[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

Aminophenyl Oxazoles and Thiazoles

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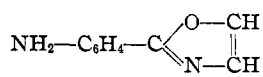
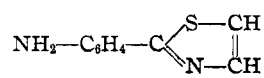
The discovery that aminophenyl oxazolines[3] and aminophenyl thiazolines[4] are local anesthetics was followed logically by a study of the corresponding aminophenyl oxazoles (I) and thiazoles (II), which differ from the oxazolines and thiazolines merely by two less hydrogens and the consequent introduction of an olefin linkage. A description of several of these substances is given in this communication.



I



II

Both classes of compounds are local anesthetics but suffer the same disadvantage as the oxazolines and thiazolines, *i. e.*, slight solubility in water. The salts are soluble but the solutions possess an acidity too high for practical use.

The methods of preparation for oxazoles are numerous and varied. Curiously enough, however, none of those known is adapted to the synthesis of 2-phenyl or substituted 2-phenyl oxazoles; in fact, neither 2-phenyloxazole nor any oxazole with merely a 2-substituent has been described in the literature.[5] As a consequence, the preparation of a few oxazoles to be tested as local anesthetics was limited to the substituted 2-phenyl-4-methyl and 2-phenyl-4,5-dimethyl derivatives.

The condensation of bromoacetone and benzamide yielded 2-phenyl-4-methyloxazole, which nitrated in the para position and then upon reduction gave 2-(*p*)-aminophenyl-4-methyloxazole. Substitution of α-chloroethyl methyl ketone for bromoacetone gave the 2-phenyl-4,5-dimethyloxazole into which the amino group was introduced in a similar way. *p*-Nitrobenzamide could not be substituted for benzamide in the initial condensations but *m*-nitrobenzamide gave small amounts of the oxazole desired.

The oxazoles in general are stable to alkali but are unstable to acids and hydrolyze very readily at higher temperatures.

The 2-phenyl thiazoles are more readily prepared than the corresponding oxazoles. The most satisfactory procedure is to condense thiobenzamide or certain substituted thiobenzamides with dichloroethyl ether or α-halogenated ketones. The nitrothiobenzamides, however, do not undergo this condensation under the usual conditions. The thiazoles are then nitrated, the nitro group entering the para position of the phenyl group, and reduced to the amines. The thiazoles are much more stable to acid hydrolysis than the oxazoles.

It is of interest that Ballowitz[6] observed local anesthetic action in 2-amino-6-ethoxybenzthiazole hydrochloride although Bogert found inactive the parent compound, benzthiazole.[7]

Experimental

2-Phenyl-4-methyloxazole.—A mixture of 60.5 g. of benzamide, 68.5 g. of bromoacetone and 25 g. of powdered calcium carbonate was heated with stirring at 120–130° for two hours. Upon cooling, dilute aqueous sodium hydroxide was added in sufficient quantities to decompose the unreacted bromoacetone and to make the product slightly alkaline. The product was then steam distilled and the oil obtained was extracted with ether. The oxazole boiled at 92–95° (5 mm.); yield 30–40%; chloroplatinate, m. p. 170°; hydrochloride, m. p. 72° by passing dry hydrogen chloride into a petroleum ether solution of pure oxazole; picrate, m. p. 111° prepared in absolute ether. Lewy[8] reports b. p. 238–241°; chloroplatinate, m. p. 170°.

If chloroacetone is used, the temperature of heating should be 115–120° and the time eight hours. The yield, however, is only 15%.

2-(*p*-Nitrophenyl)-4-methyloxazole.—To 10 cc. of concentrated sulfuric acid cooled below 0° in an ice–salt mixture, 2 cc. of 2-phenyl-4-methyloxazole was added dropwise with mechanical stirring. Then 2 cc. of a well-cooled mixture of concentrated sulfuric acid and fuming nitric acid (3 parts H_2SO_4 to 2 parts HNO_3) was added gradually with stirring. In three minutes the product was poured into ice and water and made just alkaline to litmus with dilute aqueous sodium hydroxide. The nitro compound was filtered and crystallized from ethyl alcohol as cream colored crystals, m. p. 146°; yield, 90%.

Anal. Calcd. for $C_{10}H_8N_2O_3$: N, 13.73. Found: N, 13.96.

(1) The aminophenyl thiazoles investigation was part of the research work completed in partial fulfilment for the degree of Doctor of Philosophy by B. S. Friedman, 1936.

