
Although the isomerization of *syn*-complex (IV) to *anti*-complex (V) was essentially complete at 25–35°, only partial isomerization was realized at 10°. Thus, when a benzene solution of the *syn*-aldoxime was saturated with boron fluoride at 10° and the resulting precipitate was treated with sodium bicarbonate, the yield of the *anti*-aldoxime (VI) was only 40%, and 57% of the *syn*-aldoxime (I) was recovered. However, the isomerization was found to proceed to completion on heating a sample of the precipitate obtained at 10° to about 135°, after which treatment with sodium bicarbonate liberated exclusively the *anti*-aldoxime (98%). Since the sample did not melt at 135° the isomerization apparently occurred in the solid state.

In contrast the hydrochloride salt or the boron fluoride N-coordination complex which is more stable in the *anti* configuration, the free aldoxime is more stable in the *syn* configuration; indeed, *anti*-aromatic aldoximes are known (6) to revert readily to their *syn* isomers especially in the presence of dilute acid. We have observed such a reversion to the *syn*-aldoxime on recrystallizing anti-*p*-chlorobenzaldoxime (VI) from hot dilute acetic acid. Of greater significance, we found that, whereas the preparation of the *anti*-aldoxime from the *syn*-isomer requires an equivalent of boron fluoride, the reversion of the *anti*-aldoxime to the *syn*-isomer may be effected with only a catalytic amount of this reagent. Thus, complete reversion of *anti*-*p*-chlorobenzaldoxime to the *syn*-isomer occurred on standing in ether solution at room temperatures in the presence of 10 mole-per cent of boron fluoride. No reversion occurred in a blank experiment in the absence of a catalyst, the *anti*-aldoxime being recovered unchanged. Similarly the *anti*-aldoxime reverted to the *syn*-isomer in the presence of 13 mole-per cent of hydrochloric acid in ethanol and water.

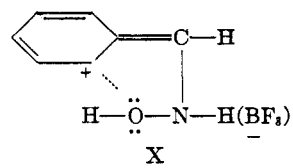


The mechanism for the isomerization of the *syn*-hydrochloride or *syn*-boron fluoride complex to the *anti* salt or complex, and also that of the reversion of the *anti*-aldoxime to the *syn*-isomer, is represented in Scheme A. The isomerizations in both directions may be considered to involve carbonium ions VIII and IX in which free rotation around the carbon-nitrogen bond is possible. Each of these carbonium ions is a resonance form of the usual salt-like structure as indicated. The equilibrium between carbonium ions VIII and IX is evidently far on the side of the latter "*anti*" structure, since the *syn*-aldoxime (I) is converted by an equivalent or more of hydrogen chloride or boron fluoride to the *anti* salt (III) or *anti* complex (V) which precipitates from the reaction medium. The free *anti*-aldoxime (VI) is obtained only on subsequent treatment of the salt or complex with a base such as sodium bicarbonate. The reversion of the *anti*-aldoxime (VI) to the *syn*-isomer (I) in the presence of a catalytic amount of boron fluoride or hydrochloric acid occurs because the free aldoxime, which is more stable in the *syn* configuration, is being continually regenerated by the action of the ether or the ethanol-water which functions as a base.

SCHEME A



It should be pointed out that certain other resonance forms may also contribute to the structure of an aromatic aldoxime hydrochloride salt or boron fluoride complex. One of these would be X, an appreciable contribution of which might offer a possible explanation of the greater stability of the *anti* configuration of the salt or complex. Thus, whereas the aromatic ring in the free aldoxime repels the hydroxyl oxygen to favor the *syn* configuration, the ring in resonance form X having a positively charged *ortho* position may attract the hydroxyl oxygen to favor the *anti* configuration.



