[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF DUKE UNIVERSITY]

THE ACYLATION OF ALDOXIMES. II.* THE INVERSION OF CONFIGURATION IN THE PREPARATION OF CARBANILINO ALDOXIMES FROM PHENYL ISOCYANATE AND *syn*-ALDOXIMES†

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The purpose of this series of papers is to study the reactions of *syn* and *anti* aldoximes with various acylating reagents, and to investigate the action of bases on the acyl derivatives thus formed. These reactions are of interest in themselves, and are of especial importance in connection with the geometrical isomerism of this series of compounds.

In spite of the rather extensive literature[1] on the acylation of aldoximes, there are still a number of unsolved problems; in fact, a perusal of the literature gives one the impression that the uncertainties outweigh the certainties in this field. In this connection Brady and McHugh[1a] have pointed out that the following problems should be considered: "(*1*) How far it is justifiable to assume that all acyl derivatives which on alkaline hydrolysis give the nitrile have a similar configuration? (*2*) If the above assumption is correct, why one reagent, *e.g.*, ethyl chloroformate, brings about inversion of some oximes but not of others, whereas another similar reagent, diphenylcarbamyl chloride, always brings about inversion, and a third, benzoyl chloride, never. (*3*) Why phenylcarbimide causes inversion, but α-naphthylcarbimide does not do so . . . ." It is hoped that with the aid of more recent results some light might be thrown on these and related problems.

At the time (1925) of the above quotation it was generally believed that of a pair of geometrically isomeric acyl aldoximes, (I and II), only the β, or *anti* isomer (II)‡ reacts with alkali to give nitrile.

* The paper on carbethoxy aldoximes by HAUSER, JORDAN, AND O'CONNER, *J. Am. Chem. Soc.*, **57**, 2456 (1935), is regarded as the first paper of this series.

† This paper is from a portion of a thesis presented by A. E. Rainsford in partial fulfilment of the requirements for the Ph.D. degree at Duke University.

[1] See especially, (*a*) BRADY AND MCHUGH, *J. Chem. Soc.*, **127**, 2417 (1925); (*b*) FREUDENBERG, "Stereochemie", **7**, 996–9 (1933).

‡ For a discussion of the evidence supporting these configurations for α, and β aldoximes and their acyl derivatives see especially, FREUDENBERG, "Stereochemie", **7**, 974–981; GILMAN, "Organic Chemistry", John Wiley and Sons, New York, N. Y.,

(I) *syn* (α) (II) *anti* (β)

This assumption then seemed plausible because with the acetyl, and carbanilino aldoximes (the most widely studied acyl derivatives) only the *anti* isomers give mainly nitrile when treated with alkali; most of the α, or *syn* isomers‡ of these derivatives give with this reagent almost entirely the corresponding α, or *syn* aldoxime.[2] We now know however, that, although all acyl *anti* aldoximes (II) probably always form nitrile more readily than the isomeric acyl *syn* derivatives (I), certain of the latter also react with hot alkali to give partly or even largely nitrile. Consequently, in certain cases in which the isomeric *anti* derivatives cannot be isolated for comparison, acyl *syn* derivatives that give considerable nitrile with alkali might easily be mistaken for *anti* isomers. This has happened with certain carbethoxy, and diphenylcarbamyl derivatives which have been isolated in only one isomeric form.

The carbethoxy derivatives, prepared from ethyl chloroformate and *syn* aldoximes in alkaline solution, were formerly assigned[1a] the *anti* configuration because when heated with alkali they gave considerable nitrile or corresponding acid. We now know however, that these derivatives must have the *syn* configuration because when treated with cold alkali* or with *n*-butylamine,[3] they give almost quantitative yields of the original *syn* aldoximes. The isomeric carbethoxy *anti* derivatives are formed presumably when *anti* aldoximes in alkaline solution are treated with ethyl chloroformate, but they are decomposed immediately by the alkali to give nitrile which is the product isolated.

The diphenylcarbamyl derivatives also are prepared from the sodium salts of *syn* aldoximes, and in a paper to be published shortly it will be shown that they likewise very probably are *syn* derivatives.

Thus, contrary to the assumption stated in (*2*) of the above quotation, no inversion of configuration occurs in the reactions of *syn* aldoximes (as sodium salts) with either ethyl chloroformate or diphenylcarbamyl chloride.

1938, p. 386. Since these configurations are now commonly accepted it seems justified to use the terms, "*syn*" and "*anti*", which have more significance than the symbols, α and β.

