[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF MICHIGAN]

Curtius Rearrangement of α-Oximino Acids[1]

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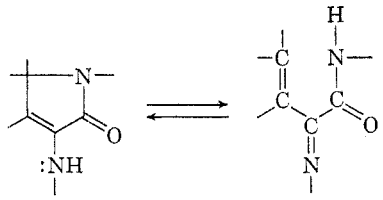
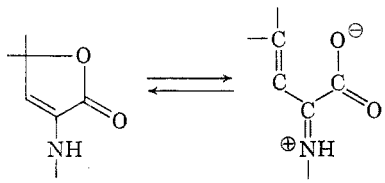
A new method of synthesis for 3-substituted 5-hydroxy-1,2,4-oxadiazoles is reported. The oxime of an α-ketoester is converted to the acid hydrazide, which in turn is converted to the azide by reaction with nitrous acid. Curtius rearrangement of the azide leads directly to the 1,2,4-oxadiazole.

In connection with studies of lactam-enamide tautomerism[3a] of the type represented by



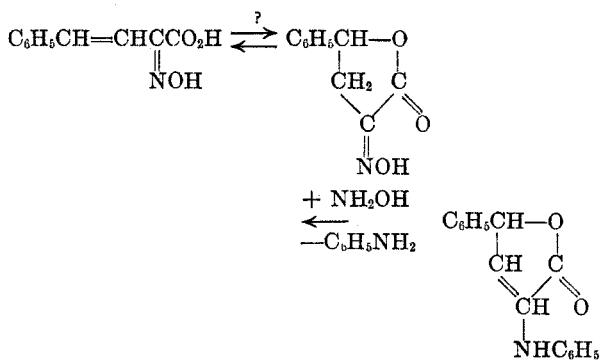
it was of interest to examine the properties of benzylidenepyruvic acid derivatives. The anilide, which is isomeric in the enamide-lactam sense with 1,5-diphenyl-2,3-pyrrolidinedione, does not partake of the tautomerism described above,[3a] but reaction of benzylidenepyruvic acid with aniline leads at once to a system in which lacto-enoic tautomerism obtains, *e.g.*



The reaction of benzylidenepyruvic acid with phenylhydrazine affords the phenylhydrazone,[4] which likewise partakes of lactoenoic tautomerism,[3b,4] but which may be irreversibly cyclized to 1,5-diphenyl-Δ^2-pyrrazoline-3-carboxylic acid.[4] The comparative ease of the latter cyclization is illustrated by the reaction of benzylidenepyruvanilide with phenylhydrazine. The phenylhydrazone is probably formed at once, but it is not isolable even though the tautomeric lactam form is known.[3,4] Instead the reaction leads at once to 1,5-diphenyl-Δ^2-pyrrazoline-3-carboxanilide.[3a]

The oxime and oxime acetate of benzylidenepyruvanilide, however, are normal and do not cyclize to the isomeric lactams; and in turn these lactams, synthesized by another method, have been shown not to open up to the acyclic isomers.[3a]

Consequently it was deemed of interest to examine the behavior of benzylidenepyruvic acid oxime, which would be especially interesting, since it is potentially tautomeric, in the lacto-enoic sense,[3b] with the oxime derived from 3-phenylamino-5-phenyl-2(5H)furanone (*pseudo*-1,5-diphenyl-2,3-pyrrolidinedione):



On the other hand it might cyclize like the analogous phenylhydrazone,[3a,4] which affords a pyrazoline, *i.e.* like chalcone oxime which affords a 2-isoxazoline.[5-7] However, the open-chain form of benzylidenepyruvic acid oxime proved to be completely resistant to either type of cyclization. Indeed the reaction of 3-phenylamino-5-phenyl-2-(5H)furanone with hydroxylamine leads to replacement of the 3-phenylamino group by hydroxylamino and ring opening to give the oxime of benzylidenepyruvic acid.

In the course of the foregoing studies the oxime of methyl benzylidenepyruvate was prepared, and it, too, resisted cyclization. In the interest of seeing whether this reluctance to cyclize could be overcome, the ester was converted to the hydrazide, which in turn was converted into the acid azide by treatment with nitrous acid. Upon heating, the azide might be expected to afford one of three different products: the amide oxime ($C_6H_5CH{=}CHC(=NOH)NH_2$), 3-amino-5-phenyl-2-isoxazoline (by cyclization of the amide oxime), or 5-hydroxy-3-styryl-1,2,4-oxadiazole (by cyclization of the intermediate isocyanate).

Upon carrying out the Curtius rearrangement, it was in fact the 1,2,4-oxadiazole which was

(1) Abstracted from a portion of the Ph.D. Dissertation of John L. Spencer, University of Michigan, 1958.