X

EXPERIMENTAL[2]

Conversion of syn-p-chlorobenzaldoxime (I) *to anti-isomer* (VI) *with boron fluoride. A. N-coordination complex* (V). *syn-p*-Chlorobenzaldoxime, m.p. 105–106°, was prepared in 87% yield from *p*-chlorobenzaldehyde, hydroxylamine hydrochloride, and sodium carbonate (3).

A solution of 7.8 g. of *syn-p*-chlorobenzaldoxime in 150 ml. of dry thiophene-free benzene was saturated with gaseous boron fluoride (evolution of white fumes) as described for the preparation of the boron fluoride N-coordination complex of benzophenone oxime (7). The resulting precipitate of complex V was collected on a funnel, washed with benzene, and dried in a vacuum desiccator overnight; yield, 11.1 g. (99%). In several experiments the yield was at least 95%. The complex appeared to be stable indefinitely at room temperatures, although it melted with decomposition at 150–151°.

B. Liberation of anti-aldoxime (VI) *from complex* V. The complex (3.0 g.) was added with stirring to 100 ml. of 5% sodium bicarbonate solution. After the evolution of carbon dioxide had ceased, the mixture was filtered. The solid on the funnel (0.2 g.) melted at 130–132°, and at 135–137° on admixture with an authentic sample of the *anti*-aldoxime (VI), m.p. 142–143°, prepared through the hydrochloride salt (see below). The filtrate on standing several hours precipitated 0.72 g. of crystals, m.p. 142–143°, which was not depressed on admixture with an authentic sample of the *anti*-aldoxime (VI). Similarly there were isolated from subsequent filtrates several more crops of crystals, the melting points and mixture melting points of which were 142–143°. The total yield of the pure *anti*-aldoxime was 1.88 g. (89%). The yield including the slightly impure product first obtained was estimated to be 98%; the over-all yield from the *syn*-aldoxime (I) was 93–98%. It should be mentioned that the melting point of the pure *anti*-aldoxime is 142–143° when the temperature is raised rapidly, and about 129–130° when the temperature is raised slowly. Previously reported melting points are 140° (3) and 142° (8).

When a benzene solution of the *anti*-aldoxime, m.p. 142–143° was saturated with boron fluoride and the resulting precipitate was treated with sodium bicarbonate solution, 95% of the *anti*-aldoxime, m.p. 142–143°, was recovered.

C. Confirmation of anti configuration. An earlier general method (5) was adapted to the present case. The *anti*-aldoxime, m.p. 142–143°, was acetylated with acetic anhydride to form the *anti*-acetate (VII) (m.p. 77–78°), 1.0 g. of which was dissolved in 5 ml. of pyridine. After standing at room temperatures for 9 hours, water was added to give 0.63 g. (92%) of *p*-chlorobenzonitrile, m.p. 93–94°; lit. m.p. 93–94° (9).

When a solution of the acetate of *syn-p*-chlorobenzaldoxime (m.p. 67–69°) was similarly allowed to stand for 9 hours and then was treated with water, 87% of the *syn*-acetate (m.p. 67–69°) was recovered.

Partial isomerization of complex IV *to complex* V *at 10°.* A benzene solution of 3.0 g. of *syn-p*-chlorobenzaldoxime was saturated with boron fluoride at 10° to give 4.05 g. (97%) of precipitate.

When a 2.0-g. sample of this precipitate was decomposed with sodium bicarbonate solution there was obtained as the first crop 0.80 g. (57%) of recovered *syn-p*-chlorobenzaldoxime, m.p. 105–106°, and as second and third crops 0.55 g. (40%) of *anti-p*-chlorobenzaldoxime, m.p. 142–143°. These two isomers were identified by the mixture melting point method.

When a second 2.0-g. sample of the precipitate was heated at 135° (bath temperature) for 20 minutes, then cooled, and decomposed with sodium bicarbonate solution there was isolated 1.35 g. (98%) of the *anti*-aldoxime, m.p. 141–143°.

