[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, DUKE UNIVERSITY]

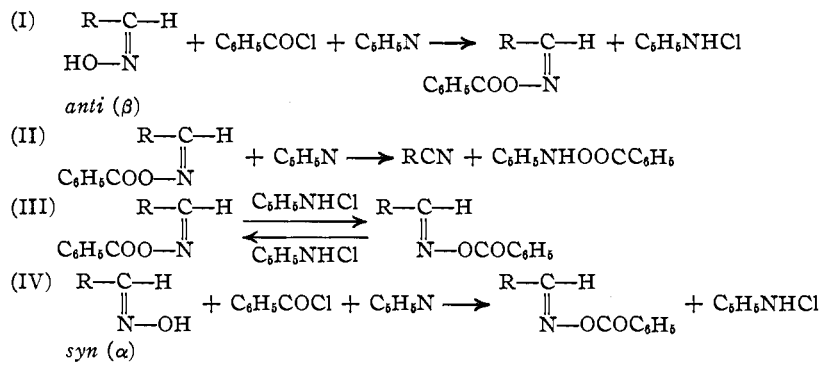
The Acylation of Aldoximes. V.[1] Isomerizations in the Benzoylation of *syn*- and *anti*-Aldoximes in Pyridine

BY GERTRUDE VERMILLION AND CHARLES R. HAUSER

In 1925 Brady and McHugh[2] reported that *anti*-aldoximes (β) react with benzoyl chloride in pyridine to give benzoyl-*syn*-aldoximes. Recently,[1] on repeating this work with three representative *anti*-aldoximes, we obtained either no benzoyl-*syn*-aldoxime or only a small yield (5–10%) of the derivative, the main product being the corresponding nitrile. In these experiments the reaction mixture was allowed to stand for twenty-four to forty-eight hours. We have now found that when the reaction is stopped within a few minutes, a higher yield of benzoyl-*syn*-derivative is obtained.

In Table I, experiments (1) to (5) inclusive, are given the yields of *syn*-derivative and nitrile obtained from the benzoylation of *anti*-3,4-methylenedioxy- and 4-methoxy-benzaldoximes in pyridine at room temperatures. It can be seen that although nitrile is the main product, a considerable yield of the *syn*-derivative is obtained (especially from the former oxime) when the reaction mixture is worked up within a few minutes, whereas no appreciable amount of the *syn*-derivative is obtained when the reaction mixture is allowed to stand for thirty-six to forty-eight hours at room temperatures. It should be mentioned that at 0°, also, both *syn*-derivative and nitrile are obtained from the benzoylation of *anti*-aldoximes in pyridine (expt. 12 of Table I).

These results may be accounted for as follows. In pyridine *anti*-aldoximes react with benzoyl chloride to give the corresponding benzoyl-*anti*-aldoxime and pyridinium chloride as represented by equation I. Part of the *anti*-derivative is decomposed by pyridine to give nitrile as represented by equation II, and part of it changed to the isomeric benzoyl-*syn*-derivative by the action of pyridinium chloride (formed in reaction I) as represented by equation III. This isomerization is reversible and although the equilibrium of this change is probably on the side of the *syn*-derivative, the latter is gradually reconverted into the *anti*-derivative which is decomposed irreversibly to nitrile (equation II). It is possible or even probable that before all of the *anti*-aldoxime is benzoylated, some of it is isomerized by the pyridinium chloride to the *syn*-isomer which is then benzoylated giving the benzoyl-*syn*-derivative. It has been shown that in pyridine which is saturated with hydrogen chloride, *anti*-3,4-methylenedioxybenzaldoxime is converted within a few minutes into its *syn*-isomer.



