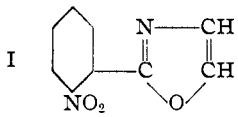
[CONTRIBUTION FROM THE NICHOLS CHEMISTRY LABORATORY OF NEW YORK UNIVERSITY]

2-Phenyloxazole and ortho-Substituted Derivatives

BY W. E. CASS

In an attempt to prepare 8-nitroisoquinoline, *o*-nitrobenzalaminoacetal was treated with concentrated sulfuric acid and phosphorus pentoxide, following the method used by Tyson[1] in the synthesis of substituted isoquinolines. The product isolated from the reaction, however, was not the expected isoquinoline derivative, but 2-(*o*-nitrophenyl)-oxazole (I).



This conclusion is based on the following evidence: (a) Analytical data for I and for several substances derived from this indicated the presence of one more oxygen atom than would be required for analogous isoquinoline derivatives. (b) Oxidation of I yielded *o*-nitrobenzamide and not a nitrophthalic acid, which would be expected from an isoquinoline. (c) The basic properties of I are weaker and the melting points of I and its derived substances are lower than might be expected for corresponding isoquinoline derivatives. (d) The synthesis of I has been accomplished by similar treatment with sulfuric acid and phosphorus pentoxide of *o*-nitrobenzoylaminoacetal.

The synthesis of I is of interest, since none of the several existing methods for the preparation of oxazoles is applicable to the synthesis of a simple 2-substituted oxazole, although the preparation of 2-phenyloxazole from benzoylaminoacetal was once attempted.[2] Further work is planned to ascertain whether other substituted benzalaminoacetals can possibly yield 2-substituted oxazoles.

The synthesis of I from *o*-nitrobenzalaminoacetal must at some time involve the oxidation of the side chain carbon atom attached to the benzene ring in the ortho position to the nitro group. It is of interest to note, however, that when the starting material was *o*-nitrobenzoylaminoacetal, in which the carbon ortho to the nitro group was already oxidized, the yield of I was much lower than when *o*-nitrobenzalaminoacetal was used.

Attempts to prepare I from *o*-nitrobenzoylaminoacetaldehyde or from *o*-nitrobenzamide and bromoacetal were unsuccessful.

(1) Tyson, THIS JOURNAL, **61**, 183 (1939).
(2) Bachstez, *Ber.*, **47**, 3163 (1914).

The hydrogenation of I to the corresponding amine, 2-(*o*-aminophenyl)-oxazole (II), was carried out over Raney nickel. From II were prepared acetyl, benzoyl and sulfanilyl derivatives. Deamination of the diazonium chloride of II with hypophosphorous acid[3] yielded 2-phenyloxazole.

Preliminary pharmacological tests on 2-(*o*-sulfanilamidophenyl)-oxazole were carried out by the Merck Institute for Therapeutic Research, Rahway, New Jersey. This substance was not toxic to mice in dose levels of 5, 10 and 20 mg. per 20 g. of animal body weight. Antistreptococcal activity in mice was of the same order as a sulfadiazine standard.

Experimental

All melting points are corrected.

Aminoacetal.—Bromoacetal[4] (50 g.) and potassium iodide (20–25 g.) in 420 cc. of ethanol–ammonia (saturated at 0°) was heated sixteen hours at 125° in a shaking autoclave. The reaction mixture, worked up as described by Marckwald,[5] yielded 13–17 g. (39–50%) of aminoacetal of b. p. 160–170°. Most of this material redistilled at 163–164°.

***o*-Nitrobenzalaminoacetal.**—Equimolar amounts of aminoacetal and *o*-nitrobenzaldehyde were heated in an oil-bath at 100–110° until the liberated water was driven off. The product, distilled under reduced pressure, was obtained as a light yellow oil in 94–96% yield; b. p. 143–146° (2 mm.).

Anal. Calcd. for $C_{13}H_{18}O_4N_2$: C, 58.62; H, 6.81; N, 10.52. Found: C, 58.3; H, 6.82; N, 10.6.