[2] See HAUSER AND JORDAN, *J. Am. Chem. Soc.*, **57**, 2450 (1935).

[3] HAUSER AND JORDAN, *ibid.*, **58**, 1772 (1936).

The reaction of phenyl isocyanate (phenylcarbimide) with aldoximes, mentioned in (*3*) of the above quotation, is somewhat different. Unlike the reactions with ethyl chloroformate and with diphenylcarbamyl chloride, which were carried out with the salts of oximes, the reaction with phenyl isocyanate has been carried out with the free oximes in ether solution. Brady and co-workers[4] showed that under these conditions *syn* aldoximes with phenyl isocyanate give carbanilino *anti* aldoximes or mixtures of *syn*, and *anti* derivatives; *anti* aldoximes with this reagent also give *anti* derivatives. The carbanilino *syn* aldoximes were generally obtained by heating the *anti* derivatives in alcoholic solution. Since it is possible to isolate certain carbanilino derivatives in two isomeric forms, their configurations are readily determined.

In this paper we have confirmed Brady's conclusions that in reaction with *syn* aldoximes phenyl isocyanate is capable of causing inversion of configuration while α-naphthyl isocyanate apparently is not. Also, we have made a further study of the phenomenon of inversion and of its prevention.

In Table I are given the melting points and probable configurations of the products obtained from the reactions of phenyl isocyanate with certain *syn*, and *anti* aldoximes in ether solution. In cases in which a similar product has been prepared previously the melting points recorded in the literature are given. The relative amounts of ether used, and the approximate time that elapsed before precipitation began are indicated also, since these factors should be considered in certain cases. In Table II are given the yields of products (with melting points in parentheses) obtained from certain pure carbanilino *syn*, and carbanilino *anti* derivatives with pyridine and with *n*-butylamine.

It can be seen from Table I that the product which precipitated within a few seconds when phenyl isocyanate was added to *syn*-3,4-methylenedioxybenzaldoxime in a minimum of ether (expt. 1) melted within a few degrees of the melting point of the product obtained from the isomeric *anti* aldoxime (expt. 2). In agreement with Brady and McHugh[1a], we believe that the product from the *syn* aldoxime consisted mostly of the carbanilino *anti* derivative since with hot alkali it gave mostly 3,4-methylenedioxybenzoic acid; the derivative from the *anti* aldoxime appeared to consist entirely of the *anti* derivative, giving with hot alkali only 3,4-methylenedioxybenzoic acid. This conclusion is supported by our pyridine-*n*-butylamine test[3] for configuration; however, the results of this test with the crude carbanilino derivatives were not very satisfactory, and attempts to recrystallize the crude derivatives always resulted in

[4] BRADY AND DUNN, *J. Chem. Soc.*, **109**, 650 (1916); also reference 1 *a*.

TABLE I

PRODUCTS OBTAINED FROM PHENYL ISOCYANATE AND SUBSTITUTED BENZALDOXIMES IN ETHER SOLUTION

EXPT.	CONFIG.	SUBSTITUENT	AMT. OF ETHER USED	TIME OF PRECIPITATION	M. P. CRUDE PRODUCT			M. P. RECRYST. PRODUCT		
					Found	Lit.	Config.	Found	Lit.	Config.
1	*syn*	3,4-CH_2O_2	Minimum	5–15 sec.	78–80	78	*anti* + (*syn*)[a]	Dec.	Dec.	—
2	*anti*	3,4-CH_2O_2	Minimum	Instantly	82–84	84	*anti*	Dec.	Dec.	—
3	*syn*	3,4-CH_2O_2	2 × minimum	1–2 min.	80–82	—	*anti* + (*syn*)[a]	—	—	—
4	*syn*	3,4-CH_2O_2	4 × minimum	1 hr.	112–115	—	*syn* + (*anti*)[a]	127	—	*syn*
5	*syn*	3,4-CH_2O_2	5 × minimum	Several hrs.[b]	123–125	—	*syn*	127	—	*syn*
6	*syn*	4-OCH_3	—	1–2 min.	78–80	74	*anti* + *syn*	—	—	—
7	*anti*	4-OCH_3	—	Instantly	74	74	*anti*	—	—	—
8	*syn*	4-OCH_3	—	10–15 min.	100–103	—	*syn* + (*anti*)[a]	110	103	*syn*
9	*syn*	3-NO_2	—	3–7 min.	114–120	105	*syn* + *anti*	148	148	*syn*
10	*anti*	3-NO_2	—	Instantly	88–90	94	*anti*	94	94	*anti*
11	*syn*	4-$N(CH_3)_2$	—	2 sec.–20 min.	114–116	—	*anti*	118	117	*anti*

[a] The parenthesis indicates that the isomer is probably present in relatively small amounts.

