in a mixed melting point with the picrate of 8-chloroisoquinoline prepared by ring closure.

Anal. Calcd. for $C_{15}H_9O_7N_4Cl$: N, 14.27. Found: N, 14.0.

o-Chlorobenzalaminoacetal.—Equimolar amounts of *o*-chlorobenzaldehyde and aminoacetal[10] were heated in an oil-bath at 110° until the liberated water was driven off. The product, distilled under reduced pressure, was obtained as an almost colorless oil in 95% yield; b. p. 114–117° (2 mm.) (oil-bath at 150–160°).

Anal. Calcd. for $C_{13}H_{15}O_2NCl$: C, 61.05; H, 7.10; N, 5.48. Found: C, 60.7; H, 7.0; N, 5.3.

8-Chloroisoquinoline.—The method of Tyson,[11] using sulfuric acid and phosphorus pentoxide, was employed for the ring closure of *o*-chlorobenzalaminoacetal. The method of working up the product, however, was modified as follows. The cooled sulfuric acid reaction mixture (from 20 g. of *o*-chlorobenzalaminoacetal) was poured on ice and made basic with ammonium hydroxide. The basic solution was extracted with three 200-cc. portions of ether. The combined ether extracts were then extracted with 100 cc. of 6 *N* hydrochloric acid. The hydrochloric acid solution was evaporated to dryness on the steam-bath, made basic with potassium carbonate solution and steam distilled. There was obtained 8-chloroisoquinoline of m. p. 55–56° in 9% yield. The picrate crystallized from alcohol as very fine yellow needles of m. p. 189.5–191.5°.

(10) Cass, THIS JOURNAL, **64**, 785 (1942).

(11) Tyson, *ibid.*, **61**, 183 (1939).

Summary

1. The preparation of 5-amino-8-nitroisoquinoline has been described.

2. Deamination of 5-amino-8-nitroisoquinoline in hydrochloric acid has been shown to yield 8-chloroisoquinoline.

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

2-Phenyloxazole; *para*-Substituted Derivatives[1]

BY JEROME J. ROSENBAUM AND W. E. CASS[2]

In an extension of previously reported work[3] on the synthesis of ortho-substituted derivatives of 2-phenyloxazole, *p*-nitrobenzalaminoacetal was treated with sulfuric acid and phosphorus pentoxide. The product isolated from this reaction proved to be 2-(*p*-nitrophenyl)-oxazole. Oxidation of this substance yielded *p*-nitrobenzamide. By reduction of the nitro group there was obtained 2-(*p*-aminophenyl)-oxazole, from which several derivatives were prepared. Deamination of 2-(*p*-aminophenyl)-oxazole resulted in the formation of 2-phenyloxazole, identical with the substance obtained by the deamination of 2-(*o*-aminophenyl)-oxazole.[3] Nitration of 2-phenyloxazole resulted in the formation of 2-(*p*-nitrophenyl)-oxazole.

The preparation of 2-(*p*-nitrophenyl)-oxazole was also accomplished by treatment of *p*-nitrobenzoylaminoacetal with sulfuric acid and phosphorus pentoxide. Unlike the case of the corresponding ortho derivative,[3] this alternate method of preparation gave 2-(*p*-nitrophenyl)-oxazole in yields comparable to those obtained from *p*-nitrobenzalaminoacetal.

Pharmacological tests on 2-(*p*-sulfanilamidophenyl)-oxazole were carried out by the Merck Institute for Therapeutic Research, Rahway, New Jersey. In staphylococcal infections in mice, this compound was not particularly effective in comparison with sulfathiazole. In streptococcal infections, although some activity was shown, the compound was not as effective as sulfanilamide.

Experimental

All melting points are corrected.

***p*-Nitrobenzalaminoacetal.**—Equimolar amounts of *p*-nitrobenzaldehyde and aminoacetal[3] were heated in an oil-bath at 110–120° until the liberated water was driven off. The reaction mixture was allowed to cool somewhat and twice its volume of dry ether was added. Cooling of the ether solution with dry-ice resulted in the precipitation of *p*-nitrobenzalaminoacetal in 80–87% yield. Further recrystallization from ether gave white plates of m. p. 56–57°. b. p. 165–168° (2 mm.) (oil-bath 200–210°).