Conversion of syn-p-chlorobenzaldoxime to the anti-isomer through hydrochloride. The hydrochloride salt was precipitated from an ethereal solution of 10 g. of *syn-p*-chlorobenzaldoxime employing dry gaseous hydrogen chloride. Yield, 11.1 g. (90%); m.p. 123–

[2] Melting points are uncorrected.

126°; reported m.p. 100–110° (3). The pure *anti*-aldoxime was obtained by adding the salt to 200 ml. of a saturated sodium bicarbonate solution and warming the suspension for a few minutes. The suspended material was collected on a funnel, sucked dry, and recrystallized from benzene, giving 7.5 g. (75%), m.p. 142–143° of *anti-p*-chlorobenzaldoxime. From the benzene filtrate there was isolated 1.3 g. (13%) of a mixture of both isomers which melted at 97–101°.

Catalyzed reversion of anti-p-chlorobenzaldoxime to the syn-isomer. A. With boron fluoride. To a solution of 1.0 g. of *anti-p*-chlorobenzaldoxime (m.p. 142–143°) in 50 ml. of anhydrous ether was added 0.065 g. (10 mole-per cent) of boron fluoride etherate. After standing for 162 hours at room temperatures the solution was shaken with 3 ml. of 10% sodium bicarbonate. The solvent was removed from the resulting ethereal solution, and the residue was recrystallized from ethanol and water to give 0.95 g. (95%) of *syn-p*-chlorobenzaldoxime (long white needles), m.p. 105–107°, which was not depressed on admixture with an authentic sample of the *syn*-aldoxime. In a blank experiment in the absence of a catalyst (187 hours), 99% of the *anti-p*-chlorobenzaldoxime was recovered unchanged, m.p. 142–143°.

B. With hydrochloric acid. To a solution of 1.0 g. of *anti-p*-chlorobenzaldoxime, m.p. 142–143° in 50 ml. of 70% ethanol was added 1 ml. (13 mole-per cent) of 1 *M* hydrochloric acid. After standing 168 hours at room temperatures 3 ml. of sodium bicarbonate solution was added, and the ethanol was removed under reduced pressure. The residue was recrystallized from ethanol and water to give 0.97 g. (97%) of *syn-p*-chlorobenzaldoxime, m.p. 100–105°. In a blank experiment in the absence of the acid (240 hours), the *anti*-aldoxime was mainly recovered.

SUMMARY

1. Similar to hydrogen chloride, boron fluoride was found to convert *syn-p*-chlorobenzaldoxime to the N-coordination complex of the *anti*-isomer at 25–35° from which the *anti*-aldoxime was obtained on treatment with sodium bicarbonate. Only partial isomerization was observed at 10°.

2. *anti-p*-Chlorobenzaldoxime reverted to the *syn*-isomer in the presence of a catalytic amount of boron fluoride in ether or of hydrogen chloride in ethanol-water.

3. Mechanisms are considered for these *syn-anti* isomerizations.

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REFERENCES

(1) See NOLLER, *Chemistry of Organic Compounds*, W. B. Saunders Company, Philadelphia, 1951, p. 523.
(2) See BREWSTER, *Organic Chemistry*, Prentice-Hall Inc., 1948, p. 634.
(3) ERDMANN AND SCHWECHTEN, *Ann.*, **260**, 63 (1890).
(4) BRADY AND DUNN, *J. Chem. Soc.*, **123**, 1783 (1923).
(5) See HAUSER AND JORDAN, *J. Am. Chem. Soc.*, **58**, 1772 (1936).
(6) BRADY AND DUNN, *J. Chem. Soc.*, **109**, 657 (1916).
(7) HAUSER AND HOFFENBERG, *J. Org. Chem.*, **20**, 1482 (1955).
(8) BRADY AND MCHUGH, *J. Chem. Soc.*, **125**, 551 (1924).
(9) REMSEN, HARTMANN, AND MACKENFUSS, *J. Am. Chem. Soc.*, **18**, 169 (1896).