

## The Synthesis of Oximes Containing the Ferroin Group (1)

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A series of oximes of substituted 2-pyridylmethyl and phenyl ketones has been prepared. These all contain the ferroin group (=N-C-C-N=). The 4-substituted pyridyl-*syn*-methyl and phenyl ketoximes form chelates with Fe(II).

The ability of *syn*-phenyl-2-pyridyl ketoxime to form chelates with various metal ions has been previously described (2). It has been shown in general that this chelating tendency is enhanced by the presence of an alkyl group in the 4-position relative to the nitrogen in the pyridine ring. Accordingly we have synthesized ketoximes of 2-acetyl-4-methyl-, ethyl-, phenyl-, and methoxypyridines, and of 2-benzoyl-4-methyl-, -ethyl and -phenylpyridines.

The requisite 2-acetylpyridines have all been prepared previously (3,4). The oximes were prepared by the general method of Huntress and Walter (5). The oximes of 2-acetylpyridines occur in only one form, which in the case of the 4-alkylpyridines is *syn*-methyl, as shown by the fact that they form red chelates with Fe(II). This would not be possible with the *anti*-methyl form due to steric factors.

The 2-benzoylpyridines, which have not been previously described, were synthesized by the action of phenylmagnesium bromide on 4-methyl-, -ethyl, and -phenyl-2-cyanopyridine (3), followed by hydrolysis. From each of these ketones, two oximes were obtained, one of which forms a chelate with iron and hence has the *syn*-alkyl or phenyl configuration, while the other forms no chelate. A further confirmation of the configuration of the chelating oxime of 2-benzoyl-4-methylpyridine was the fact that a Beckmann rearrangement yielded benzoic acid.

In the separation of the two oximes of 4-methyl-2-benzoylpyridine and of 4-ethyl-2-benzoylpyridine the procedure of Huntress and Walter (5) was used. The mixed oximes were dissolved in dilute hydrochloric acid and the chelating oxime precipitated by cupric sulfate solution. After decomposition of the copper precipitate with hydrogen sulfide, the oxime was precipitated by neutralizing to a faint acidity with ammonium hydroxide. The other oxime was isolated from the filtrate after removal of the excess cupric ion with hydrogen sulfide.

The mixed oximes of 4-phenyl-2-benzoylpyridine were

insoluble in dilute hydrochloric acid and hence the above method of separation could not be used. However, separation was effected by fractional crystallization, and the *syn*-phenyl configuration assigned to the one which formed a chelate with Fe(II).

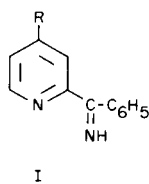
In addition to the above-mentioned oximes the oximes of a number of 6-methyl- and phenyl-2-acetyl- and benzoylpyridines were prepared with the expectation that they would form chelates with Cu(I) but not Fe(II) as in the case of cuproin and neocuproin, in which the ring nitrogen is adjacent to a substituting group. The preparation of 2-acetyl-6-phenyl- and 6-methylpyridine has already been described (3,6). These yielded single oximes, which give an orange and a red color, respectively, with Cu(I). They have been shown to have the *syn*-methyl configuration by Beckmann rearrangements, which yielded 2-amino-6-phenyl- and 2-amino-6-methylpyridine, respectively.

2-Benzoyl-6-methyl- and 6-phenylpyridines were prepared by the action of phenylmagnesium bromide, followed by hydrolysis, on 6-methyl and 6-phenyl-2-cyanopyridine, respectively (7,3).

By using the copper sulfate method previously described, it was possible to separate the two oximes of 2-benzoyl-6-methylpyridine. The one which was not precipitated by Cu(II) in dilute hydrochloric acid yielded benzoic acid in a Beckmann rearrangement and hence had the *syn*-phenyl configuration.

From 2-benzoyl-6-phenylpyridine only one oxime could be isolated. It also was shown by a Beckmann rearrangement in a similar way to have the *syn*-phenyl configuration.