Anal. Calcd. for $C_{13}H_{15}O_4N_2$: C, 58.62; H, 6.81; N, 10.52. Found: C, 58.7; H, 6.5; N, 10.6.

2-(*p*-Nitrophenyl)-oxazole from *p*-Nitrobenzalaminoacetal.—The reaction of *p*-nitrobenzalaminoacetal with sulfuric acid and phosphorus pentoxide was carried out following the method used in the preparation of 2-(*o*-nitrophenyl)-oxazole.[3] The crude product, however, was not purified by steam distillation but by recrystallization from alcohol, using decolorizing charcoal. 2-(*p*-Nitrophenyl)-oxazole was thus obtained as yellowish needles in 40% yield, m. p. 163.5–164.5°.

(1) Constructed, in part, from the B.A. research paper of Jerome J. Rosenbaum, New York University, University College, June, 1942.

(2) Present address: Research Laboratory, General Electric Company, Schenectady, New York.

(3) Cass, THIS JOURNAL, **64**, 785 (1942).

Anal. Calcd. for $C_9H_6O_3N_2$: C, 56.85; H, 3.18; N, 14.73. Found: C, 56.8; H, 3.3; N, 14.6.

2-(*p*-Nitrophenyl)-oxazole was weakly basic, dissolving in concentrated hydrochloric or sulfuric acid, but reprecipitating on dilution of the solution with water. The substance could be recrystallized from benzene as stout yellowish needles. A test for the nitro group was positive. Steam distilled, the substance passed over as small white crystals, which, however, crystallized from benzene as yellowish needles.

Oxidation of 2-(*p*-nitrophenyl)-oxazole was carried out using potassium permanganate or bromine water as previously described for the oxidation of 2-(*o*-nitrophenyl)-oxazole.[3] In each case the product of oxidation, recrystallized from water plus a small amount of ammonium hydroxide, was identified as *p*-nitrobenzamide by a mixed melting point determination with an authentic sample of *p*-nitrobenzamide (m. p. 199–202°).

2-(*p*-Nitrophenyl)-oxazole from *p*-Nitrobenzoylaminoacetal.—*p*-Nitrobenzoylaminoacetal[4] (10.8 g., 0.038 mole) was added slowly with constant stirring to 70 cc. of concentrated sulfuric acid cooled to −5°. This cold solution was allowed to drop during eight minutes onto a mixture of 25 g. of phosphorus pentoxide and 6 cc. of sulfuric acid in a flask fitted with an efficient reflux condenser and maintained at 180–190° in an oil-bath. The flask was occasionally shaken and, after the addition was complete, the reaction mixture was allowed to stand twenty-five minutes at 180–190°. After cooling, the reaction mixture was poured on ice and made basic with ammonium hydroxide. The crude product was filtered and recrystallized from alcohol, using decolorizing charcoal. There was obtained 3.3 g. (45%) of product as almost white needles of m. p. 163.5–164.5°. This substance showed no depression in a mixed melting point determination with 2-(*p*-nitrophenyl)-oxazole prepared from *p*-nitrobenzalaminoacetal.

2-(*p*-Aminophenyl)-oxazole.—Hydrogenation of a suspension of 2-(*p*-nitrophenyl)-oxazole in absolute ethanol was carried out, using Raney nickel, as previously described for the corresponding ortho derivative.[3] After filtration of the catalyst and evaporation of the alcohol under reduced pressure, the crude product (obtained in nearly quantitative yield) was recrystallized several times from benzene as white needles of m. p. 121–123°.

Anal. Calcd. for $C_9H_8ON_2$: C, 67.49; H, 5.04; N, 17.49. Found: C, 67.5; H, 5.0; N, 17.5.