[b] In this experiment the precipitate was obtained only after cooling the reaction mixture.

TABLE II

YIELDS OF PRODUCTS[a] FROM PURE CARBANILINO DERIVATIVES OF SUBSTITUTED BENZALDOXIMES WITH PYRIDINE AND *n*-BUTYLAMINE

CARBANILINO DERIV.		WITH PYRIDINE		With *n*-BUTYLAMINE	
Config.	Substituent	% Nitrile	% Orig. Deriv. Recov.	% Nitrile[b]	% *syn*-Oxime
syn	3,4-CH_2O_2		93 (m.p. 126°)		70 (m.p. 110°)
syn	3-NO_2		93 (m.p. 140°)		90 (m.p. 118°)
anti	3-NO_2	82 (m.p. 114°)		93 (m.p. 110–112°)	
syn	4-$(CH_3)_2N$		93 (m.p. 154°)		90 (m.p. 140°)
anti	4-$(CH_3)_2N$	80 (m.p. 70–72°)		88 (m.p. 72–74°)	

[a] The melting points of the products on which these yields are based are given in parentheses; after recrystallization of the products, their melting points agreed with those reported in the literature.

[b] The addition of *n*-butylamine to most *anti* derivatives generates considerable heat.

decomposition. The crude derivatives (from expts. 1 and 2) were decomposed by pyridine to give nitrile but only a low yield of this product could be isolated. With *n*-butylamine, the reaction was not vigorous as is generally the case with pure carbanilino-anti-derivatives, and a small amount of *anti* oxime** was obtained instead of nitrile. It can be seen from Table II that recrystallized (pure) *anti* derivatives with pyridine or *n*-butylamine (hot) give high yields of nitrile.

The product that precipitated within two minutes when phenyl isocyanate was added to *syn*-3,4-methylenedioxybenzaldoxime in about twice the minimum of ether (expt. 3) also probably consisted mostly of the *anti* derivative, but the products that precipitated after an hour or more when four or five times the minimum of ether was used (expts. 4 and 5) undoubtedly consisted mostly if not entirely of the *syn* derivative. Recrystallization of these products gave pure carbanilino-*syn*-3,4-methylenedioxybenzaldoxime, melting at 127°. Brady and co-workers did not obtain this product, having carried out the reaction only in a minimum of ether. They reported that the *syn* derivative (m.p. 104°) was obtained on heating the *anti* derivative in alcohol. We were able to isolate a similar product (m.p. 107–109°) in very small yield but it was not the pure *syn* derivative. That our product melting at 127° is the pure *syn* derivative is shown by analysis and by the fact that it is stable in pyridine but is decomposed by *n*-butylamine or hot alkali to give the original *syn* aldoxime. (See Table II.)

Similar results have been obtained with phenyl isocyanate and the other aldoximes studied. The precipitate that formed within about a minute from *syn*-4-methoxybenzaldoxime (expt. 6) probably consisted mostly of the *anti* derivative, since Brady and McHugh[1c] have shown that a similar product (m.p. 74°) is decomposed by alkali to give nitrile. The precipitate that formed after 10–15 minutes (expt. 8), however, very likely consisted almost entirely of the *syn* derivative, which was obtained in the pure condition on recrystallization.

The crude product from *syn*-3-nitrobenzaldoxime (expt. 9), although melting somewhat higher than the product obtained by Brady and Dunn,[4] probably consisted of a mixture of the *syn*, and *anti* derivative; the pure *syn* derivative was obtained on recrystallizing the product from hot alcohol.

** The addition of *n*-butylamine to pure *anti* derivatives generates sufficient heat to give nitrile; see reference 3. Crude carbanilino-*anti*-3,4-methylenedioxybenzaldoxime apparently does not generate enough heat when treated with *n*-butylamine to give an appreciable amount of nitrile and *anti* oxime is obtained instead. In this connection it should be noted that when *n*-butylamine is added to an acetyl *anti* aldoxime and the reaction mixture cooled, the anti aldoxime is the main product. See HAUSER AND JORDAN, *J. Am. Chem. Soc.*, **58**, 1419 (1936).