It was found that in the hydrolysis of the Grignard addition products with ammonium chloride solution followed by dilute ammonium hydroxide, only in one case (2-benzoyl-6-phenylpyridine) was the pure ketone obtained. When phenylmagnesium bromide was treated with 4-methyl-2-cyanopyridine and 4-phenyl-2-cyanopyridine,



the pure ketimine (I) resulted, while 4-ethyl- and 6-methyl-2-cyanopyridine yielded a mixture of ketimine and ketone. Hydrolysis with dilute hydrochloric acid yielded the pure ketone. For the preparation of oximes, the ketimine could be used as well as the oxime. These ketimines were found to give a very deep blue coloration when treated with Fe(II). Their preparation will be further investigated. Similar ketimines have been reported by Bourbon and Puig (8) who decomposed the Grignard adduct with anhydrous oxalic acid.

Although the configuration of the various oximes was determined adequately either by chelation by Fe(II) or by the results of a Beckmann rearrangement, it was felt that perhaps infrared data might serve to distinguish between the members of the oxime pairs. It is evident that intramolecular hydrogen bonding between the oxime hydrogen and the pyridine nitrogen is possible only for the *anti*-methyl or phenyl form. If the tendency for intramolecular *H* bonding is sufficiently great, the *anti*-methyl or phenyl form should be distinguishable from the *syn* form by observing the effect of dilution on the infrared absorption bands arising from associated *H* stretching modes. A study carried out by A. A. Schilt and P. J. Taylor of Northern Illinois University showed that conclusive evidence for the presence of intramolecular *H* bonding was lacking. A sharp band between 3580 and 3610  $\text{cm}^{-1}$  due to free OH and, depending on dilution, a broad band between 2860 and 3240  $\text{cm}^{-1}$  due to associated OH stretching modes were observed for each compound. Other details of the infrared spectra lacked significance.

#### EXPERIMENTAL

##### Phenyl-4-methyl-2-pyridyl Ketimine.

The Grignard reagent prepared from 16 g. of bromobenzene and 2.1 g. of magnesium in 135 ml. of dry ether was added slowly to an ice cold solution of 8 g. of 2-cyano-4-methylpyridine dissolved in 25 ml. of benzene and 50 ml. of dry ether. After 3 hours of stirring the mixture was hydrolyzed with a saturated solution of ammonium chloride made alkaline with ammonium hydroxide, the ether layer separated and dried over anhydrous sodium sulfate. The residue from the removal of ether and benzene was distilled *in vacuo*, yielding 9.2 g. (68.7%) of an oil boiling at 165-170° (3 mm.). This compound gives a deep blue ferroun test.

*Anal.* Calcd. for  $\text{C}_{13}\text{H}_{12}\text{N}_2$ : C, 79.56; H, 6.16; N, 14.27. Found: C, 79.64; H, 6.20; N, 14.11.

TABLE I  
Oximes of 2-Acetylpyridines

2-Acetyl-X- pyridine used X	m.p., °C.	Yield (%)	Cryst'n. solvent	Carbon		Analysis Hydrogen		Nitrogen	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
4-methyl	98-99	82.5	benzene- pet. ether	63.98	64.21	6.71	6.62	18.65	18.41
4-ethyl	62-63	50.0	pet. ether	65.83	65.75	7.37	7.03	17.06	17.11
4-methoxy	120	90.9	benzene- pet. ether	57.82	57.86	6.06	6.00	16.86	16.68
4-phenyl	132-133	64.8	benzene	73.57	73.76	5.70	5.79	13.20	13.19
6-methyl	49-50	66.7	pet. ether	63.98	64.01	6.71	6.69	18.65	18.95
6-phenyl	87-88	90.9	benzene- pet. ether	73.57	73.75	5.70	5.73	13.20	13.02

## 2-Benzoyl-4-methylpyridine.

The above directions were repeated except that hydrolysis was effected by adding 20 ml. of water, followed by 40 ml. of 1:1 aqueous hydrochloric acid. After stirring 1 hour, the solution was made alkaline with ammonium hydroxide and the ether layer separated and dried as before. Removal of ether left an oil which still gave a positive ferroin test indicating the presence of ketimine. It was therefore dissolved in 30 ml. of 1:1 aqueous hydrochloric acid and allowed to stand overnight. After making alkaline with sodium carbonate solution and extraction with ether the pure ketone was obtained as an oil (9.5 g., 68.8%) boiling at 160-165° (3 mm.).