(2) National Science Foundation predoctoral fellow 1956–58.

(3) (a) W. L. Meyer and W. R. Vaughan, *J. Org. Chem.*, **22**, 1565 (1957). (b) W. L. Meyer and W. R. Vaughan, *J. Org. Chem.*, **22**, 1560 (1957).

(4) W. R. Vaughan, *J. Org. Chem.*, **20**, 1619 (1955).

(5) A. H. Blatt, *J. Am. Chem. Soc.*, **71**, 1861 (1949).

(6) R. P. Barnes, *et al.*, *J. Am. Chem. Soc.* **76**, 276 (1954).

(7) H. H. Blecker, Dissertation, Rutgers (1955).

obtained. The course of the reaction may be likened to the Curtius rearrangement of β-hydroxy acid azides[8] which afford oxazolidones. Thus, the hydroxy group of the oxime is structurally analogous to the β-hydroxyl of the latter compounds.

In order to determine the generality of the reaction, it was applied to the oximes of benzoylformic acid azide and phenylpyruvic acid azide with identical results. The structure of each of the 3-substituted-5-hydroxy-1,2,4-oxadiazoles was confirmed by unequivocal synthesis from the appropriate amide oxime by treatment with ethyl chloroformate followed by sodium hydroxide.[9]

One might possibly have expected some difficulty arising from the possible interchange of oximino and hydrazido groups or sensitivity of the oximino group to the nitrous acid used in converting the hydrazide to azide, but no undesirable side reactions were encountered. Thus, the procedure appears to be well suited for general synthesis of compounds of this type. It is only necessary to call attention to the rather large melting ranges for the oximes, which may of course be attributed to the presence of both *syn* and *anti* forms, for no attempt was made to separate isomers. However, such ranges were also encountered by Blatt[5] in the course of his work on the chalcone oximes even after the isomers had been separated. In any case the substances had good analyses and upon reaction afforded good yields of products.

EXPERIMENTAL[10-12]

Benzylidenepyruvic acid oxime. Benzaldehyde and pyruvic acid were condensed in methanol by means of methanolic sodium hydroxide according to the directions of Stecher and Ryder.[13] When needed, the free acid was obtained from the salt according to directions of the same authors.

The oxime was obtained under each of the following sets of conditions: (A) From equimolar quantities of the acid salt and hydroxylamine hydrochloride in the presence of excess potassium hydroxide; (B) From the acid salt and hydroxylamine hydrochloride in glacial acetic acid; (C) From equimolar quantities of the free acid and hydroxylamine hydrochloride in aqueous ethanol[14] at room temperature (at reflux,[14] 4 hr., only cinnamonitrile was obtained): m.p. 158–160° dec., reported[15] m.p. 168°, dec. Samples of the oxime were allowed to stand in concd. sulfuric acid for from 3 hr. to 3 days, but upon pouring any of the solutions onto ice, only the unchanged oxime was obtained.

Methyl benzylidenepyruvate oxime. Methyl benzylidenepyruvate,[16] 9.5 g. (0.050 mole) was refluxed with 5.1 g. (0.075 mole) of hydroxylamine in 50 ml. of methanol for 4 hr., during which time the original yellow color of the solution almost completely disappeared. The solution was then cooled and the resulting precipitate collected. An additional quantity of crude product was obtained by concentrating the filtrate and adding water. In this manner there was obtained 8.0 g. (78%), m.p. 115–120°. Recrystallization from methanol-water afforded 6.5 g. of white solid, m.p. 116–126°. Subsequent recrystallizations from the same solvent pair or from benzene–petroleum ether (b.p. 60–75°) did not improve the melting point.

Anal. Calcd. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.49; H, 5.35; N, 6.88.

A sample of the product was hydrolyzed with 10% sodium hydroxide, and the acid obtained by acidification was shown to be identical with the oxime of benzylidenepyruvic acid by mixed melting point determination and identity of infrared spectra. Attempts to cyclize the ester oxime by standing in concd. sulfuric acid for periods from 1 night to 1 week afforded only unaltered starting material or the acid oxime.

The ester oxime reacts with hydrogen bromide in carbon tetrachloride to produce a white solid, m.p. 75–120°, but this turns yellow on exposure to the atmosphere and upon standing again becomes colorless and identical with the original oxime (mixed melting point determination). However, when a solution of 3.0 g. (0.016 mole) of bromine in carbon tetrachloride was added to a solution of 2.0 g. (0.01 mole) of the ester oxime in warm carbon tetrachloride and the resulting solution refluxed for 2 hr., there was obtained a large quantity of solid from the cooled reaction mixture: 2.9 g. (77%), m.p. 179–186° dec. An analytical sample was prepared by thrice recrystallizing from benzene, m.p. 186–190° dec.