(2) The aminophenyl oxazole investigation was part of the research work completed in partial fulfilment for the Degree of Doctor of Philosophy by Meredith Sparks, 1936.

(3) Leffler and Adams, THIS JOURNAL, **59**, 2252 (1937); Novelli and Adams, *ibid.*, **59**, 2259 (1937).

(4) Babcock and Adams, *ibid.*, **59**, 2260 (1937).

(5) Bachstez, *Ber.*, **47**, 3163 (1914).

(6) Ballowitz, *Arch. Exptl. Path. Pharm.*, **163**, 687 (1932).

(7) Bogert, Anchel and Husted, *Proc. Soc. Exptl. Biol. Med.*, **26**, 721 (1929).

(8) Lewy, *Ber.*, **21**, 2192 (1888).

When heated on a steam cone with constant boiling hydrochloric acid for three hours, the nitrophenyloxazole hydrolyzed and a white precipitate formed which proved to be *p*-nitrobenzoic acid.

2-(*m*-Nitrophenyl)-4-methyloxazole.—From 20 g. of *m*-nitrobenzamide, 11 g. of chloroacetone and 6 g. of powdered calcium carbonate, after seventeen hours heating at 115–120° only 1.2 g. (5% of theoretical) of 2-(*m*-nitrophenyl)-4-methyloxazole was obtained; white fluffy crystals from alcohol, m. p. 100°.

Anal. Calcd. for $C_{10}H_8N_2O_3$: N, 13.73. Found: N, 13.58.

2-Phenyl-4,5-dimethyloxazole.—From a mixture of 19.8 g. of α-chloroethyl methyl ketone, 34 g. of benzamide and 9.3 g. of powdered calcium carbonate, after ten hours of heating at 110–120°, 10 g. of pure 2-phenyl-4,5-dimethyloxazole was obtained, b. p. 128–130° (5 mm.), m. p. 50°; yield, 24%. Diels and Riley report a m. p. of 50–55°.[9]

2-(*p*-Nitrophenyl)-4,5-dimethyloxazole.—This product was obtained by nitration of the corresponding phenyl compound, using the nitration procedure previously described: light yellow crystals, m. p. 211°; yield 50%.

Aminophenyl Oxazoles.—These were prepared by an iron powder and water reduction of the nitro compounds and extraction with benzene as white crystals when purified from benzene.

TABLE I

AMINOPHENYL OXAZOLES

Oxazoles	M. p., °C.	Formula	Analyses for N, % Calcd.	Found
2-(*p*-Aminophenyl)-4-methyl	129	$C_{10}H_{10}ON_2$	16.09	16.12
2-(*m*-Aminophenyl)-4-methyl	97	$C_{10}H_{10}ON_2$	16.09	16.14
2-(*p*-Aminophenyl)-4,5-dimethyl	153	$C_{11}H_{12}ON_2$	14.84	14.81

2-Phenylthiazole and 2-Phenyl-4-methylthiazole.—These substances were prepared by the method of Hubacher[10] except that the products were extracted directly from the reaction mixture with ether: 2-phenylthiazole, b. p. 266° (743 mm.), 110–115° (8 mm.); 2-phenyl-4-methylthiazole, b. p. 275–277° (750 mm.), 111° (6 mm.). Hubacher reported 267–269° (732 mm.) and 278–279° (750 mm.), respectively.

2-Phenyl-4,5-dimethylthiazole.—Equivalent molecular amounts of α-chloroethyl methyl ketone, thiobenzamide and sodium acetate, were mixed with 5 cc. of ethyl alcohol for each gram of thiobenzamide and heated on a steam-bath until the alcohol had evaporated. Water was then added and the product extracted with ether. The ether was evaporated, after which the product, a straw-colored oil, distilled over at 126–128° (6 mm.); yield 65%.

2-Phenyl-4-ethylthiazole.—By a procedure similar to that just described using chloromethyl ethyl ketone in place of α-chloroethyl methyl ketone, 2-phenyl-4-ethylthiazole was obtained. The crude material, after distillation of the ether, was dissolved in boiling xylene and after long standing yellow crystals separated which, when pure, melted at 117–118°; yield 67%.