*Anal.* Calcd. for  $C_{13}H_{11}NO$ : C, 79.17; H, 5.62; N, 7.10. Found: C, 79.27; H, 5.96; N, 7.16.

## 2-Benzoyl-6-methylpyridine.

The reagents and quantities were the same as above except that 2-cyano-6-methylpyridine was substituted for 2-cyano-4-methylpyridine. Since hydrolysis with ammonium chloride solution had previously been shown to yield a mixture of ketone and ketimine, the Grignard adduct was decomposed by adding first 20 ml. of water and then 40 ml. of 1:1 aqueous hydrochloric acid. After stirring 1 hour, ammonium hydroxide was added, and the ether solution separated and dried as before. Removal of ether and benzene yielded 11.5 g. (83.3%) of an oil boiling at 152-156° (3 mm.). It gave no ferroin test.

*Anal.* Calcd. for  $C_{13}H_{11}NO$ : C, 79.17; H, 5.62; N, 7.10. Found: C, 78.97; H, 5.91; N, 7.11.

## 2-Benzoyl-4-ethylpyridine.

The procedure was similar to that used for 2-benzoyl-4-methylpyridine except that 2-cyano-4-ethylpyridine (9 g.) was substituted for the methyl derivative and proportional amounts of other reagents were used. The hydrolysis procedure was exactly the same. The resulting 2-benzoyl-4-ethylpyridine (9.5 g., 64.3%) boiled at 172-176° (3 mm.). It gave no ferroin test.

*Anal.* Calcd. for  $C_{14}H_{13}NO$ : C, 79.59; H, 6.20; N, 6.63. Found: C, 79.55; H, 6.29; N, 6.43.

## 2-Benzoyl-6-phenylpyridine.

A procedure similar to that used for 2-benzoyl-4-methylpyridine was used except that 2-cyano-6-phenylpyridine (14.4 g.) was substituted for the methyl derivative and proportional amounts of other reagents were used. In this case, however, hydrolysis with saturated ammonium chloride solution, followed by ammonium hydroxide yielded the pure ketone (10 g., 48.3%) boiling at 240-245° (4 mm.). On standing this oil solidified and was crystallized from benzene-petroleum ether. An analytical sample melted at 65-66°.

*Anal.* Calcd. for  $C_{18}H_{13}NO$ : C, 83.38; H, 5.05; N, 5.40. Found: C, 83.25; H, 5.21; N, 5.53.

## Phenyl-4-phenyl-2-pyridyl Ketimine.

The Grignard reagent prepared from 15 g. of bromobenzene and 2.2 g. magnesium in 100 ml. of dry ether was added slowly to an ice cold solution of 6 g. of 2-cyano-4-phenylpyridine dissolved in a mixture of 35 ml. of benzene and 35 ml. of ether. After the mixture was allowed to stand 1 hour, it was hydrolyzed with a saturated solution of ammonium chloride, made alkaline with ammonium hydroxide, the ether layer separated, and dried over anhydrous sodium sulfate. The oil remaining after removal of ether (5 g., 58.8%) boiled at 235-239° (3 mm.). On standing it solidified and was crystallized from benzene-petroleum ether. An analytical sample melted at 96-97°. It gave a deep blue color with Fe(II).

*Anal.* Calcd. for  $C_{18}H_{14}N_2$ : C, 83.69; H, 5.46; N, 10.84. Found: C, 83.79; H, 5.53; N, 10.69.

## 2-Benzoyl-4-phenylpyridine.

The above ketimine (3.5 g.) was dissolved in 10 ml. of 1:1 aqueous hydrochloric acid, and the solution allowed to stand overnight. Treatment with sodium carbonate solution, extraction with ether and crystallization of the resulting solid from benzene-petroleum ether yielded the pure ketone (2.7 g.) melting at 63-64°.