In support of this explanation it should be pointed out that nitriles formed in benzoylations undoubtedly result from the decomposition of intermediate benzoyl-*anti*-derivatives (equation II), since benzoyl-*syn*-derivatives (and *syn*- and *anti*-aldoximes) are stable in pyridine,[3] whereas acetyl-*anti*- and carbanilino-*anti*-derivatives (two types of *anti*-derivatives that have been isolated) are readily decomposed by pyridine[3] to form nitriles. The isomerization of *anti*-aldoximes and benzoyl-*anti*-derivatives to their *syn*-isomers by means of pyridinium chloride in pyridine (equation III) has its analog in the water system in which hydronium chloride (*i. e.*, aqueous hydrochloric acid) readily changes *anti*-aldoximes and their derivatives to *syn*-isomers. Also, the reversibility of the isomerization in the water system is demonstrated by the well-known inversion of *syn*-aldoximes into their *anti*-isomers,

(1) For paper IV of this series see, Vermillion, Jordan and Hauser, *J. Org. Chem.*, **5**, 75 (1940).

(2) Brady and McHugh, *J. Chem. Soc.*, **127**, 2415 (1925).

(3) See Hauser and Jordan, THIS JOURNAL, **58**, 1772 (1936).

TABLE I

PERCENTAGE YIELDS OF BENZOYL-*syn*-DERIVATIVE AND NITRILE FROM SUBSTITUTED *anti*-BENZALDOXIMES AND BENZOYL CHLORIDE IN VARIOUS MEDIA AT ROOM TEMPERATURES (22–32°)

Expt.	Substituent	Media	Time	*syn*-Derivative Yield, %	*syn*-Derivative M. p., °C. Obsd.[a]	*syn*-Derivative M. p., °C. Lit.	Nitrile Yield, %	Nitrile M. p., °C. Obsd.[a]	Nitrile M. p., °C. Lit.
1	$3,4\text{-}O_2CH_2$	Pyridine	5 min.	20	154–157	168	20	84–87	94–95
2	$3,4\text{-}O_2CH_2$	Pyridine	10 min.	16	161–163	168	58	90–93	94–95
3	$3,4\text{-}O_2CH_2$	Pyridine	36 hrs.	trace	...	...	75	90–93	94–95
4	$4\text{-}OCH_3$	Pyridine	10 min.	8	105–107	109–110	16	56–57	60
5	$4\text{-}OCH_3$	Pyridine	48 hrs.	0	...	...	46	59–60	60
6	$3,4\text{-}O_2CH_2$	Pyridine-HCl[b]	5 min.	49	163–165	168	28	83–89	94–95
7	$3,4\text{-}O_2CH_2$	Pyridine-HCl[c]	10 min.	33	150–155	168	46	80–82	94–95
8	$3,4\text{-}O_2CH_2$	Pyridine-HCl[b]	36 hrs.	trace	...	...	75	90–92	94–95
9	$4\text{-}OCH_3$	Pyridine-HCl[c]	10 min.	21	106–108	109–110	trace	...	...
10	$3,4\text{-}O_2CH_2$	Pyridine, $(C_2H_5)_3N$[d]	5 min.	0	...	...	22	90–92	94–95
11	$3,4\text{-}O_2CH_2$	Pyridine, $(C_3H_7)_3N$[d]	5 min.	0	...	...	64	80–90	94–95
12	$3,4\text{-}O_2CH_2$	Pyridine[e]	20 min.	13	160–161	168	44	83–85	94–95

[a] The melting points of products were raised by recrystallization to those reported in the literature. [b] Both *anti*-aldoxime and benzoyl chloride were dissolved in pyridinium chloride solution. [c] The *anti*-aldoxime was dissolved in pyridine and the benzoyl chloride in pyridinium chloride soln. [d] This experiment was carried out at about 8°. [e] This experiment was carried out at 0°.

which is effected by passing hydrogen chloride into a suspension of the *syn*-aldoxime in concentrated hydrochloric acid.

On the basis of the ideas discussed above one should expect that if the benzoylation were carried out with pyridinium chloride present from the beginning of the reaction a higher yield of *syn*-derivative (and a correspondingly lower yield of nitrile) would be obtained, whereas if the benzoylation were carried out in the presence of a sufficiently strong base none of the *syn*-derivative would be obtained; these expectations have been realized. In Table I, experiments (6) to (9) inclusive, are given the yields of products obtained from the benzoylation of *anti*-aldoximes in pyridine saturated with hydrogen chloride. A comparison of experiments (6), (7) and (9) with experiments (1), (2) and (4) shows that the presence of pyridinium chloride in the media favors the formation of the *syn*-derivative; it should be noted that in these experiments the reaction mixture was worked up within a few minutes. Also, in Table I, experiments (10) and (11), are given the yields of products obtained when the benzoylation was carried out in pyridine together with triethylamine or tri-*n*-propylamine. It can be seen that in the presence of these stronger bases (in sufficient amount) no *syn*-derivative is obtained, the only product being the nitrile.