The reaction of phenyl isocyanate with *anti*-3-nitrobenzaldoxime (expt. 10) gave a crude product which on recrystallization from cold acetone gave the pure *anti* derivative. The configurations of these derivatives is established by their reactions with pyridine and *n*-butylamine (See Table II), and with alkali.[4]

The reaction with *syn*-4-dimethylaminobenzaldoxime (expt. 11) is of especial interest. Although the isomeric *anti* aldoxime has never been isolated, the carbanilino *anti* derivative is readily obtained by the action of phenyl isocyanate on *syn*-4-dimethylaminobenzaldoxime, even when the precipitation is retarded for half an hour by the use of a relatively large amount of ether. In fact, of the *syn* aldoximes studies by us, this is the only one that gave pure *anti* derivative. The latter was obtained by recrystallization of the crude product from cold acetone. When heated

TABLE III

PRODUCTS[a] FROM α-NAPHTHYLCARBANILINO DERIVATIVES OF SUBSTITUTED BENZALDOXIMES WITH PYRIDINE AND *n*-BUTYLAMINE

BENZALDOXIME USED TO PREPARE DERIVATIVE		PRODUCT FROM DERIVATIVE WITH PYRIDINE		PRODUCT FROM DERIVATIVE WITH *n*-BUTYLAMINE	
Config.	Substituent	% Nitrile	% Deriv. recov.	% Nitrile	% α-Oxime
syn	3,4-CH_2O_2		80 (m.p. 225)		75 (m.p. 110)
syn	4-OCH_3		89 (m.p. 160)		38 (m.p. 64)
syn	4-$N(CH_3)_2$		70 (m.p. 141–144)		—
anti	3,4-CH_2O_2	88 (m.p. 92)		78 (m.p. 91)	
anti	3-NO_2	46 (m.p. 114)		25 (m.p. 117)	

[a] The melting points of the products on which these yields are based are given in parentheses.

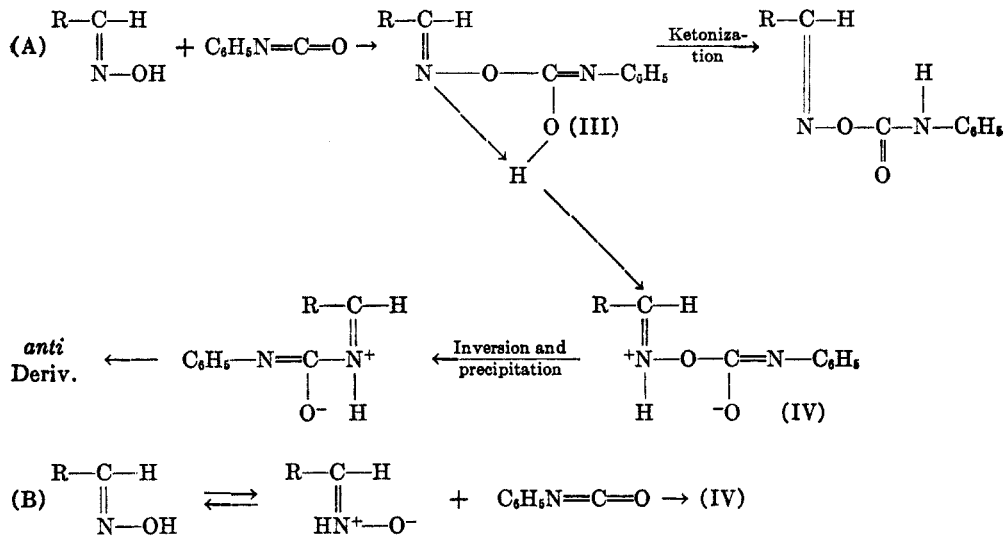
in alcohol this *anti* derivative is converted into the *syn* isomer as reported by Brady. The configurations of these isomeric derivatives seems well established; the *syn* derivative may be recovered unchanged from pyridine, but is decomposed by *n*-butylamine or hot alkali[4] to give the original *syn* aldoxime, whereas the *anti* isomer is decomposed by pyridine, *n*-butylamine (hot) or alkali[4] to give nitrile (See Table II).