*Anal.* Calcd. for  $C_{18}H_{13}NO$ : C, 83.38; H, 5.05; N, 5.40. Found: C, 83.27; H, 5.12; N, 5.78.

## Preparation of Oximes.

To a mixture of one molar proportion of ketone, 1.3 moles of hydroxylammonium chloride, 10 moles of ethanol and an equal volume of water was added a weight of sodium hydroxide equal to that of the hydroxylammonium chloride used. After heating 5 minutes under reflux, the contents of the flask were poured into ice water, the mixture made alkaline with ammonium hydroxide and acidified to pH 6 with acetic acid. The resulting precipitate was removed by filtration, dried and crystallized from the solvent indicated.

## Beckmann Rearrangement of 2-Acetyl-6-methylpyridine Oxime.

To the oxime (1.7 g.) dissolved in 10 ml. of chloroform was added slowly 3 ml. of thionyl chloride. After standing for 2 days, solution was nearly complete. It was then evaporated to dryness *in vacuo* and refluxed for 3 hours with 15 ml. of 6N hydrochloric acid. After making alkaline the solution was extracted with ether. The residue from removal of the ether was then acetylated, yielded a solid melting at 88°. This was found by mixed melting point to be identical with 6-methyl-2-acetamidopyridine (9), m.p. 88°.

## Beckmann Rearrangement of 2-Acetyl-6-phenylpyridine Oxime.

Following the above procedure, a solid acetyl derivative was obtained, melting at 163-164°. The product was the hitherto undescribed 6-phenyl-2-acetamidopyridine.

*Anal.* Calcd. for  $C_{13}H_{12}N_2O$ : C, 73.57; H, 5.70; N, 13.20. Found: C, 73.49; H, 5.78; N, 13.09.

## Oximes of 2-Benzoyl-4-methylpyridine.

The crude oxime mixture, prepared from 3.7 g. of ketone according to the general procedure, was dissolved in 27 ml. of 3N hydrochloric acid, and treated with a saturated solution of 2.7 g. of cupric sulfate pentahydrate. After standing several hours the green precipitate was removed by filtration and suspended in 45 ml. of 3N hydrochloric acid. The solution was saturated with hydrogen sulfide and the resulting black precipitate removed and discarded. The solution was then made alkaline with ammonium hydroxide and acidified to pH 6 with acetic acid. The precipitated *syn*-phenyl oxime was removed by filtration, dried and crystallized from benzene, yielding 2 g. of pure oxime melting at 163-164° and giving a positive ferroin test.

*Anal.* Calcd. for  $C_{13}H_{12}N_2O$ : C, 73.57; H, 5.70; N, 13.20. Found: C, 73.67; H, 5.78; N, 12.89.

## Beckmann Rearrangement.

The above oxime (1 g.) was dissolved in 5 ml. of chloroform. One ml. of thionyl chloride was slowly added and the solution allowed to stand overnight. The chloroform and excess thionyl chloride were then removed at 90° *in vacuo*, and the residue refluxed for 3 hours with 10 ml. of 6N hydrochloric acid. Extraction with ether, and crystallization of the residue from water yielded 0.5 g. of benzoic acid, m.p. 120°.

The filtrate from the above green copper compound was treated with hydrogen sulfide, and the excess Cu(II) removed as sulfide. To this filtrate was added ammonium hydroxide, then acetic acid to pH 6. The resulting precipitate was dried and crystallized from benzene, yielding 0.4 g. of pure *anti*-phenyl oxime, melting at 197°. The ferrioin test was negative.

*Anal.* Calcd. for C<sub>13</sub>H<sub>12</sub>N<sub>2</sub>O: C, 73.57; H, 5.70; N, 13.20. Found: C, 73.58; H, 5.70; N, 13.11.

#### Oximes of 2-Benzoyl-4-ethylpyridine.

The crude oxime mixture from 2.8 g. of ketone was subjected to the same procedure used for 2-benzoyl-4-methylpyridine, using proportional amounts of reagents. From the green copper precipitate there was obtained, after crystallization from benzene-petroleum ether, 0.9 g. of pure *syn*-phenyl oxime melting at 134-135°. This oxime gave a red ferrioin test.