2-(*o*-Nitrophenyl)-oxazole (I) from *o*-Nitrobenzalaminoacetal.—*o*-Nitrobenzalaminoacetal (20 g.) was added slowly with mechanical stirring to 100 cc. of concentrated sulfuric acid maintained at 0–5°. The resulting cold, orange-yellow solution was added during five minutes with vigorous stirring to a mixture of 40 g. of phosphorus pentoxide and 10 cc. of sulfuric acid in a flask fitted with an efficient reflux condenser and maintained at 180° in an oil-bath. Much sulfur dioxide as well as some sulfur trioxide was evolved. The mixture was stirred and maintained at 180° for an additional twenty minutes, then cooled, poured on ice and, with cooling, neutralized with ammonium hydroxide. After standing overnight in an ice box, the precipitate was filtered. The crude product was purified by steam distillation. The oily steam distillate crystallized on standing in an ice box as white needles. When steam distilled onto ice, the product crystallized immediately as small white plates. The yield of I was 7.8 g. or 54.5%; m. p. 38–39°. In other runs, in which the addition of *o*-

(3) Adams and Kornblum, THIS JOURNAL, **63**, 188 (1941).
(4) Späth, *Monatsh.*, **36**, I (1915).
(5) Marckwald, *Ber.*, **25**, 2354 (1892).

nitrobenzalaminoacetal to the cold sulfuric acid was not carried out with careful stirring and cooling, the yield was about 35%. Attempts to prepare I from *o*-nitrobenzalaminoacetal under milder conditions, using sulfuric acid or phosphorus pentoxide alone as condensing agent, were unsuccessful.

Anal. Calcd. for $C_9H_6O_3N_2$: C, 56.85; H, 3.18; N, 14.73; mol. wt., 190.15. Found: C, 56.8; H, 3.27; N, 14.8; mol. wt., 198.

I was very soluble in most organic solvents and slightly soluble in water. It had a faint, characteristic odor. It dissolved in concentrated sulfuric and hydrochloric acids, but was re-precipitated on dilution of the solution with water. It was insoluble in sodium hydroxide solution and showed no reaction with phenylhydrazine or Schiff reagent. It gave a positive test for the nitro group.[6] After long boiling of I with concentrated hydrochloric acid, the solution became brown in color; however, no hydrolysis product could be isolated and much of the starting material could be recovered unchanged. Heating I with concentrated hydrochloric acid in a sealed tube for forty minutes at 150° resulted in extensive decomposition; again no hydrolysis product was isolated.

Picrate.—The picrate of I was prepared with an aqueous solution of picric acid. Recrystallization attempted from water resulted in hydrolysis to I and picric acid, demonstrating the weakly basic character of I. Recrystallization from a dilute aqueous picric acid solution yielded very fine crystals of m. p. 90–92°.

Anal. Calcd. for $C_{15}H_9O_{10}N_5$: N, 16.71. Found: N, 16.7.

Oxidation of I.—(a) With Potassium Permanganate: to 0.4 g. of I was gradually added with heating 1% potassium permanganate solution (150 cc. in all), until the purple color persisted. The mixture was boiled ten minutes, filtered, acidified with hydrochloric acid and decolorized with sodium bisulfite. After concentration of the solution to a small volume, a crystalline precipitate appeared. Recrystallization from water yielded white needles of m. p. 173.5–175.5°. Analysis of the substance indicated *o*-nitrobenzamide.

Anal. Calcd. for $C_7H_6O_3N_2$: C, 50.60; H, 3.64; N, 16.86. Found: C, 50.7; H, 3.59; N, 17.0.

A mixed melting point of the oxidation product with an authentic sample of *o*-nitrobenzamide showed no depression.

(b) With Bromine Water: to a small amount of I was added dilute bromine water with heating until the brown color persisted. The solution was evaporated to small volume, cooled and the precipitate filtered. Recrystallized from water the substance melted at 173–175.5° and again gave no depression when mixed with an authentic sample of *o*-nitrobenzamide.

2-(*o*-Nitrophenyl)-oxazole (I) from *o*-Nitrobenzoylaminoacetal.—When *o*-nitrobenzoylaminoacetal[7] was dissolved in cold sulfuric acid and added to a hot mixture of phosphorus pentoxide and sulfuric acid, as above, there was obtained a small yield of I. From 5.8 g. of *o*-nitrobenzoylaminoacetal was obtained only 0.25 g. (6%) of product of m. p. 38–39°. A mixed melting point with I previously prepared showed no depression Further identification was obtained by hydrogenation of the product over Raney nickel. The resulting amine gave a picrate which melted at 153–154° (dec.) and showed no depression in a mixed melting point with the picrate of 2-(*o*-aminophenyl)-oxazole, described below.