In confirming Brady's conclusion that α-naphthyl isocyanate is apparently not capable of causing inversion of configuration, we have prepared derivatives from this reagent and certain representative *syn*, and *anti* aldoximes in a minimum of ether. The melting points of the derivatives prepared by us agreed essentially with those reported in the literature. From a study of the reactions with alkali Brady and co-workers[5] concluded

[5] BRADY AND RIDGE, *J. Chem. Soc.*, **123**, 2163 (1923); also reference 1*a*.

that the derivatives obtained from *syn* aldoximes have the *syn* configuration and that those from *anti* oximes, the *anti* configuration. We have confirmed this conclusion by means of our pyridine-*n*-butylamine test for configuration. It can be seen from Table III that the derivatives obtained from *syn* aldoximes are recovered unchanged from pyridine but are aminolyzed by *n*-butylamine to regenerate the original *syn* aldoxime, the derivatives from *anti* aldoximes are decomposed by pyridine or *n*-butylamine (hot) to give nitrile. The rather low yields of nitrile and oxime obtained in certain cases is due at least in part to the difficulty of isolating these products.

The mechanism for the inversion of configuration brought about by the action of phenylisocyanate on *syn* aldoximes is not entirely clear, but certain suggestions can be made in this connection. Since *syn* aldoximes are commonly converted into their *anti* isomers through the intermediate formation of their hydrochloride salts, it seems possible that the inversion effected by phenyl isocyanate likewise involves the formation of a "salt-like" intermediate with a positive charge on the nitrogen atom. Such a substance might be formed by the reaction of either tautomeric form of the aldoxime with phenylisocyanate as represented by A and B.



In A the addition of the oxime to the carbon-oxygen double bond of the isocyanate†† would give an acid (III), which might either undergo ketoni-

†† The addition of other hydroxy compounds to phenyl isocyanate has been formulated in this way. See ALLEN AND BLATT, Gilman's "Organic Chemistry", John Wiley and Sons, New York, N. Y., **1938**, p. 574.

zation to give the *syn* derivative, or form the "inner" salt (IV). The tendency for chelation (hydrogen bond formation), involving the acid hydrogen and the free pair of electrons on the oxime nitrogen, should facilitate the formation of (IV). As represented by B, IV might result from the direct action of the nitrone (amine oxide) form of the oxime with phenyl isocyanate. Also, it is possible, as suggested by Brady and Dunn,[4] that the nitrone form of the *syn* oxime itself undergoes inversion to the nitrone form of the *anti* oxime which then reacts with phenyl isocyanate.

In connection with this explanation two questions arise. First, why with *syn*-3,4-methylenedioxybenzaldoxime, phenyl isocyanate causes inversion in a minimum of ether but not in several times the minimum of ether; and second, why phenyl isocyanate is capable of causing inversion, whereas α-naphthyl isocyanate is apparently not. At first sight it might appear that inversion occurs also in the relatively dilute solution, but before the *anti* derivative precipitates it isomerizes, giving the *syn* derivative. While this is a possible explanation of the result, it is also possible that in the relatively dilute solution, an appreciable amount of *anti* derivative is never formed, because under these conditions the concentration of the acid (III) and salt (IV) is never sufficiently great to bring about appreciable inversion. The failure of α-naphthyl isocyanate to cause inversion might be explained in a similar manner; that is, the intermediate salt corresponding to IV might never be formed in sufficient concentration to cause inversion. In this connection it should be mentioned that α-naphthyl isocyanate appears to be less active than phenyl isocyanate towards *syn* aldoximes; in no case were we able to cause a derivative of the former to precipitate within less than eight minutes, whereas with phenyl isocyanate under similar conditions the derivative generally precipitated within a few seconds.

On the basis of the ideas discussed above it was predicted that no inversion should occur if the reaction of *syn* aldoximes with phenyl isocyanate were carried out in the presence of a base of sufficient strength to prevent the formation of an intermediate with a positive charge on the nitrogen atom; and, in agreement with this, it has been found that no inversion occurs when the reaction is carried out in the presence of triethylamine or tri-*n*-propylamine.

In Table IV are given the melting points and configurations of the derivatives obtained from *syn* aldoximes and phenyl isocyanate in the presence of approximately equivalent amounts of certain tertiary amines and a minimum of ether; the approximate time of precipitation is also given in this table. Except for the presence of the amines (and slightly less ether) these experiments were carried out under essentially the same conditions as those used in the experiments represented in Table I.

It can be seen from Table IV that in the presence of triethylamine or tri-*n*-butylamine (expts. 1–7), the four *syn* benzaldoximes studied in this work reacted with phenyl isocyanate to give high yields of the corresponding carbanilino *syn* derivative. With *syn*-3,4-methylenedioxybenzaldoxime, practically pure *syn* derivative was obtained directly, even in the presence of only one-fourth of an equivalent of triethylamine (expt. 2). With the other three *syn* benzaldoximes, the precipitates melted within a few degrees of the melting points recorded for the *syn* derivatives; the pure *syn* derivatives were obtained on recrystallization of the precipitates.