*Anal.* Calcd. for C<sub>14</sub>H<sub>14</sub>N<sub>2</sub>O: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.41; H, 6.19; N, 12.16.

The filtrate from the green precipitate yielded, after removal of excess Cu(II), 0.5 g. of pure *anti*-phenyl oxime, crystallizing from benzene, and melting at 150-151°.

*Anal.* Calcd. for C<sub>14</sub>H<sub>14</sub>N<sub>2</sub>O: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.53; H, 6.22; N, 12.47.

#### Oximes of 2-Benzoyl-4-phenylpyridine.

The dry, crude oxime mixture from 2.8 g. of ketone yielded, after repeated crystallization from benzene, 0.6 g. of pure *syn*-phenyl oxime, melting at 166-167°. A positive ferrioin test was noted.

*Anal.* Calcd. for C<sub>18</sub>H<sub>14</sub>N<sub>2</sub>O: C, 78.81; H, 5.14; N, 10.21. Found: C, 78.81; H, 5.21; N, 10.09.

From the filtrates of the above oxime, by further crystallization from benzene, was obtained 0.5 g. of the *anti*-phenyl oxime, melting at 186-187°. No ferrioin test was obtained.

*Anal.* Found: C, 78.68; H, 5.20; N, 10.18.

#### Oximes of 2-Benzoyl-6-methylpyridine.

The crude oxime mixture from 2 g. of ketone was subjected to the same procedure used for 2-benzoyl-4-methylpyridine, using proportionate amounts. From the green precipitate, which formed

after 2 days' standing, there was obtained after crystallization from benzene-petroleum ether, 0.4 g. of pure *anti*-phenyl oxime, melting at 141-142°.

*Anal.* Calcd. for C<sub>13</sub>H<sub>12</sub>N<sub>2</sub>O: C, 73.57; H, 5.70; N, 13.20. Found: C, 73.57; H, 5.61; N, 13.11.

In another experiment starting from the oxime-mixture obtained from 3 g. of ketone, fractional crystallization from benzene yielded 0.7 g. of *syn*-phenyl oxime melting at 156-157°.

*Anal.* Found: C, 73.66; H, 6.08; N, 13.16.

A Beckmann rearrangement on this oxime, performed as before, yielded benzoic acid.

#### Oxime of 2-Benzoyl-6-phenylpyridine.

The crude, dry oxime mixture from 2.1 g. of ketone, after repeated crystallization from benzene, yielded 0.9 g. of the *syn*-phenyl oxime melting at 168-169°.

*Anal.* Calcd. for C<sub>18</sub>H<sub>14</sub>N<sub>2</sub>O: C, 78.81; H, 5.14; N, 10.21. Found: C, 78.53; H, 5.32; N, 9.90.

A Beckmann rearrangement yielded benzoic acid. No other oxime could be isolated.

### REFERENCES

- (1) This work was supported by a grant (G 9645) from the National Science Foundation.
- (2) H. Diehl and G. F. Smith, "The Copper Reagents," G. F. Smith Chemical Co., Columbus, Ohio, 1958.
- (3) F. H. Case and T. J. Kasper, *J. Am. Chem. Soc.*, **78**, 5842 (1956).
- (4) F. H. Case and W. A. Butte, *J. Org. Chem.*, **26**, 4415 (1961).
- (5) E. H. Huntress and H. C. Walter, *J. Am. Chem. Soc.*, **70**, 3702 (1948).
- (6) H. Erlenmeyer, J. Jenni and B. Prijs, *J. Med. Pharm. Chem.*, **3**, 561 (1961).
- (7) G. Mayurnik, A. F. Moschetto, H. S. Bloch and J. V. Scudi, *Ind. Eng. Chem.*, **44**, 1630 (1952).
- (8) P. Bourbon and P. Puig, *Compt. Rend.*, **258**, (12) 3323 (1964).
- (9) H. Meyer, *Rec. Trav. Chim.*, **44**, 328 (1925).

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