Further attempts to prepare I from *o*-nitrobenzoylaminoacetal under milder conditions, using sulfuric acid alone, phosphorus pentachloride or phosphorus pentoxide in toluene, failed. Likewise without success were several attempts to prepare I from *o*-nitrobenzoylaminoacetaldehyde,[7] using sulfuric acid or phosphorus pentachloride, or from *o*-nitrobenzamide and bromoacetal under various conditions in the presence and absence of condensing agents.

2-(*o*-Aminophenyl-oxazole (II).—Hydrogenation of I (3.85 g.) in 50 cc. of absolute ethanol over 1.5 g. of Raney nickel under 3 atm. of hydrogen was complete in forty minutes. After filtration of the catalyst and evaporation of the alcohol under reduced pressure, there was obtained an oil which crystallized on cooling. The yield was 3.1 g. (97%). II was recrystallized as white platelets by dissolving in alcohol, treating with decolorizing charcoal and filtering onto ice; m. p. 32–33°.

Anal. Calcd. for $C_9H_8ON_2$: C, 67.49; H, 5.04; N, 17.49. Found: C, 67.4; H, 5.01; N, 17.6.

II was very soluble in alcohol and benzene, less soluble in ligroin and slightly soluble in water. It had a characteristic odor, somewhat resembling thymol. Its alcohol solution showed bluish fluorescence in daylight.[8]

Picrate.—Recrystallized from dilute alcohol as fine yellow needles; m. p. 154–155° (dec.).

Anal. Calcd. for $C_{15}H_{11}O_8N_5$: N, 17.99. Found: N, 18.0.

2-(*o*-Acetylaminophenyl)-oxazole.—II was acetylated in acetic acid using a slight excess of acetic anhydride. Neutralization with dilute ammonium hydroxide precipitated the crude product in nearly quantitative yield. Recrystallization from dilute alcohol, using decolorizing charcoal, gave fine white needles of m. p. 104–105°.

Anal. Calcd. for $C_{11}H_{10}O_2N_2$: N, 13.86. Found: N, 13.7.

2-(*o*-Benzoylaminophenyl)-oxazole.—Benzoylation of II was carried out in pyridine using a slight excess of benzoyl chloride. The crude product, precipitated by the addition of water, was obtained in nearly quantitative yield. The compound was recrystallized from 50% alcohol as white needles; m. p. 149–150°.

Anal. Calcd. for $C_{16}H_{12}O_2N_2$: N, 10.60. Found: N, 10.5.

2-(*o*-(N⁴-Acetylsulfanilamido)-phenyl)-oxazole.—To an acetone solution of II containing a molar excess of pyridine was added an equimolar amount of acetylsulfanilyl chloride. After refluxing for fifteen minutes, the product was precipitated with cold water in 90% yield. Recrystallization from absolute ethanol, using decolorizing charcoal, gave small white prisms; m. p. 207–208°.

(6) Mulliken, "Identification of Pure Organic Compounds," Vol. II, 1st ed., 1916, p. 32.

(7) Löb, *Ber.*, **27**, 3093 (1894).

(8) Lister and Robinson, *J. Chem. Soc.*, **101**, 1297 (1912), found that certain aminophenyloxazoles, unlike the corresponding nitro derivatives, showed bluish fluorescence.

Anal. Calcd. for $C_{17}H_{15}O_4N_3S$: N, 11.76. Found: N, 11.8.

2-(*o*-Sulfanilamidophenyl)-oxazole.—The preceding acetyl derivative was hydrolyzed by refluxing the substance with twenty-five times its weight of 12% hydrochloric acid for forty minutes. By neutralization with ammonium hydroxide the product was precipitated in 80% yield. On recrystallization from 65% alcohol, using decolorizing charcoal, white prisms were obtained; m. p. 172.5–173.5°.

Anal. Calcd. for $C_{15}H_{13}O_3N_3S$: C, 57.13; H, 4.16; N, 13.33. Found: C, 57.2; H, 4.32; N, 13.4.