Anal. Calcd. for $C_{11}H_{11}Br_2NO_3$: C, 36.19; H, 3.03; Br, 43.79; N, 3.84. Found: C, 36.04; H, 3.22; Br, 43.79; N, 3.89.

Benzylidenepyruvic acid oxime hydrazide. To a solution of 2.0 g. (0.0097 mole) of methyl benzylidenepyruvate oxime in 12 ml. of methanol was added 2 ml. of hydrazine. The solution was warmed on the steam bath for 20 min., during which time a white precipitate formed. An equal volume of water was added, and the solution was cooled. This afforded 1.9 g. (95%) of crude hydrazide, m.p. 193–202° dec. The melting point was found to be very dependent on the rate of heating. An analytical sample was obtained by two recrystallizations from ethanol, m.p. 192–193° dec. heated at 2°/min.

Anal. Calcd. for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.51; H, 5.50; N, 20.43.

Benzylidenepyruvic acid oxime azide. A solution of 0.5 g. (0.0024 mole) of the above oxime hydrazide in 20 ml. of acetic acid with 5 ml. of water was cooled in an ice bath, and a solution of 0.25 g. (0.0036 mole) of sodium nitrite in 5 ml. of water was added dropwise to it. This yielded 0.4 g. (76%) of white solid, m.p. 104° vig. dec. A sample for analysis was prepared by dissolving in cold methanol, filtering, and reprecipitating with water, m.p. 108° vig. dec.

Anal. Calcd. for $C_{10}H_8N_4O_2$: C, 55.55; H, 3.73; N, 25.92. Found: C, 55.46; H, 3.81; N, 25.95.

5-Hydroxy-3-styryl-1,2,4-oxadiazole. (a) *By rearrangement of the azide in ethanol.* Refluxing 0.2 g. of the above azide in 30 ml. of ethanol for 2 hr. gave on evaporation of the alcohol and trituration with water 0.1 g. of white solid, m.p. 192–200°. An analytical sample, m.p. 198.5–200.0°, was obtained by recrystallization from ethanol-water.

Anal. Calcd. for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.29; N, 14.89. Found: C, 63.54; H, 4.42; N, 14.82.

(b) *By rearrangement of the azide in benzene.* Refluxing 0.2 g. of the above azide in 20 ml. of benzene for 2 hr. gave after filtering and cooling 0.1 g. of white solid, m.p. 187–197°. Recrystallization from carbon tetrachloride raised the melting point to 196–200°.

(c) *From amidoxime.* The oxadiazole was prepared according to the procedure of Wolff[9] from cinnamamidoxime

(8) W. J. Close, *J. Am. Chem. Soc.*, **73**, 95 (1951).
(9) H. Wolff, *Ber.*, **22**, 2400 (1889).
(10) Melting points are uncorrected.
(11) Microanalyses by Spang Microanalytical Laboratory, Ann Arbor, Mich.
(12) Infrared spectra of Nujol mulls obtained by means of a Perkin-Elmer model 21 infrared spectrophotometer.
(13) E. D. Stecher and H. F. Ryder, *J. Am. Chem. Soc.*, **74**, 4392 (1952).
(14) A. H. Blatt, *J. Am. Chem. Soc.*, **53**, 1133 (1931).
(15) R. Ciusa and A. Bernardi, *Gazz. chim. ital*, **41**, 152 (1911).
(16) M. Reimer, *J. Am. Chem. Soc.*, **46**, 783 (1924).

and ethyl chloroformate followed by treatment with sodium hydroxide.

The identical nature of these three compounds was shown by superimposable infrared spectra and no depression of the melting points on mixing.

Ethyl benzoylformate oxime. The oxime was prepared according to Gabriel[17] by the treatment of ethyl benzoylformate[18] with hydroxylamine hydrochloride and sodium carbonate in aqueous ethanol.

Benzoylformic acid oxime hydrazide. To a solution of 1.0 g. of ethyl benzoylformate oxime in 6 ml. of ethanol was added 1 ml. of hydrazine. The solution was refluxed for 10 min. and evaporated to approximately one third its volume. The addition of water afforded 1.0 g. of crude solid, m.p. 150–170°. An analytical sample was prepared by recrystallization from alcohol–carbon tetrachloride and alcohol–water, m.p. 164–172°.

Anal. Calcd. for $C_8H_9N_3O_2$: C, 53.62; H, 5.06; N, 23.45. Found: C, 53.81; H, 5.19; N, 23.45.

Benzoylformic acid oxime azide. To a solution of 0.1 g. of the above hydrazide in 4 ml. of acetic acid and 1 ml. of water was added dropwise a solution of 60 mg. of sodium nitrite in 1 ml. of water. An additional 2 ml. of water was added to yield 70 mg. of white solid, m.p. 110° vigorous dec. It was not purified due to its instability. The infrared spectrum of this compound showed an absorption band at *ca.* 2160 cm.$^{-1}$.