2-*p*-Ethoxythiobenzamide.—A solution of 3 g. of *p*-ethoxybenzonitrile[11] in absolute alcohol which had been saturated at room temperature with ammonia was then saturated with hydrogen sulfide at room temperature and the mixture heated in a pressure bottle at 100° for three to four hours. After partial evaporation of the alcohol, water was added, the precipitate filtered and purified from ethyl alcohol: yellow plates, m. p. 159–161.5°; yield 65–85%. Wheeler reported m. p. 158°.[12]

2-(*p*-Ethoxyphenyl)-thiazole, 2-(*p*-Ethoxyphenyl)-4-methylthiazole, 2-(*p*-Ethoxyphenyl)-4,5-dimethylthiazole and 2-(*p*-Ethoxyphenyl)-4-ethylthiazole.—These were prepared from *p*-ethoxythiobenzamide and, respectively, α,β-dichloroethyl ether, chloroacetone, α-chloroethyl methyl ketone and chloromethyl ethyl ketone by the general procedure previously employed. The constants found were 2-(*p*-ethoxyphenyl)-thiazole, b. p. 139–141° (6 mm.); 2-(*p*-ethoxyphenyl)-4-methylthiazole, b. p. 160–161° (6 mm.); 2-(*p*-ethoxyphenyl)-4,5-dimethylthiazole, buff-colored needles, m. p. 84.6–86°; 2-(*p*-ethoxyphenyl)-4-ethylthiazole, b. p. 150–152° (6 mm.).

Nitration of Phenyl Thiazoles.—To 10 cc. of concentrated sulfuric acid cooled in an ice–salt bath, 2.5 g. of a phenyl thiazole was added with vigorous stirring (one minute). A previously cooled mixture of 4 cc. of fuming nitric acid (sp. gr. 1.5) and 6 cc. of concentrated sulfuric acid was added dropwise (thirty seconds). The mixture was stirred twenty seconds longer and then poured into a mixture of 200 g. of crushed ice and 85 cc. of 20% aqueous sodium hydroxide. The precipitate was filtered and crystallized from ethyl alcohol and water.

Nitration of *p*-Ethoxyphenylthiazole.—One gram of *p*-ethoxyphenylthiazole was added gradually with vigorous stirring to 3 cc. of fuming nitric acid (sp. gr. 1.5) well cooled in an ice-bath. After about one minute the bath was replaced by one containing water at 20° and the mixture was stirred for thirty minutes. Upon pouring into a mixture of 200 g. of crushed ice and 25 cc. of 20% aqueous sodium hydroxide, the product separated and was purified from ethyl alcohol and water.

Reduction of Nitrophenyl and Nitro-*p*-ethoxyphenyl Thiazoles.—Iron powder, water and a drop or two of hydrochloric acid were used for reduction of the nitro compound. No deviation from the usual procedure was necessary.

Position of the Nitro Group in Nitrated Phenyl Thiazoles.—To a solution of 5 g. of potassium dichromate in 20 cc. of concentrated sulfuric acid and 15 cc. of water was added 0.5 g. of 2-nitrophenylthiazole, and the mixture was boiled for two hours. The product obtained in this way was *p*-nitrobenzoic acid, m. p. 239–240°.

2-(*p*-Nitrophenyl)-4-chloromethylthiazole.—2-Phenyl-4-chloromethylthiazole[13] was nitrated by the same procedure used for nitrating 2-phenylthiazole: yellow needles from dilute alcohol, m. p. 120°.

2-(*p*-Nitrophenyl)-4-diethylaminomethylthiazole Hydrochloride.—A mixture of 1 cc. of diethylamine, 5 cc.

(9) Diels and Riley, *Ber.*, **48**, 897 (1915).
(10) Hubacher, *Ann.*, **259**, 234 (1889).
(11) Karrer, Rebmann and Zeller, *Helv. Chim. Acta*, **3**, 266 (1920).
(12) Wheeler, *Am. Chem. J.*, **26**, 360 (1901).
(13) Hooper and Johnson, THIS JOURNAL, **56**, 470, 484 (1934).