TABLE IV

PRODUCTS OBTAINED FROM PHENYL ISOCYANATE AND SUBSTITUTED *syn*-BENZALDOXIMES IN PRESENCE OF TERTIARY AMINES AND MINIMUM OF ETHER

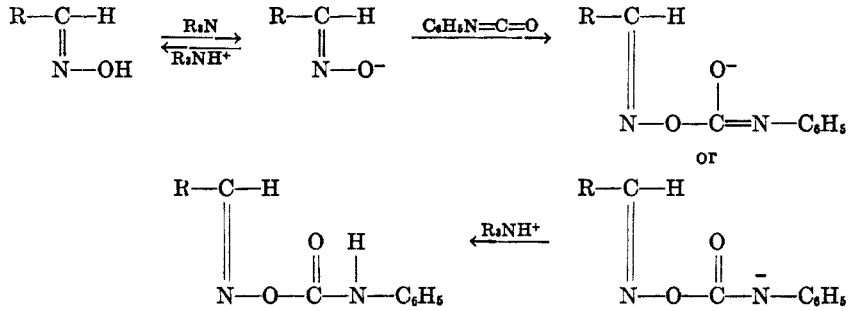
EXPT.	SUBSTITUENT IN *syn*-BENZALDOXIME	TERTIARY AMINE USED	TIME OF PRECIPITATION	M.P. OF PRODUCT	CONFIGURATION OF PRODUCT
1	3,4-CH_2O_2	Triethylamine	5–15 sec.	126–127	*syn*
2	3,4-CH_2O_2	Triethylamine[a]	5–15 sec.	123–124	*syn*
3	4-CH_3O	Triethylamine	10 min.	103–105	*syn*
4	3-NO_2	Triethylamine	3 min.	135–137	*syn*
5	4-$N(CH_3)_2$	Triethylamine	10 sec.	144–148	*syn*
6	3,4-CH_2O_2	Tri-*n*-propylamine	50 sec.	126–127	*syn*
7	4-$N(CH_3)_2$	Tri-*n*-propylamine	20 min.	145–148	*syn*
8	3,4-CH_2O_2	Dimethylaminobenzaldehyde	20–50 sec.	82	*anti*
9	3,4-CH_2O_2	Dimethylaniline	20–30 min.	125–126	*syn*
10	4-$N(CH_3)_2$	Dimethylaniline	1–2 min.	114–117	*anti* + (*syn*)
11	4-$N(CH_3)_2$	Dimethylaniline[b]	8–9 min.	142–144	*syn*
12	4-$N(CH_3)_2$	Pyridine	1–3 min.	108–110	*anti*
13	3,4-CH_2O_2	Pyridine	—	—	*anti* ?

[a] In this experiment only one-fourth equivalent of triethylamine was used.

[b] In this experiment approximately thirteen times the equivalent of dimethylaniline was used.

It should be noted that in the presence of these amines, the *syn* derivative has been precipitated in most cases within the time in which the *anti* derivative was obtained in the absence of these bases (compare Table I). Thus it can hardly be argued that the *anti* derivative was also obtained first in the presence of the amine, and then isomerized to the *syn* derivative; this becomes still more unlikely when one considers that the *anti* derivatives are readily decomposed by tertiary amines to form nitriles. There seems little doubt therefore that, in the presence of these tertiary amines, phenyl isocyanate reacts with *syn* aldoximes to form the corresponding *syn* deriva-

tive directly. In this connection it should be pointed out that in the presence of these bases, the anion of the *syn* aldoxime, rather than the free oxime, may react with phenyl isocyanate; the reaction may be represented as follows:



Experiments 8 to 13 of Table IV were carried out in the presence of tertiary amines that are much less basic than triethylamine or tri-*n*-propylamine. It can be seen from the table that dimethylaminobenzaldehyde (expt. 8) and pyridine (expt. 13) are apparently not sufficiently basic to prevent inversion when *syn*-3,4-methylenedioxybenzaldoxime is treated with phenyl isocyanate. In the presence of pyridine no pure derivative was obtained, but since nitrile was isolated from the reaction mixture, the *anti* derivative was apparently formed and then decomposed.