3-Phenyl-5-hydroxy-1,2,4-oxadiazole. (a) *By rearrangement of the azide.* Refluxing 60 mg. of the above azide, in 5 ml. of ethanol for 1 hr., adding water, and cooling afforded 30 mg. of white solid, m.p. 192–199°. Recrystallization from benzene raised the melting point to 197.0–200.5°.

(b) *From amidoxime.* The procedure of Falck[19] was used to obtain the oxadiazole from benzamidoxime.

Anal. Calcd. for $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.23; H, 3.80; N, 17.22.

The identity of these two compounds is shown by identical infrared spectra and undepressed mixture melting point.

Ethyl phenylpyruvate oxime. The oxime was prepared by refluxing ethyl phenylpyruvate (from phenylpyruvic acid[20]) with hydroxylamine in ethanol for 3 hr. The preparation of the same substance by the action of nitrosylsulfuric acid on benzylacetoacetate ester is reported.[21]

Phenylpyruvic acid oxime hydrazide. To a solution of 5.0 g. (0.025 mole) of the above oxime in 25 ml. of ethanol was added 5 ml. of hydrazine. The solution was refluxed 15 min. and 50 ml. of water was added. Cooling afforded 2.3 g. (49%) of white needles, m.p. 138–143° dec. An analytical sample, m.p. 143–146°, was obtained by recrystallizations from benzene, ethanol-water, and chloroform–carbon tetrachloride.

Anal. Calcd. for $C_9H_{11}O_2N_3$: C, 55.95; H, 5.74; N, 21.75. Found: C, 55.96; H, 5.73; N, 21.78.

Phenylpyruvic acid oxime azide. To a solution of 1.2 g. of the above hydrazide in 50 ml. of 5% hydrochloric acid cooled in an ice bath was added dropwise 0.6 g. of sodium nitrite in 5 ml. of water. This yielded 1.0 g. of solid, m.p. 95° vig. dec., whose infrared spectrum had an absorption band at *ca.* 2160 cm.$^{-1}$. It was not purified due to its instability.

3-Benzyl-5-hydroxy-1,2,4-oxadiazole. (a) *By rearrangement of the azide.* Refluxing 1.0 g. of the above azide in 25 ml. of benzene for 30 min. caused the solution to darken. Evaporation left a dark residue which was recrystallized from water to give 0.4 g. of solid, m.p. 60–100°. Recrystallizations from carbon tetrachloride, water, and petroleum ether (b.p. 60–75°) with a trace of benzene gave an analytical sample, m.p. 112–115°.

Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.41; H, 4.58; N, 15.94. Found: C, 61.36; H, 4.58; N, 15.90.

(b) *From amidoxime.* Phenylacetamidoxime[22] was converted to the oxadiazole[23] with ethyl chloroformate and base. Identical infrared spectra and undepressed mixture melting point showed these two samples to be the same compound.

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(17) S. Gabriel, *Ber.*, **16**, 519 (1883).

(18) B. B. Corson, *et al.*, in *Org. Syntheses*, **Coll. Vol I**, John Wiley and Sons, Inc., New York, 1932, p. 241.

(19) E. Falck, *Ber.*, **18**, 2469 (1885).

(20) R. M. Herbst and D. Shemin, in *Org. Syntheses*, **Coll. Vol. II**, John Wiley and Sons, Inc., New York, 1943, p. 519.

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(23) G. Ponzio and B. Zanardi-Lamberti, *Gazz. chim. ital.*, **53**, 818 (1923).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

Nitration of Unsaturated Alcohols[1]

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The nitration of several aliphatic alcohols containing carbon-carbon unsaturation has been accomplished using acetyl nitrate as the reagent. In specific cases, the normal nitration procedure could be modified to afford good yields but in most cases only 10 to 30% yields were obtained. These low yields are ascribed to subsequent addition of the elements of acetyl nitrate to the double bond with the formation of high boiling by-products. A number of new unsaturated nitrates, dibromoalcohols, and dibromoalcohol nitrates are described. The last can be obtained in good yields by both nitration of the dibromoalcohols and bromination of the unsaturated nitrates.

The most attractive method for the synthesis of molecules containing both nitrate ester functions and carbon-carbon unsaturation is the nitration of the corresponding unsaturated alcohol. A wide variety of general nitration media have been employed by different workers.[2,3] Most of these media, if not all, are composed of reagents which in

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(3) R. Boschan, R. T. Merrow, and R. W. Van Dolah, *Chem. Revs.*, **55**, 485 (1955).