TABLE II

NITROPHENYL[a] AND AMINOPHENYL[b] THIAZOLES

Thiazoles	M. p., °C.	Formula	Analyses for N, % Calcd.	Found
2-(*p*-Nitrophenyl)	147.5–148.5			
2-(*p*-Aminophenyl)	123–124	$C_9H_8N_2S$	15.99	16.02
2-(*p*-Nitrophenyl)-4-methyl	105.5–106.5			
2-(*p*-Aminophenyl)-4-methyl	112.5–113.5	$C_{10}H_{10}N_2S$	14.73	14.52
2-(*p*-Nitrophenyl)-4,5-dimethyl	169–169.5			
2-(*p*-Aminophenyl)-4,5-dimethyl	130.5–131.5	$C_{11}H_{12}N_2S$	13.72	13.62
2-(*p*-Nitrophenyl)-4-ethyl	79.5–80			
2-(*p*-Aminophenyl)-4-ethyl	106.5–107	$C_{11}H_{12}N_2S$	13.72	13.66
2-(*p*-Ethoxy-*m*-nitrophenyl)	107.3–108.3			
2-(*p*-Ethoxy-*m*-aminophenyl)	96.5–97.5	$C_{11}H_{12}ON_2S$	12.72	12.96
2-(*p*-Ethoxy-*m*-nitrophenyl)-4-methyl	130.5–132			
2-(*p*-Ethoxy-*m*-aminophenyl)-4-methyl	126–127	$C_{12}H_{14}ON_2S$	11.95	11.87
2-(*p*-Ethoxy-*m*-nitrophenyl)-4,5-dimethyl	140.2–141.2			
2-(*p*-Ethoxy-*m*-aminophenyl)-4,5-dimethyl	163.5–164.5	$C_{13}H_{16}ON_2S$	11.28	11.37
2-(*p*-Ethoxy-*m*-nitrophenyl)-4-ethyl	71–71.5			
2-(*p*-Ethoxy-*m*-aminophenyl)-4-ethyl	109–109.5	$C_{13}H_{16}ON_2S$	11.28	11.53

[a] The nitro compounds were all obtained in about 80% yields. They formed yellowish matted needles which were purified from dilute alcohol. [b] The amino compounds were white or slightly yellowish microcrystalline compounds or needles. They were obtained in yields of 60–80% and were purified from dilute alcohol, except in the case of 2-(*p*-aminophenyl)-4-methylthiazole when water was used.

of benzene and 0.1 g. of 2-(*p*-nitrophenyl)-4-chloromethylthiazole was refluxed for twelve hours. After evaporation of the solvent, the residue was treated with aqueous sodium bicarbonate and the base extracted with ether. The ether solution was dried and the hydrochloride precipitated with dry hydrogen chloride. The product was purified from a mixture of chloroform and carbon tetrachloride; colorless prisms, m. p. 202–204°.

Nitration of Thiobenzamide.—When thiobenzamide was nitrated according to the directions used for nitrating phenylthiazole, a colorless product was obtained, m. p. 89–90°. It proved to be 3,5-diphenyl-1,2,4-thiadiazol, a compound previously prepared by oxidizing thiobenzamide with alcoholic iodine[14] or ammonium persulfate.[15]

Summary

2-Aminophenyl oxazoles and 2 aminophenyl thiazoles have been prepared. They are local anesthetics.

(14) Hofmann, *Ber.*, **2**, 646 (1869); Hofmann and Gabriel, *ibid.*, **25**, 1578 (1892).

(15) Walther, *J. prakt. Chem.*, [2] **69**, 45 (1904).

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[CONTRIBUTION FROM THE DIVISION OF PLANT BIOLOGY, CARNEGIE INSTITUTION OF WASHINGTON]

Sources of *d*-Sorbitol

BY HAROLD H. STRAIN

A number of plant materials have been examined as possible sources of the rare sugar alcohol, *d*-sorbitol. This investigation was facilitated by the use of pyridine for the isolation of the crystalline sorbitol–pyridine compound from the mixture of substances extracted from leaves with ethanol.[1] Of those materials investigated thus far, the best sources for the isolation of sorbitol in quantity are fruits of *Pyrus, Sorbus, Photinia, Crataegus, Pyracantha*, and *Cotoneaster*. Since these species are widely distributed in the temperate zones, material for the isolation of sorbitol is readily available.

Examination of the leaves of pear, peach, apple, apricot, cherry, and Toyon trees has also revealed the presence of small quantities of sorbitol. It thus appears that sorbitol may play the same role in the metabolism of plants of the genus *Rosacae* that sugar alcohols play in the metabolism of some marine algae.[2]

Since fruits of the *Rosacae*, such as cherries, peaches, pears, apples, etc., are consumed in large quantities by man, sorbitol must be a significant constituent of the human diet. The ready conversion of sorbitol into reducing sugars in the animal body[3] suggests that many fruits may be

(1) Strain, THIS JOURNAL, **56**, 1756 (1934).

(2) Haas and Hill, *Biochem. J.*, **26**, 987 (1932); Hassid, THIS JOURNAL, **55**, 4163 (1933); Hassid, *Plant Physiology*, **8**, 480 (1933).

(3) Embden and Griesbach, *Z. physiol. Chem.*, **91**, 251 (1914).