The reaction of *syn*-3,4-methylenedioxybenzaldoxime with phenyl isocyanate in the presence of dimethylaniline (expt. 9) gave the *syn* derivative, but in this case, it was not possible to cause precipitation within less than twenty minutes and in this time the *syn* derivative might have been obtained even in the absence of the amine.

The reaction of *syn*-4-dimethylaminobenzaldoxime with phenyl isocyanate in the presence of an equivalent of dimethylaniline (expt. 10) or of pyridine (expt. 12) gave products that appeared to consist mostly of the *anti* derivative, since on dissolving them in pyridine they were decomposed to give partly nitrile; a little of the *syn* derivative was also isolated from the product of experiment 10. It is of interest to note that in the presence of a relatively large amount of dimethylaniline, (expt. 11), the product obtained consisted apparently only of the *syn* derivative which could be recovered unchanged from pyridine; after recrystallization practically pure *syn* derivative (m.p. 150–152°) was obtained.

Thus, although certain tertiary amines prevent inversion of configuration in the reaction of phenyl isocyanate with *syn* aldoximes, certain weaker bases do not; apparently, inversion is prevented only when the

medium is sufficiently basic to prevent the formation of a "salt-like" intermediate with a positive charge on the nitrogen atom.

Finally, it should be pointed out that the results presented in this paper are in agreement with the view held in this laboratory that the acylation of *syn* aldoximes in sufficiently basic solution involves no inversion of configuration.

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EXPERIMENTAL

Reactions of syn, *and* anti *aldoximes with phenyl isocyanate.*—(See Table I). To 2 g. of *syn*-3,4-methylenedioxybenzaldoxime in a minimum of dry ether (approx. 10 cc.) was added 2 cc. of phenyl isocyanate according to the method of Brady and McHugh.[1a] The precipitate that formed within a few seconds was collected by filtration, washed with dry ether, and pressed on a porous plate. Attempts to recrystallize the crude carbanilino derivative (m.p. 78–80°) from several types of solvents resulted in decomposition. The crude derivative, on heating with 2*N* sodium hydroxide gave an 80% yield of 3,4-methylenedioxybenzoic acid. Treatment of the crude derivative with pyridine according to the general directions given below, gave a mixture of products from which only a 10–15% yield of nitrile could be isolated. Addition of *n*-butylamine to the crude derivative failed to generate much heat, and it was difficult to isolate a pure substance from the products; however, a small amount of *anti* aldoxime (m.p. 136–140°) was isolated.

The addition of phenyl isocyanate to *anti*-3,4-methylenedioxybenzaldoxime in dry ether gave a precipitate instantaneously. Attempts to recrystallize the crude carbanilino derivative (m.p. 82–84°) resulted in decomposition. The crude derivative, on heating with alkali gave a 90% yield of 3,4-methylenedioxybenzoic acid. Treatment of the crude carbanilino derivative with pyridine gave a mixture of products (apparently diphenylurea and nitrile) from which a 20–25% yield of pure nitrile was isolated. The high yield of nitrile reported previously[2] for this reaction was based apparently on the crude product. Addition of *n*-butylamine to the crude carbanilino derivative at room temperature failed to generate much heat, and, contrary to an earlier report[2], no appreciable amount of nitrile could be isolated. On working up the mixture (involving an acid extraction of the amine) a 30% yield of the *syn* aldoxime (m.p. 110°) was isolated. The *anti* aldoxime was probably first formed in the reaction with *n*-butylamine, but was converted to the *syn* isomer during the acid extraction.

The reaction of *syn*-3,4-methylenedioxybenzaldoxime with phenyl isocyanate has been carried out also in the presence of excess ether. In the presence of about twice the minimum of ether the product was similar to that obtained with less ether, but in the presence of four or five times the minimum of ether, the precipitate formed much more slowly and apparently consisted mostly if not entirely of the *syn* derivative. On recrystallization from alcohol pure carbanilino-*syn*-3,4-methylenedioxybenzaldoxime, melting at 127°, was obtained. Since this substance has apparently not been isolated previously in the pure state, it was analyzed.

Anal. Calc'd for $C_{15}H_{10}N_2O_4$: N, 9.86. Found: N, 9.84.

The reactions of certain other *syn*, and *anti* aldoximes with phenyl isocyanate

were carried out in a similar manner. The results are summarized in Table I. In experiment 6 of this table, 10 cc. of ether to 1 g. of *syn*-4-methoxybenzaldoxime was used; this is more than the minimum of ether required for solution of the oxime. In experiment 11, *syn*-4-dimethylaminobenzaldoxime was dissolved in a minimum of ether, but the same product has been obtained using several times the minimum of ether.