Recently, we reported[1] that *syn*-3,4-methylenedioxybenzaldoxime with benzoyl chloride in pyridine gives partly the *syn*-derivative and partly the nitrile, and that *syn*-4-methoxybenzaldoxime with benzoyl chloride gives entirely the nitrile. In these experiments the reaction mixture was allowed to stand at room temperatures generally for twenty-four to forty-eight hours. We have now found that when the reaction is stopped within a few minutes a high yield of the corresponding benzoyl-*syn*-derivative (and only a very small yield of nitrile) is obtained even from *syn*-4-methoxybenzaldoxime.

In Table II are given the yields of products obtained from the benzoylation of three *syn*-aldoximes in pyridine solution at room temperatures. It can be seen that although the *syn*-derivative is practically the only product obtained from *syn*-4-methoxy- and *syn*-4-dimethylamino-benzaldoximes when the reaction is stopped within a few minutes (experiments 2 and 6), none of the *syn*-derivative is obtained when the reaction mixture is allowed to stand for forty-eight hours (experiments 4 and 8), the only product being the corresponding nitrile. Evidently, the *syn*-aldoximes with benzoyl chloride in pyridine first give the corresponding benzoyl-*syn*-derivative as represented by equation IV, but on standing in the reaction mixture the *syn*-derivative is converted into nitrile. This conversion is assumed to be effected by the pyridinium chloride as discussed above. In agreement with this assumption it has been shown that when the benzoylation of *syn*-aldoximes is carried out in pyridine together with a sufficient amount of the stronger base, triethylamine or tri-*n*-

TABLE II

PERCENTAGE YIELDS OF BENZOYL-*syn*-DERIVATIVE AND NITRILE FROM SUBSTITUTED *syn*-BENZALDOXIMES AND BENZOYL CHLORIDE IN VARIOUS MEDIA AT ROOM TEMPERATURE (22–32°)

				syn-Derivative			Nitrile		
				Yield,	M. p., °C.		Yield,	M. p., °C.	
Expt.	Substituent	Media	Time	%	Obsd.[a]	Lit.	%	Obsd.[a]	Lit.
1	3,4-O_2CH_2	Pyridine	48 hr.	25	164–165	168	44	88–90	94–95
2	4-OCH_3	Pyridine	14–17 min.	83	105–108	109–110	3	49–52	60
3	4-OCH_3	Pyridine	9–12 hr.	49	104–109	109–110	19	55–57	60
4	4-OCH_3	Pyridine	48 hr.	0	...	...	61	56–57	60
5	4-OCH_3	Pyridine[b]	60 hr.[b]	59	105–110	109–110	8	52–55	60
6	4-$N(CH_3)_2$	Pyridine	14–17 min.	81	136–138	138	3	68–70	75–76
7	4-$N(CH_3)_2$	Pyridine	9–12 hr.	46	138	138	25	70–72	75–76
8	4-$N(CH_3)_2$	Pyridine	48 hr.	0	...	...	56	74–76	75–76
9	4-OCH_3	Pyridine, $(C_2H_5)_3N$	48 hr.	84	104–106	109–110	0	...	...
10	4-OCH_3	Pyridine, $(C_3H_7)_3N$	48 hr.	89	105–107	109–110	0	...	...
11	4-$N(CH_3)_2$	Pyridine, $(C_2H_5)_3N$	24 hr.	87	138	138	0	...	...