2-Phenyloxazole.—To a solution of 1.3 g. (0.0081 mole) of II in 20 cc. of 18% hydrochloric acid, cooled to 0–10°, was added with stirring 0.585 g. (0.0085 mole) of sodium nitrite in 5 cc. of water. After standing fifteen minutes at 0–10°, there was added 15 cc. of 50% hypophosphorous acid. The reaction mixture was placed in an icebox for eight hours and then let stand overnight at room temperature. The solution was cooled in ice and made basic with 20% sodium hydroxide solution. An inorganic precipitate was filtered and washed with ether. The filtrate was extracted with ether and the ether extracts dried over anhydrous potassium carbonate. After removal of the ether, the residue was distilled from an oil-bath. There was obtained 0.25 g. (21%) of a colorless oil; b. p. 225–228° (760 mm.), (oil-bath at 270°). The substance had a pronounced odor, somewhat resembling methyl salicylate.

Anal. Calcd. for C_9H_7ON: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.2; H, 4.78; N, 9.40.

Picrate.—Recrystallized from dilute alcohol as yellow needles; m. p. 115–116°.

Anal. Calcd. for $C_{15}H_{10}O_8N_4$: C, 48.13; H, 2.69; N, 14.97. Found: C, 48.1; H, 2.56; N, 14.8.

Summary

1. 2-Phenyloxazole and certain ortho-substituted derivatives have been prepared.

2. Preliminary pharmacological tests on 2-(*o*-sulfanilamidophenyl)-oxazole indicated antistreptococcal activity.

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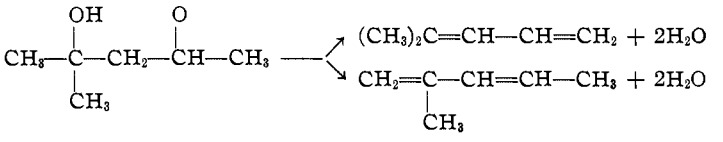
The Preparation and Isolation of 4-Methyl-1,3-pentadiene[1,2]

BY G. BRYANT BACHMAN AND CHARLES G. GOEBEL

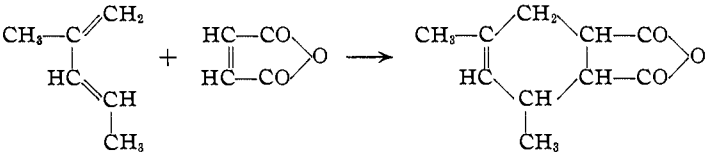
The preparation of pure 4-methyl-1,3-pentadiene has occasioned considerable difficulty.[3] Its formation by dehydration of the readily available 2-methyl-2,4-pentanediol is easily accomplished,



but the principal product is the isomeric 2-methyl-1,3-pentadiene from which it cannot be separated satisfactorily by physical means.[3c]

Turning to the chemical methods, we have found that reaction with maleic anhydride under controlled conditions effects a clean separation of the two isomers and permits the isolation of the desired diene. The 2-methyl derivative reacts under all conditions to form an addition compound, 3,5-dimethyl-Δ^4-tetrahydrophthalic anhydride, and to some extent to form a polymer, but the 4-methyl compound forms only a polymer and no adduct.[3e] In the presence of antipolymerization catalysts, at low temperatures, and with a suitable choice of solvents, the polymerization reactions may be suppressed almost completely and pure 4-methyl-1,3-pentadiene isolated from the reaction mixture.

Table I summarizes the results of these changes in conditions on the yields of polymer and adduct and on the molecular weight of the polymer. It



will be noted that the temperature exerts a far greater influence on the yield than does the nature of the solvent, except in the case of water, in which hydrolysis of the anhydride changes one of the reactants. The maximum yield of polymer (52.6%) and the maximum yield of adduct (77%) total more than 100%, hence it is clear that under

(1) Presented before the Organic Division at the Atlantic City meeting of the American Chemical Society, September 8–12, 1941.

(2) From the M.S. dissertation of Charles G. Goebel.

(3) *Cf.* (a) Van Keersbilck, *Bull. soc. chim. Belg.*, **38**, 205 (1929); (b) Krestinski, *Ber.*, **55**, 2760 (1922); (c) Kyriakides, THIS JOURNAL, **36**, 994 (1914); (d) Diels and Alder, *Ann.*, **470**, 98 (1929); (e) Farmer, *et al.*, *J. Chem. Soc.*, 511 (1930); 3221 (1931); 1065 (1937); (f) Whitby and Gallay, *Can. J. Research*, **6**, 281 (1932); (g) Dupont and Darmon, *Bull. soc. chim. Memoires*, **6**, 1208 (1939).