Reactions of syn *aldoximes with phenyl isocyanate in the presence of certain tertiary amines.*—(See Table IV). Except for the presence of the amines, these experiments were carried out in essentially the same manner as those described above with the corresponding *syn* aldoxime in a minimum of ether. It seemed to make no difference whether the tertiary amine was mixed with the phenyl isocyanate and the mixture added to the oxime in ether, or the amine dissolved in the ether solution of the oxime and the phenylisocyanate added to this solution; in all cases the corresponding carbanilino *syn* derivative was obtained. The presence of the amine appeared to retard the precipitation of the derivative. However, by using less ether in these experiments than was used in corresponding experiments in the absence of the amine it was possible in most cases to cause precipitation of the *syn* derivative in the presence of the amine within the time required for precipitation of the *anti* derivative in the absence of this base. A typical experiment was carried out as follows. Two grams of *syn*-3,4-methylenedioxybenzaldoxime was dissolved in a warm mixture of approximately 7 cc. of ether and 1 cc. of triethylamine. After the solution had cooled to room temperature 2 cc. of phenyl isocyanate was added, and the solution was cooled slightly with cold water. The *syn* derivative began to precipitate within ten seconds; the precipitation was complete within one minute. A summary of results with other *syn* aldoximes is given in Table IV.

*The pyridine-*n*-butylamine test for configuration.*—One-gram samples of the derivative to be tested were placed in each of two 50-cc. Erlenmeyer flasks and 4–5 cc. of pyridine added to one, and the same amount of normal butylamine added to the other in ½-cc. portions from a medicine dropper. Addition of butylamine to *anti* compounds was usually accompanied by an evolution of considerable heat. The flasks were stoppered and allowed to stand overnight at room temperature. The solutions were poured into about 40 cc. of crushed ice and water and the mixture was filtered. The *anti* derivative with both pyridine and *n*-butylamine gave nitrile, while *syn* derivatives with pyridine gave unchanged derivative, and with *n*-butylamine gave *syn* aldoxime. In the case of *syn* derivatives with butylamine, high yields of *N*-phenyl-*N'*-*n*-butylurea were also obtained. In these cases the precipitated mixture was thoroughly washed in the crucible with 2*N* sodium hydroxide, and the oxime was isolated from the washings in the usual manner by acidifying with carbon dioxide. In certain instances when yields at first appeared to be low, both from pyridine and butylamine solutions, the filtrates from the original precipitate were extracted with 50 cc. of ether. The ether layer was washed with water and evaporated, yielding additional quantities of products. The results obtained from these reactions with pure carbanilino derivatives are shown in Table II.

Reactions of syn, *and* anti *aldoximes with α-naphthyl isocyanate.*—The reaction of certain *syn*, and *anti* aldoximes with α-naphthyl isocyanate were carried out essentially as described by Brady and Ridge.[5] The melting points of the derivatives obtained agreed essentially with those reported by these earlier workers.

The results of the reactions of these derivatives with pyridine and *n*-butylamine are summarized in Table III. These reactions were carried out essentially as described above with the carbanilino derivatives, except that in isolating the nitrile, it was necessary to dissolve α-naphthylamine in hydrochloric acid.

SUMMARY

1. Brady's conclusion that phenyl isocyanate is capable of converting certain *syn* aldoximes into carbanilino *anti* derivatives has been confirmed. An explanation is suggested for this inversion of configuration.

2. We have shown that inversion does not occur when *syn* aldoximes are treated with phenyl isocyanate in the presence of certain tertiary amines. This supports the hypothesis that there is no inversion of configuration during the preparation of acyl derivatives when the reaction is carried out in solution in the presence of a sufficiently strong base.

3. Carbanilino-*syn*-3,4-methylenedioxybenzaldoxime has been prepared in the pure condition for the first time.

4. Further results on the reactions of carbanilino *syn*, and carbanilino *anti* aldoximes with pyridine and with *n*-butylamine are reported.

5. Brady's conclusion that there is no inversion of configuration when *syn* aldoximes are treated with α-naphthyl isocyanate has been confirmed. It has been shown that α-naphthylcarbanilino *syn* aldoximes may be recovered unchanged from pyridine, but are decomposed by *n*-butylamine to give *syn* aldoximes; the corresponding *anti* isomers with pyridine or *n*-butylamine give nitrile.