[a] The melting points of products were raised by recrystallization to those reported in the literature. [b] This experiment was carried out at approximately 0°.

propylamine, only the benzoyl-*syn*-derivative is obtained even when the reaction mixture is allowed to stand for forty-eight hours (experiments 9, 10 and 11). The influence of substituents on the conversion of benzoyl-*syn*-derivatives to nitriles in the presence of pyridinium chloride will be discussed in a later paper.

Experimental

Benzoylation of *anti*-Aldoximes.—Eastman Kodak Co. pyridine and benzoyl chloride were dried and distilled as described previously.[1] The procedure of benzoylation[1] was modified. To 1 g. of *anti*-aldoxime dissolved in 3 cc. of pyridine was added with shaking during a period of about two minutes a solution of 1 cc. of benzoyl chloride in 3 cc. of pyridine. The temperature of the reaction mixture was kept at 22–32° by cooling the flask occasionally in cold water. After the periods of time designated in Table I, the reaction mixture was poured on approximately 45 g. of crushed ice. The mixture was shaken and filtered through a sintered glass crucible. The precipitate was washed with water until free from pyridine. Two 10-cc. portions of 95% alcohol were allowed to run slowly through the precipitate. The nitrile dissolved, leaving the relatively insoluble benzoyl-*syn*-derivative in the funnel. In certain cases a small amount of the derivative was obtained by partial evaporation of the alcohol. The nitrile was recovered by evaporation of the alcohol. An additional amount of nitrile was generally obtained by acidifying the original pyridine–water filtrate, extracting it with ether, and, after extracting the ether solution with alkali to remove oxime, evaporating the ether. The yields of benzoyl-*syn*-derivative and nitrile obtained and the melting points of the products on which these yields are based are given in Table I. The products were recrystallized until their melting points agreed with those reported in the literature.

In experiments (7) and (9) of Table I, 1 g. of *anti*-aldoxime was dissolved in 3 cc. of pyridine and 1 cc. of benzoyl chloride was dissolved in 3 cc. of pyridine that had previously been saturated with hydrogen chloride at room temperature (22–32°). The benzoyl chloride solution (which generally contained a precipitate) was added to the pyridine solution of oxime at 22–32° and the products isolated essentially as described above. In experiments (6) and (8) of Table I, the *anti*-aldoxime as well as the benzoyl chloride was dissolved in pyridine saturated with hydrogen chloride and the benzoylation carried out immediately.

In experiment (10) of Table I, 1 g. of *anti*-aldoxime was dissolved in 3 cc. of pyridine and 1 cc. of benzoyl chloride dissolved in 3 cc. of pyridine and 2 cc. (approximately 2 equivalents) of triethylamine. The reaction was carried out at approximately 8° essentially as described above. The benzoylation in the presence of tri-*n*-propylamine (expt. 11 of Table I) was carried out in a similar manner.

Conversion of *anti*-3,4-Methylenedioxybenzaldoxime to its *syn*-Isomer by Means of Pyridinium Chloride.—One gram of the *anti*-aldoxime (m. p. 144–145°) was dissolved in 5 cc. of pyridine which had been previously saturated with hydrogen chloride at room temperatures. After standing for ten minutes at room temperatures (22–32°) the solution was poured on 45 g. of ice and water containing 0.5 g. of sodium bicarbonate. The mixture was extracted with two 20-cc. portions of ether. The ether solution was extracted with cold sodium hydroxide solution. On passing carbon dioxide into the alkaline solution, the *syn*-aldoxime was precipitated, melting at 101–105°, and after two recrystallizations, at 109–110°; this is the recorded melting point for the *syn*-aldoxime.

In other experiments the *anti*-aldoxime (m. p. 144–145°) was dissolved in the pyridinium chloride solution and within a few seconds the mixture poured on ice water and bicarbonate or on ice water alone. The *anti*-aldoxime was recovered practically unchanged, the crude product melting at 143–144°.