The reduction of 2-(*p*-nitrophenyl)-oxazole was also carried out using stannous chloride. A solution of 5 g. (0.0263 mole) of the nitro compound in 22.5 cc. of concentrated hydrochloric acid was added to 18.5 g. (0.0812 mole) of stannous chloride dissolved in 22.5 cc. of concentrated hydrochloric acid. The reaction mixture was warmed on the steam-bath and then, with cooling, made strongly basic with 33% sodium hydroxide solution. The precipitated crude product was obtained in 92% yield.

Unlike the corresponding ortho derivative,[3] 2-(*p*-aminophenyl)-oxazole in alcohol solution did not show fluorescence in daylight. In ultraviolet light, however, a bluish fluorescence was observed.

(4) Löb, *Ber.*, **27**, 3093 (1894).

Derivatives of 2-(*p*-Aminophenyl)-oxazole.—The picrate and the acetyl, benzoyl and acetylsulfanilyl derivatives of 2-(*p*-aminophenyl)-oxazole were prepared as previously described for the corresponding ortho derivatives,[3] essentially the same yields being obtained. These derivatives are listed in Table I.

TABLE I

2-(—)-oxazole	M. p., °C.	*Anal.* Calcd.	N, % Found
p-Aminophenyl, picrate[a,c]	182.5–184 (dec.) $C_{15}H_{11}O_8N_5$	17.99	18.0
p-Acetylaminophenyl[a,d]	191.5–192.5 $C_{11}H_{10}O_2N_2$	13.86	13.9
p-Benzoylaminophenyl[a,e]	163.5–164.5 $C_{16}H_{12}O_2N_2$	10.60	10.7
p-(N^4-Acetylsulfanilamido)-phenyl[b,d]	226.5–228 $C_{17}H_{15}O_4N_3S$	11.76	11.7

[a] Recrystallized from 50% alcohol. [b] Recrystallized from absolute alcohol. [c] Yellow needles. [d] Needles. [e] Plates or prisms.

2-(*p*-Sulfanilamidophenyl)-oxazole.—Hydrolysis of 2-(*p*-(N^4-acetylsulfanilamido)-phenyl)-oxazole was effected by boiling the substance under reflux with ten times its weight of 12% hydrochloric acid for thirty minutes. By neutralization of the solution with ammonium hydroxide the product was precipitated in 95% yield. The substance was recrystallized from 50% alcohol, using decolorizing charcoal, as small plates; m. p. 191.5–192.5°.

Anal. Calcd. for $C_{15}H_{13}O_3N_3S$: C, 57.13; H, 4.16; N, 13.33. Found: C, 57.2; H, 4.1; N, 13.2.

2-Phenyloxazole.—Deamination of 2-(*p*-aminophenyl)-oxazole, as described previously for the corresponding ortho derivative,[3] resulted in the formation of 2-phenyloxazole (b. p. 226–228°) in 34% yield. The picrate (m. p. 115–116°) prepared from this substance showed no depression in a mixed melting point with the picrate of 2-phenyloxazole previously prepared.[3]

Nitration of 2-Phenyloxazole.—To 0.2 g. of 2-phenyloxazole in 5 cc. of concentrated sulfuric acid was added 0.2 g. (excess) of potassium nitrate. The mixture was stirred until the potassium nitrate was dissolved, allowed to stand one hour at room temperature and then warmed to 70° for ten minutes. Ice was added and the mixture neutralized with ammonium hydroxide. The crude yield was 0.2 g. (77%); however, the product was impure as was shown by its low melting point (below 100°). Recrystallization from alcohol followed by recrystallization from benzene and ligroin gave a small amount of yellowish needles of m. p. 162.5–164°. No depression was observed in a mixed melting point with 2-(*p*-nitrophenyl)-oxazole prepared from *p*-nitrobenzalaminoacetal.

Summary

1. Certain para-substituted derivatives of 2-phenyloxazole have been prepared.

2. Pharmacological tests on 2-(*p*-sulfanilamidophenyl)-oxazole have been reported.

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