Benzoylation of *syn*-Aldoximes.—The procedure described previously[1] was modified. To 1 g. of *syn*-aldoxime dissolved in 5 cc. of pyridine contained in a three-necked, bolt-head flask fitted with a thermometer, mercury-sealed stirrer and dropping funnel, was added slowly with stirring a solution of 1 cc. of benzoyl chloride in 5 cc. of pyridine. The temperature of the reaction mixture was kept at 22–32° by cooling the reaction flask in water. After the periods of time designated in Table II, the reaction mixture was poured on 45 g. crushed ice, and the benzoyl-*syn*-

derivative and nitrile separated essentially as described above under the procedure for *anti*-aldoximes.

In experiments (9), (10) and (11) of Table II, 1 g. of the *anti*-aldoxime was dissolved in 5 cc. of pyridine and 2 cc. of triethylamine or 2.5 cc. (2 equivalents) of tri-*n*-propylamine and the solution treated with 1 cc. of benzoyl chloride dissolved in 5 cc. of pyridine. The products were isolated essentially as described above.

Summary

1. The reaction of *anti*-aldoximes with benzoyl chloride in pyridine presumably first gives the corresponding benzoyl-*anti*-aldoxime (not isolated), which is partly decomposed to nitrile and partly isomerized to the benzoyl-*syn*-aldoxime, these two products being isolated. On standing in the reaction mixture the *syn*-derivative is slowly converted to nitrile, presumably through the intermediate formation of the *anti*-derivative.

2. Benzoylation of *anti*-aldoximes in pyridine saturated with hydrogen chloride gives a higher yield of the benzoyl-*syn*-derivative, whereas benzoylation of the *anti*-aldoximes in the presence of triethylamine or tri-*n*-propylamine gives none of the *syn* derivative, the only product being the nitrile.

3. The reaction of *syn*-aldoximes with benzoyl chloride in pyridine gives a high yield of the corresponding benzoyl-*syn*-aldoxime, which, on standing in the reaction mixture, is gradually converted to nitrile.

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Magnetic Studies of Ferrihemoglobin Reactions. II. Equilibria and Compounds with Azide Ion, Ammonia, and Ethanol[1]

BY CHARLES D. CORYELL[2] AND FRED STITT[3]

Introduction.—In the first paper of this series dealing with the magnetic properties and structure of ferrihemoglobin (methemoglobin) and some of its compounds,[4] it was shown that the ferric atom is held in the structure with essentially ionic bonds in the acid forms and in the fluoride complex, but that complex formation with hydrosulfide ion or cyanide ion leads to the formation of essentially octahedral covalent bonds between the iron atom and the porphyrin, globin and added group. Complex formation with hydroxide ion (corresponding to an apparent acid-group pK of 8.15 at ionic strength 0.2) leads to magnetic properties intermediate between these two classes, corresponding apparently to the existence of three unpaired electrons or the use of one $3d$ orbital for covalent bond formation.

There are presented in this paper the data which establish the fact that ferrihemoglobin azide contains octahedral covalent bonds to the iron atom. Further studies presented here show that ferrihemoglobin hydroxide forms hitherto unrecognized compounds with ammonia and with ethanol for which equilibrium constants have been determined. Studies of the pH dependence of the ethanol equilibrium indicate that acid ferrihemoglobin also forms ethanol compounds. It is also shown that the magnetic properties of ferrihemoglobin and its hydroxide complex are affected appreciably by methanol and *n*-propanol.

The high sensitivity of the magnetic susceptibilities of ferrihemoglobin and its hydroxide compound to chemical environment, in many cases exceeding the sensitivity of their visual absorption spectra, makes possible quantitative studies of chemical changes which may not directly involve the heme part of the molecule. In the hope of throwing new light on structural relationships in the heme group and between the heme and the protein, globin, we present some of this work from an empirical magnetic standpoint. At some later time, we hope to be able to explain the structural causes of the changes in magnetic susceptibility in the systems containing ammonia and alcohol, and in other systems to be reported in the near future.

Technique of the Measurements.—The various ferrihemoglobin solutions were prepared from cow's blood by the technique described previously[4] involving self-trans-

(1) A portion of this material was presented at the Stanford Meeting of the Pacific Division of the American Association for the Advancement of Science, June, 1939.

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(4) C. D. Coryell, F. Stitt and L. Pauling, THIS JOURNAL, **59**, 633 (1937).